Jan Dirk Blom · Iris E.C. Sommer *Editors*

Hallucinations

Research and Practice

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Foreword

When the editors approached me to write a foreword for this book, I was naturally flattered. They were generous enough to say that they had found some of my publications on the topic nearly 20 years ago to have been a useful starting point for some of their own investigations (Nayani and David 1996).[1] However, it wasn't long before vanity got the better of me and I started to react against being cast far too prematurely as a grand old man. More importantly, I also started to worry that, while I have maintained an interest in the topic, I wasn't confident that I had kept up with all of the latest developments. I should not have been so concerned. This volume is itself the perfect antidote. It reminds us of how diverse and engaging the topic of hallucinations continues to be as well as paying tribute to the truly ancient body of literature that has grown up around the effort to understand it. It is indeed humbling to realise that most seemingly new contributions to the study of hallucinations echo previous thinking.

The scientific study of hallucinations is, however, relatively youthful – perhaps a mere 150 years old, beginning with Esquirol and others. The nineteenth and twentieth centuries were a 'Golden Age' as far as descriptive psychopathology goes, but of course the neuroscientific contribution to psychopathology is more recent, beginning with electroencephalography but now fuelled by functional magnetic resonance imaging. Indeed those of us in the 1990s who had the opportunity to use this 'toy' thought that hallucinations were an obvious target and that they would be explained once and for all. All we needed to do was show that the sensory processing areas of the brain 'lit up' in response to an hallucination in the same way as they did to an external stimulus and the riddle was solved. Such hubris! In fact this early work did lend support to the idea that hallucinations were indeed sensory phenomena to some extent (David et al. 1996) but, like most research, raised new questions about, for example, the relationships between hallucinations, mental imagery and perception; between the generation and reception of images; and, most challenging of all, the nature of belief and reality. In fact, the study of hallucinations was, for me, a salutary

[1] This foreword is dedicated to the memory of Dr. Tony Nayani (1962–2009).

lesson in the limits of neuroimaging and the need to draw on philosophy, the social sciences as well as biomedical science. This book exemplifies this approach and is a tangible demonstration of the benefits of multidisciplinary discourse.

At risk of labouring this point, here is an anecdote. I, like many others, was inspired by Oliver Sacks' observations on musical hallucinations. A review of personal cases and the literature led to a comprehensive review on the topic (Keshavan et al. 1992). It was clear that hallucinations of music and those of voices – a core symptom of schizophrenia – were entirely different. The link with hearing impairment and tinnitus in the former was almost universal as was the lack of associated psychopathology. At last, we had confirmed a clear basis for diagnostic classification. That was until my mentor Alwyn Lishman drew my attention to a case described of an old lady who heard the hymn *The Old Rugged Cross* emanating from her vagina. This led to a pause and consideration that the origin of such a hallucination probably went beyond the scope of the oto-naso-laryngologist.

Another service that this volume provides is to put the spotlight on the variety and modalities of hallucinations. A comparison of these and identification of similarities and differences is long overdue. Why is it that auditory verbal hallucinations (AVHs) are such an important part of psychotic disorders – pointing specifically to language systems and dialogic construction of the Self? Why on the other hand are visual hallucinations the hallmark of 'organic' disorders – pointing to perhaps release phenomena and more diffuse consequences of cerebral perturbation? And why do AVHs in schizophrenia usually respond well to antipsychotic medication while the apparently same phenomena are unresponsive in people with borderline personality disorder? This volume extends to all these modalities and distinctions and will provide much stimulus for integration.

There are other recent developments which have broadened the context for hallucination research and to which Dutch scientists and commentators have made a distinct contribution. In particular, we now know that there are many people who experience hallucinations, of a sort that were once held to be entirely pathological, as part of their daily lives and that these are benign or even positively valued. This prompts the obvious question – what makes, for example, a hallucinated voice a scourge for one person, and a guardian angel for another? Asking voice hearers themselves is a good place to start.

Finally, the editors and their well-chosen contributors demonstrate that these conundrums are not purely theoretical. There is now an array of treatment interventions from psychotherapies to brain stimulation which may be offered to those for whom hallucinations are less than positive, with the added value of informing theoretical advances by a process of reverse translation.

London, UK Anthony S. David

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Chapter 1
General Introduction

Iris E.C. Sommer and Jan Dirk Blom

Hallucinations are fascinating phenomena. The mere possibility of perceiving things that are not there is the stuff that campfire tales are made of. It is one thing to be in a dream state, to be asleep, and to conjure up people, scenes, and landscapes that do not actually exist. But it is quite another to hallucinate: to be wide awake and yet hear that ethereal music, see those costumed figures strolling by, smell the roses that used to grow in your grandfather's garden, feel his hand upon your shoulder, sense his presence somewhere near – and to be the only one able to experience all that. How strange, how fascinating, and how absolutely mind-boggling that would be. And how frightening perhaps, since not all hallucinations involve a walk in the park with loved ones. As clinical psychiatrists, we have come in contact with a great many people who are plagued by voices and visions which compete for priority with what we call "reality." "The voices have completely shaken up my life," as Steven Scholtus – a long-time voice hearer and field expert at the Voices Clinic in Utrecht – writes in this book. "A normal way of living, with a full-time job, a family, the raising of children, is no longer within my reach."

Imagine what that is like.

Or imagine what Christine Blanke, another field expert at the Voices Clinic, has had to endure since she started to hear voices. As she recalls in Chap. 8, "Perhaps for being so busy with other things, I hardly paid any attention to the gentle voices inside my head. Then other people came into my head, conveying evil messages.

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I also started to see blood in the streets, and arms, legs, and heads that had apparently been chopped off." It is not difficult to picture the impact of such horrifying hallucinations on the very foundations of one's existence. And yet there are millions of people who experience hallucinations without being overly bothered by them, and who may even find comfort and solace in such experiences. We know that many of them are as intrigued as we are about the nature of their idiosyncratic experiences, whether they attribute them to psychological, neurobiological, or metaphysical sources.

The fact that a person can see or hear things that remain imperceptible to others touches upon a number of fundamental issues. One of those issues is whether there is such a thing as a general – shared – reality. Many philosophers tell us that such a reality does not exist. What we call reality is always perceived by an observer, and is therefore subjective (Schopenhauer 1958). In that sense, the world that we perceive is a creation of our own mind, one that is based only in part on the input provided by our sense organs. Kant even maintained that we are fundamentally incapable of discerning what the real world is like. The mind imposes concepts ("categories") on the information gathered by our senses, thereby determining the way we experience the world (Kant 1933). Since those concepts are applied without our being able to keep track of the way it is done, we have no access to the world beyond the realm of our consciousness.

Plato illustrated this line of thought in his *Allegory of the Cave*, a dialogue between his brother Glaucon and his teacher Socrates. In the Allegory, Socrates describes a group of people who have spent their lives chained to the wall of a cave, facing a blank wall. As they watch the shadows cast onto that wall by the people and things passing between them and a fire which is burning behind them, they begin to interpret those shadows. According to Socrates, those interpretations are as close as we will ever get to grasping what the real world looks like. He then explains how one of the prisoners is freed, and leaves the cave in search of the sun, the world, nature, and all its creatures. That prisoner realizes that the shadows on the wall are quite different from the real world, which he can now perceive in its true shapes and colors. When he returns to the cave, his fellow prisoners do not believe a word of what he says, preferring to stick to their drab, two-dimensional version of reality (Plato 1974). Perhaps some people suffering from complex or compound hallucinations feel like that returning prisoner, as they try to convince their treating physician of the reality of their perceptions.

From a neuroscientific point of view, these philosophical musings make perfect sense, especially when we conceptualize consciousness as a brain function involved in the creation of representations of the external world (Behrendt 2010). Animal experiments have shown that the hippocampus is able to provide rapid representations of our surroundings based on sensory input signals and memory patterns of situations previously experienced (Kahn et al. 2008). As we all have varying experiences, our memories are different and – to some extent – unique. As a consequence, the concepts we apply to the information from our sense organs also tend to be unique, thus providing us with our own idiosyncratic shadows on the wall, i.e., our

subjective representations of reality. The study of hallucinations touches upon such neuroscientific topics as perception and consciousness and allows us to explore them in depth.

Another question involves the source of hallucinations. When, as the Bible tells us, the Virgin Mary heard an angel speak to her, was she in fact hallucinating, in the sense that her brain was conjuring up a being that was not there? Socrates, one of the most famous voice hearers, was convinced that a *daimon*, or benevolent spirit, always warned him when he was on the verge of making a grave mistake. Joan of Arc claimed that she was guided by the voices of various saints and even God himself and that they helped her to take command of an army and defeat the British. Although unconfirmed by scholars, it has been maintained that René Descartes also heard voices. Clinical lore holds that they seemed to come from behind, and that they were so realistic that he thought he was actually being followed (Winslow 1840). Did all these historical figures experience hallucinations? Or could it be that gods, angels, demons, *djinns* – and even an evil genius – are readily perceptible to some individuals but not to others?

While the spiritual and religious among us may be more interested in the possible metaphysical sources of such experiences, it is the task of neuroscientists to explore the brain and its functions in order to ascertain their origin. Often it seems as if the two possibilities cancel each other out. By demonstrating brain activity on the fMRI scan of a test person who is experiencing auditory hallucinations, it may seem as if their intracerebral source can be proved. But obviously, a BOLD signal on a scan does not count as a valid argument against the possibility that those hallucinated voices have an external origin. If that same person were to perceive a voice from an actual person (or from God?), then similar speech perception areas may be expected to light up on the scan. The apparent contrast between such spiritual and neurobiological explanations has somehow influenced popular opinion, which holds that hallucinations occurring in the context of psychosis or borderline personality disorder derive from brain dysfunction, while those experienced by people without a psychiatric diagnosis may well stem from metaphysical sources. It is not up to us to give a verdict in this matter, but as clinicians and neuroscientists, we would like to stress the role of the brain in all types of perceptual experience. The involvement of speech *production* areas, for example, as established by our own research group, is hardly commensurable with an external source of verbal auditory hallucinations (Sommer et al. 2008).

A final reason why over the years hallucinations have continued to fascinate so many people is the fact that they compel us to think about the brain in ways that go beyond our current neurobiological discourse. Many fundamental brain mechanisms have been discovered by means of the detailed examination of individuals suffering from pathological conditions. Thus, the function of Wernicke's area in deciphering of speech sounds was discovered by performing an autopsy on a patient with severe sensory aphasia. Similarly, the role of the fusiform gyrus in face recognition was unraveled following the examination of patients with prosopagnosia (i.e., the specific inability to recognize faces while the ability to recognize other

objects remains relatively intact). Hallucinations have the potential to shed light on a great number of brain mechanisms currently unknown to us and to provide new insights into perception, consciousness, and many other fundamental brain functions.

For all the above reasons, the brain mechanisms underlying hallucinations have proved to be a popular topic within neuroscience. The technical possibilities currently available to visualize cerebral processes have significantly accelerated our attempts to unravel the neurobiology of hallucinations. But at least as much can be learned from individuals who themselves experience hallucinations. Detailed clinical descriptions and first-person accounts are still a treasure trove for researchers in the field. This book focuses on both aspects. Part I presents various basic approaches to hallucinations which range from the philosophical to the conceptual and neuroscientific. Part II consists of detailed descriptions of the phenomena themselves and the various ways in which they are experienced by patients and by healthy individuals. Part III offers a comprehensive update of findings in the fields of structural and functional neuroimaging, electrophysiology, psychopharmacology, and cognition, while Part IV provides an overview of state-of-the-art treatment methods.

It has been an honor and a pleasure to prepare this book in collaboration with so many experts in the field of hallucinations research. It is gratefully dedicated to the many patients and healthy hallucinators who have inspired them and us.

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Part I
Conceptual Issues

Chapter 2
The Construction of Visual Reality

Donald D. Hoffman

2.1 Illusions: What and Why

Many people, when viewing a windmill in the distance, report that the blades sometimes seem to rotate in the wrong direction. This is an example of a visual illusion. The standard account of such illusions says that each is an incorrect perception seen by most people when they view a specific stimulus. Illusions are rare, but the situations that trigger one person to see an illusion are likely to trigger others to see a similar illusion. Hallucinations, by contrast, are incorrect perceptions that are seen by few people and that occur in the absence of an appropriate stimulus. A person with delirium tremens, for instance, might see a spider that no one else sees.

This standard account of visual illusions naturally raises the question as to why our perceptions should be fallible. What is wrong with our visual system that allows false perceptions to occur?

To answer this question, we must understand visual perception as a biological system that has been shaped by natural selection. Each organ of the body has been shaped by natural selection to contribute in specific ways to the fitness of the person. The visual system can be considered as one of the many organs of the body that makes its specific contribution to the fitness of the whole organism.

This still leaves the puzzling question as to why our perceptions are fallible. The standard account of perceptual evolution is that more accurate perceptions are more fit. For instance, the textbook *Vision Science* states that "Evolutionarily speaking, visual perception is useful only if it is reasonably accurate… Indeed, vision is useful precisely because it is so accurate. By and large, *what you see is what you get*. When this is true, we have what is called *veridical perception* … This is almost always the

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case with vision …" (Palmer 1999, p. 6). Geisler and Diehl (2003) say, "In general, (perceptual) estimates that are nearer the truth have greater utility than those that are wide of the mark." Knill et al. (1996, p. 6) say, "Visual perception … involves the evolution of an organism's visual system to match the structure of the world and the coding scheme provided by nature."

The idea here is that in the struggle for survival, those of our predecessors that saw the world more truly had a fitness advantage over those that saw less truly. Predecessors with truer perceptions had a better chance of becoming our ancestors. Over many generations, this shaped *Homo sapiens* to have more accurate perceptions. We are the offspring of those who saw more truly, and in consequence our perceptions are usually veridical.

From this evolutionary perspective, one answer to the question as to why our perceptions are fallible is simply that evolution is not yet done with us. We are a species in process, not a species that is the end product of an evolutionary great chain of being.

While this last answer is, as far as it goes, correct, it is far from a complete account of why perception is fallible and visual illusions occur. A more complete account requires us to understand that (1) vision is a constructive process and (2) evolution has shaped this constructive process not to deliver truth but to guide adaptive behavior. When these points are understood, we find that we must redefine the notion of illusion. We also find that illusions are an unavoidable feature of perception and cannot be eradicated by further evolution.

2.2 Vision as Construction

Roughly half of the brain's cortex is engaged in vision. Billions of neurons and trillions of synapses are engaged when we simply open our eyes and look around. This is, for many of us, a surprise. We think of visual perception as being a simple process of taking a picture. There is an objective physical world that exists whether or not we look, and vision is just a camera that takes a picture of this preexisting world. We can call this the camera theory of vision. Most of us, to the extent that we think about vision at all, assume that the camera theory of vision is true.

That billions of neurons are involved in vision is a surprise for the camera theory. So much computational power is not necessary to take a picture. Cameras existed long before computers.

The eye is, of course, like a camera. It has a lens that focuses an image on the retina at the back of the eye. But this is just the starting point of the visual system. From there, billions of neurons are engaged in cortical and subcortical processing. Why all this processing power?

The story that has emerged from research in cognitive neuroscience is that vision is a constructive process. When we open our eyes, our visual system constructs in a fraction of a second all the shapes, depths, colors, motions, textures, and objects that we see. The computational power required for such construction is massive, but the

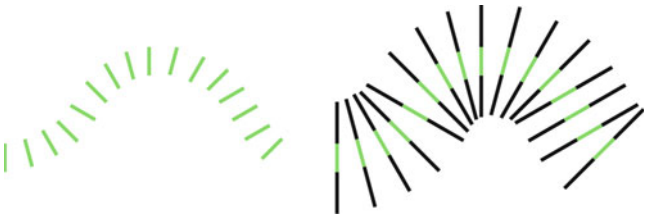

Fig. 2.1 Neon color spreading. The green glowing worm on the *right side* of the figure is a perceptual illusion

construction is done so quickly that we are fooled into thinking that there is no construction at all, that we are simply taking a snapshot of the world as it is.

Why does the visual system bother to do all this construction? Why does it not simply take a picture and be done? That would certainly require less computation, and would reduce the chance of illusions.

The visual system constructs our visual worlds because it must. The starting point of vision is the photoreceptor mosaic in the retina of the eye. Each eye has roughly 120 million photoreceptors, and the activation of each photoreceptor is proportional to the number of photons it catches. One can think of the retina as starting with an array of 120 million numbers, describing the number of photons caught by each photoreceptor. There are no colors, shapes, objects, textures, motions, or depths. There is only a description that says something like, "This photoreceptor caught 5 photons, this one caught 12, this one caught…." From this array of 120 million numbers, the visual system must proceed to construct all the colors, shapes, objects, and depths that constitute our visual world.

This point is painfully clear to computer scientists building robotic vision systems. The input to such a system is an array of numbers from a video camera. If the computer is going to see anything more than just this meaningless array of numbers, then it must have sophisticated programs that set about to construct visual worlds from the video input. Writing such programs has proved exceedingly difficult and has led to great respect for the constructive powers of biological vision systems.

For any image given to the computer, there are always an infinite number of visual worlds that could be constructed and that are compatible with that image. For instance, an infinite number of 3D constructions are always, in principle, compatible with any given 2D image: An ellipse in an image could be the projection of a circle seen at an angle or the projection of any one of an infinite number of different ellipses at different angles. This makes the construction process nontrivial.

A concrete example of visual construction is illustrated in Fig. 2.1. On the left is a collection of green lines. On the right is the same collection of green lines but with black lines attached. Notice that on the right, the green appears to fill in the space between the lines to create a glowing green worm with fairly sharp edges. The glowing green and the sharp edges are all constructed by your visual system, an effect known as neon color spreading (Redies and Spillmann 1981). You can check that you are constructing the neon worm: If you cover the black lines the worm disappears.

Neon color spreading is often used as an example of a visual illusion. It fits the standard definition of an illusion. Most observers see the color spreading when they look at such a figure, and the perceived green spreading where there is no green ink is, most would agree, an incorrect perception. So here we see a case where the constructive power of the visual system leads to a visual illusion. Indeed, each standard visual illusion is in fact a case where we catch the visual system in the act of a construction that is apparently incorrect (for hundreds of illusions and their explanations, see Hoffman (1998) and Seckel (2009)). Illusion and construction are inextricably linked.

Now, the standard view of visual constructions is that they are, in the normal case, *re*constructions. There is an objective physical world with depths, shapes, and colors, and the constructions of the visual system are, in the normal case, fairly accurate reconstructions of the true physical properties. According to this standard view, the reason that visual constructions are usually accurate reconstructions is due to evolution by natural selection. The more accurately an organism's visual system reconstructs the objective physical properties of its environment, the more fit is the organism and the better its chances of surviving long enough to reproduce.

So, the standard view of visual illusions is that they are the result of visual constructions that are not accurate reconstructions of the objective physical world. Evolution by natural selection has made sure that such incorrect constructions are rare.

2.3 Perceptual Evolution

One problem with the standard view of visual illusions is that it is based on an incorrect understanding of evolution by natural selection. As we noted earlier, Geisler and Diehl (2003) say, "In general, (perceptual) estimates that are nearer the truth have greater utility than those that are wide of the mark." Most vision researchers agree that truer perceptions have greater utility and therefore contribute to greater fitness of the organism.

But this assumption, though perhaps plausible, is in fact incorrect. Truth and utility are distinct concepts, and conflating them is a fundamental error. Utility depends on the organism and the world. One cannot assign a utility to the true state of the world unless one specifies an organism. For instance, being 5,000 ft below sea level has high utility for a benthic fish, but is fatal for a person. The same objective feature of the world has radically different utility for people and fish. Mathematically we can write that utility, u, is a function from the objective world, W, and an organism, O, into the real numbers, $\boldsymbol{R}$.

$$u : W \times O \rightarrow R \tag{2.1}$$

So utility and truth are related as shown in (2.1) and therefore are not the same concepts. Now, it might still be the case that although utility and truth are distinct,

nevertheless, it happens to be an empirical fact that truer perceptions have greater utility. But this needs to be demonstrated. It cannot simply be assumed to be true.

One way to test this assumption is through the mathematical theory of evolution, known as evolutionary game theory (Maynard Smith 1974; Nowak 2006). Using computer simulations, one can create a wide variety of objective worlds and of organisms with different kinds of perceptual systems. The organisms can compete with each other in evolutionary games, and one can determine whether the organisms that see more truly are in fact the ones that tend to outcompete other organisms and have more offspring.

Results of such simulations have recently been published by Mark et al. (2010). They simulate a variety of worlds with varying numbers of resources and allow organisms to compete. Some see the whole truth, others part of the truth, and still others none of the truth. The organisms in the simulations that see none of the truth have perceptions that are tuned to utilities rather than to the objective structure of the world. For instance, a particular world might have several territories, each having a resource, such as food or water or salt, that can vary in quantity from 0 to 100. The utility of the resource is varied across simulations. Sometimes utility might be a monotonic function of the quantity of the resource, and other times it might be a Gaussian or some other nonmonotonic function.

What Mark et al. find is that true perceptions are not, in general, more fit. In most cases of interest, an organism that sees none of the truth, but instead sees abstract symbols related to utility, drives the truth perceivers to swift extinction. Natural selection does not usually favor true perceptions. It generally drives them to extinction.

One reason is that perceptual information does not come free. There are costs in time and energy for each bit of information that perception reports about the environment. For every calorie an organism spends on perception, it must kill something and eat it to get the calorie. As a result, natural selection pressures perception to be quick and cheap. Getting a detailed description of the truth is too expensive in time and energy. It is also not usually relevant, since utility, not truth, is what perception needs to report.

2.4 Interface Theory of Perception

Simulations using evolutionary game theory show that perceptual systems that report the whole truth or just part of the truth are not as fit as those that report utility (Mark et al. 2010). How shall we understand these fitter perceptual systems? Are there intuitions that can help us understand why they are more fit?

The key idea is that perception serves to guide adaptive behavior. Guiding adaptive behavior is not the same as constructing veridical perceptions. An example of the difference is the windows desktop of a personal computer (Hoffman 1998, 2009). The desktop interface is not there to present a veridical report of the diodes, resistors, magnetic fields, voltages, and software inside the PC. Instead, it is there to

allow the user to be ignorant of all this, and yet still interact effectively with the PC to get work done.

If the icon for a file is orange, rectangular, and in the center of the display, this does not mean, of course, that the file itself is orange, rectangular, and in the center of the PC box. The color of the icon is not the true color of the file; files have no colors. The rectangular shape of the icon is not the true shape of the file. The position of the icon on the screen is not the true position of the file in the computer. No property of the icon on the screen is veridical. But this does not mean that the windows interface is useless, or misleading, or an illusion. It means that the purpose of the windows interface is to guide useful interactions with the PC while allowing the user to be free of the burden of knowing its complex details.

So, with the windows interface example, we see that reporting the truth is not the only way to be helpful, and that in fact reporting the truth can be an impediment to progress rather than a help. Perception can be useful even though it is not veridical. Indeed, perception is useful, in part, precisely because it is not veridical and does not burden us with complex details about objective reality. Instead, perception has been shaped by natural selection to be a quick and relatively inexpensive guide to adaptive behavior.

The view of visual perception that emerges from this evolutionary understanding can be summarized as follows: Perceived space and time are simply the desktop of the perceptual interface of *Homo sapiens*. Objects, with their colors, shapes, textures, and motions, are simply the icons of our space-time desktop. Space, time, objects, colors, shapes, and motions are not intended to be approximations to the truth. They are simply a species-specific interface that has been shaped by natural selection to guide adaptive behaviors that increase the chance of having kids.

One objection that often comes to mind at this point is the following: If that bus hurdling down the road is just an icon of your perceptual interface, why do you not step in front of the bus? After you are dead, and your interface theory with you, we will know that perception is not just an interface and that it is indeed a report of the truth.

The reason not to step in front of the bus is the same reason one would not carelessly drag a file icon to the trashcan. Even though the shape and color of the file icon do not resemble anything about the true file, nevertheless if one drags the icon to the trash one could lose the file and many hours of work. We know not to take the icons literally. Their colors and shapes are not literally correct. But we also know to take the icons seriously.

Our perceptions operate the same way. They have been shaped by natural selection to guide adaptive behavior. We had better take them seriously. Those of our predecessors who did not take them seriously were at a selective disadvantage compared to those who did take them seriously. If you see a cliff, do not step over. If you see a spider, back away. If you see a moving bus, do not step in front of it. Take your perceptions seriously. But this does not logically require that you take them to be literally true.

Another objection that often comes to mind regards consensus. If a bus is hurdling down the road, any normal observer will agree that they indeed see a bus

hurdling down the road. So, since we all agree about the bus, since there is consensus, does that not mean that we are all seeing the same truth?

But consensus does not logically imply that we are all seeing the truth. It simply implies that we have similar perceptual interfaces and that the rules of visual construction that we use are similar. Just because an icon appears as orange and rectangular on different desktops and to different users does not mean that orange and rectangular are the true color and shape of the file. It just means that the various desktops have similar conventions that they observe.

2.5 Biological Examples

It is one thing to argue from simulations of evolutionary game theory, and from analogies with computer interfaces, that visual perception is simply a species-specific user interface that has been shaped by natural selection to guide adaptive behavior and to hide the complexities of the truth. It is quite another thing to present concrete evidence that this is how perception really works in living biological systems.

Such concrete evidence is abundant. Some of the most salient examples are seen in the phenomena of mimicry, camouflage, supernormal stimuli, and ecological traps. Each of these phenomena can be understood as resulting from natural selection shaping perception to be a quick and inexpensive guide to adaptive behavior rather than a veridical report.

Many dragonflies, for instance, lay their eggs in water. For millions of years, their visual systems have guided them to bodies of water appropriate for oviposition. This is an impressive feat and might suggest that their visual systems have evolved to report the truth about water. Experiments reveal instead that they have evolved a quick and cheap perceptual trick (Horvath et al. 1998). Water slightly polarizes the light that reflects from it, and dragonfly visual systems have evolved to detect this polarization. Unfortunately for the dragonfly, *Homo sapiens* have recently discovered uses for crude oil and asphalt, and these substances polarize light to an even greater degree than does water. Dragonflies find pools of oil even more attractive than bodies of water, and end up dying in large numbers. They also are attracted to asphalt roads. Pools of oil and asphalt roads are now ecological traps for these dragonflies. Apparently their visual system evolved a quick trick to find water: Find something that polarizes light, the more polarization the better. In the environment in which they evolved, this trick was a useful guide to behavior and allowed them to avoid constructing a complex understanding of the truth.

Mimicry and camouflage can be understood as arms races between organisms in which one organism exploits vulnerability in the perceptual interface of a second and in which the second organism in turn sometimes evolves its perceptual interface to remedy that particular vulnerability. Since perception has not evolved to report truth, but is instead a quick and cheap interface that has evolved to guide adaptive behavior, there will always be a myriad of vulnerabilities that can be exploited.

Hence, we find an endless and entertaining variety in the strategies of mimicry and camouflage.

2.6 A New Theory of Illusions and Hallucinations

Vision has evolved to guide adaptive behavior, not to report truth. Our perceptions of space, time, objects, colors, textures, motion, and shapes are useful because they are not true, just as the icons of a computer desktop are useful because they are not true, but simply serve as guides to useful behavior.

Given that none of our perceptions are true, then we must revise the standard definition of illusions, which says that each illusion is an incorrect perception seen by most people when they view a specific stimulus. The key to a new theory of illusions is to think about the evolutionary purpose served by perceptual systems: They have evolved to be guides to adaptive behavior.

This suggests the following new definition: An illusion is a perception, experienced by most people in a specific context, that is not an adaptive guide to behavior.

The windmill illusion, for instance, in which one misperceives the movement of the blades, is an illusion because such a perception is not an adaptive guide. One could be injured by a blade whose movement is misperceived (although, fortunately, the windmill illusion usually disappears if one gets close to the windmill). Similarly, the neon color spreading shown in Fig. 2.1 is an illusion because it is not an adaptive guide and leads the observer to see a surface with certain chromatic properties when it is not adaptive to do so.

We must also revise the standard definition of hallucination, which says that hallucinations are incorrect perceptions that are seen by few people and that occur in the absence of an appropriate stimulus. An evolutionary framework suggests the following new definition: A hallucination is a perception experienced by few people that occurs in the absence of an appropriate context and that is not an adaptive guide to behavior.

The key move in the new definitions of illusion and hallucination is to replace the central role of incorrect perception in the old definitions with the new central role of guiding adaptive behaviors. Our perceptual constructions have been shaped by evolution to be cheap and quick guides to adaptive behaviors in the niches that constituted our environment of evolutionary adaptiveness. Occasionally a situation arises that triggers in most members of the species perceptual constructions that are not adaptive guides to behavior. These are illusions. And occasionally a perceptual system of a member of the species engages in an idiosyncratic perceptual construction that is not an adaptive guide to behavior. This is a hallucination.

The new definitions of illusion and hallucination incorporate an evolutionary understanding of normal perception. They alert us that, when we try to understand the nature and provenance of illusions and hallucinations, it is important to consider how our perceptual systems evolved to serve as guides to adaptive behavior in our environment of evolutionary adaptiveness.

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Chapter 3
Consciousness, Memory, and Hallucinations*

Ralf-Peter Behrendt

> * *"… the 'world' of the hallucinator is no less real to the participant during a hallucinatory phase than is the 'world' of the sane person when awake. To understand the nature of hallucinations it is not sufficient to simply determine the conditions under which non-real mental events (e.g. images, thoughts) somehow become invested with reality. This mistake is made by virtually all investigators of hallucinations in the recent past … It makes no sense to regard a hallucination as a unique and generally pathological instance of subjective-turned-objective phenomenon, and to enquire into the reason for this, if, according to Kant and Schopenhauer, normal perception is achieved in exactly the same way, …"*
>
> (Cutting 1997, p. 83)

3.1 Philosophical Idealism

Everyday experience makes us believe that we observe an objective reality that is independent of our presence. The world is experienced as being observable to everybody; hence, it is believed to be observer-independent. Common sense suggests that events and objects are part of an objective reality that exists independently from our mind. Conversely, Kant (1781) and Schopenhauer (1844) recognized that the world around us is a "dreamlike creation." According to philosophical idealism, objects and events are creations of the mind and conform to the rules of the mind. The things that we see, hear, or feel around us are not part of the physical world and do not conform to rules of the physical world. Objects and events that populate our world do not exist without our awareness of them. Objects in the world are conditioned by the subject and only exist for the subject; there being "no object without subject" (Schopenhauer

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1844). Objects and events incorporate meaning and fundamentally depend on observation, including observation of constancy or change over time. Although everything that we perceive around us is part of a dreamlike creation, there has to be a material world that is independent of our mind, because the consciously experienced world changes in accordance with learned behavior. Kant and Schopenhauer did not deny the existence of a physical world but pointed out that we have no possibility of knowing what the real world is like. There is a world "in itself," which exists independently of the subject and which, according to Schopenhauer (1844), is wholly undifferentiated; it is only at the level of subjective representation that differentiation occurs. The mind, according to Kant, imposes its "categories" (concepts) upon sensory data emanating from the material world (the world "in itself"). Certain ideas and knowledge are "a priori" (basic) conditions for our experience; they rule our experience of the world. "Categories" of object, event, and causation are examples of such "a priori" knowledge; they are basic to our experience of particular instances of objects, events, and causations. Kant (1781) argued that we automatically apply "a priori" concepts to every observation and have no choice in this. Thus, we see the world in terms of our concepts but have no genuine access to the material world that lies beyond the realm of our conscious experiences.

Gestalt psychologists agreed that perception cannot be broken down into patterns of sensory stimulation and that it is not a derivative of sensory stimulation from the external world (Koehler 1940). Instead, they maintained that perceptual experience is an active achievement of the nervous system. Sensory stimulation serves to link the internally created image of the world to the physical world, ensuring that our internally generated stream of consciousness is adaptive. Sensory information derived from the physical world is not a necessary condition for perceptual experience. The richness and detail of conscious experience in dreaming suggests that even wakeful perception does not have to derive from sensory information to be as complex as it is. Similarly to wakeful perception, objects and sceneries that we see in dreams are substantial and seem to surround us. Dream images are real to the dreamer, and even grotesque violations of logic do not provoke questioning of their reality. Only when we wake up and start interacting with the external world do we understand that those sceneries were a fantasy and must have been produced in our mind. Similarly, images, smells, and sounds that surround us in the state of wakefulness are not identical to what is out there in the physical world. We are prevented from gaining insight into the dreamlike nature of the perceived world in the wakeful state for as long as the phenomena into which the conscious stream differentiates are compatible with behavioral interaction with the external physical world.

True hallucinations, as opposed to pseudohallucinations, are experientially identical to normal conscious perception. These hallucinations appear real to the hallucinator. Patients with acute psychosis typically have no insight into the unreality of their perceptual experiences; they react to their hallucinations as if these were normal perceptions (Jaspers 1946; Cutting 1997). Pseudohallucinations, by contrast, are experienced as "unreal"; they share certain characteristics with mental imagery and are accompanied by preserved insight (Jaspers 1946). From a perspective of "realism," according to which the world around us is an objective reality, true hallucinations are defined as "false perceptions" (Hamilton 1974). What is considered

to distinguish hallucinations from normal perception is that hallucinations arise in the absence of a corresponding external object or event. Hallucinations, unlike normal perceptions, are thought to come from within the person's mind (Hamilton 1974). The "realist" approach to hallucinations suggests that hallucinations and normal perception are generated by fundamentally different mechanisms. Hallucinations are suspected to derive from "inner" mental phenomena, such as mental imagery or inner speech. The notion that hallucinations are a derivative of "inner" mental imagery requires the postulation of a process of "external misattribution" – a process that would explain how mental imagery acquires vivid perceptual qualities and becomes alienated from the "self." Cognitive models of hallucinations not only provide unsatisfactory accounts of misattribution, they also fail to explain obvious differences in content and grammatical form between verbal auditory hallucinations in patients diagnosed with schizophrenia (third-person or, less typically, second-person verbal auditory hallucinations) and mental imagery (which may involve first-person inner speech) (Behrendt 1998).

The nature and phenomenology of hallucinations can be explained more fruitfully within a framework that accepts that, similarly to hallucinations and dream imagery, normal conscious awareness of the world during wakefulness is a fundamentally subjective and dreamlike experience (Behrendt and Young 2004). Philosophical idealism predicts that normal perception, hallucinations, and dream imagery are principally manifestations of the same physiological process. Hallucinations and dream imagery differ from normal wakeful conscious experience only with regard to the extent to which they are *constrained* by sensory information from the external physical world. Hallucinations are similar to dreaming in that a lack of sensory constraints on the physiological mechanisms of conscious experience makes these forms of conscious experience maladaptive for interaction with the physical world. Attentional mechanisms modulate the content of conscious experience, whether or not conscious experience is externally constrained by sensory input. In hallucinations, attentional mechanisms are in a position to determine the content of conscious experience without regard for external sensory stimulation. Clinical observation suggests that content and context of verbal auditory hallucinations are crucially dependent on psychological factors relating to personality, psychological conflicts, and social concerns. Hallucinatory experiences that accompany acute psychotic states or chronically persist in patients diagnosed with schizophrenia are characteristically interpersonal in form and content, featuring derogatory voices, verbal commands, or third-person comments on one's actions, often reflecting patients' social anxieties and preoccupations (Linn 1977; Nayani and David 1996; Birchwood et al. 2000). At times of increased social stress and anxiety, patients prone to hallucinations increase their attention to social cues, and it is in the focus of attention where voices talking about or to the patient would emerge. Recognizing the role of attentional pressures attributable to social sensitivities suffered by patients diagnosed with schizophrenia, we can arrive at an explanation of the phenomenology of verbal auditory hallucinations in terms of grammatical form, content, and circumstances of occurrence. Hallucinations experienced by neurological patients have a different phenomenology (Manford and Andermann 1998); however, attentional factors likely play a role in determining form and content of these experiences, too (Behrendt and Young 2004).

3.2 Resonance in Thalamocortical Networks

The thalamus and cerebral cortex constitute a unified oscillatory system (Llinás and Ribary 1993). Projection neurons in specific and nonspecific thalamic nuclei and inhibitory neurons in the adjacent reticular thalamic nucleus form neuronal circuits with interneurons and pyramidal neurons in the cerebral cortex. Neurons connected in thalamocortical circuits have intrinsic resonance rhythmicity that is released by cholinergic input. In the depolarized state, these neurons exhibit subthreshold oscillations of membrane potential around 40 Hz, predisposing them to fire at γ rhythms in response to synaptic excitation (Steriade et al. 1993). Rhythmic discharges from thalamic or cortical neurons can entrain oscillatory activity in connected neurons. Synchronized firing of several neurons will elicit temporally overlapping excitatory postsynaptic potentials in other cells and increase their chance of firing, too. γ Activities in interconnected thalamocortical circuits globally synchronize to form "large functional states" (Llinás and Ribary 1993). Llinás and Paré (1991) pointed out that most of the connectivity in thalamocortical circuits is geared to the generation of internal functional modes, only a minor part of thalamocortical connectivity being devoted to the transfer of sensory information. Thus, consciousness can be viewed as a "closed-loop property" of the thalamocortical system (see Fig. 3.1). Dream imagery associated with paradoxical sleep differs from conscious perception during wakefulness in that, during paradoxical sleep, sensory input exerts only a weak influence over intrinsic thalamocortical resonance. Synchronized thalamocortical γ activity and conscious experience are generated during both wakefulness and paradoxical sleep, but during paradoxical sleep, the external world is mostly excluded from conscious experience (Llinás and Paré 1991; Llinás and Ribary 1993).

Reverberating activity in large assemblies of thalamocortical circuits produces γ (40 Hz) oscillations in magnetic or electrical field potentials recorded over the neocortex (Ribary et al. 1991). Neocortical γ oscillations characterize states of increased attention and alertness (Herculano-Houzel et al. 1999), accompany paradoxical sleep (Llinás and Ribary 1993), and can be recorded in association with hallucinations (Spencer et al. 2009). During wakefulness, sensory stimulation can reset and enhance γ oscillatory activity recorded from the neocortex (Ribary et al. 1991). Such resetting is not observed during paradoxical sleep when random bursts of neocortical 40-Hz oscillations occur in a manner unrelated to sensory stimulation (Llinás and Ribary 1993).

Electroencephalographic activation involves the release of acetylcholine from cholinergic fibers into the thalamus where acetylcholine acts on muscarinic receptors to induce delayed and prolonged membrane depolarization in thalamic projection neurons, thus enabling γ discharge activity (Curro Dossi et al. 1991; Munk et al. 1996). Cholinergic activation during arousal especially affects intralaminar (nonspecific) thalamic nuclei (Steriade et al. 1993). Intralaminar thalamic nuclei project to superficial layers of all neocortical areas in a spatially continuous manner. Neurons in these nuclei have a particularly strong intrinsic 40-Hz rhythmicity that may entrain oscillatory discharge activities in cortical neurons. By distributing

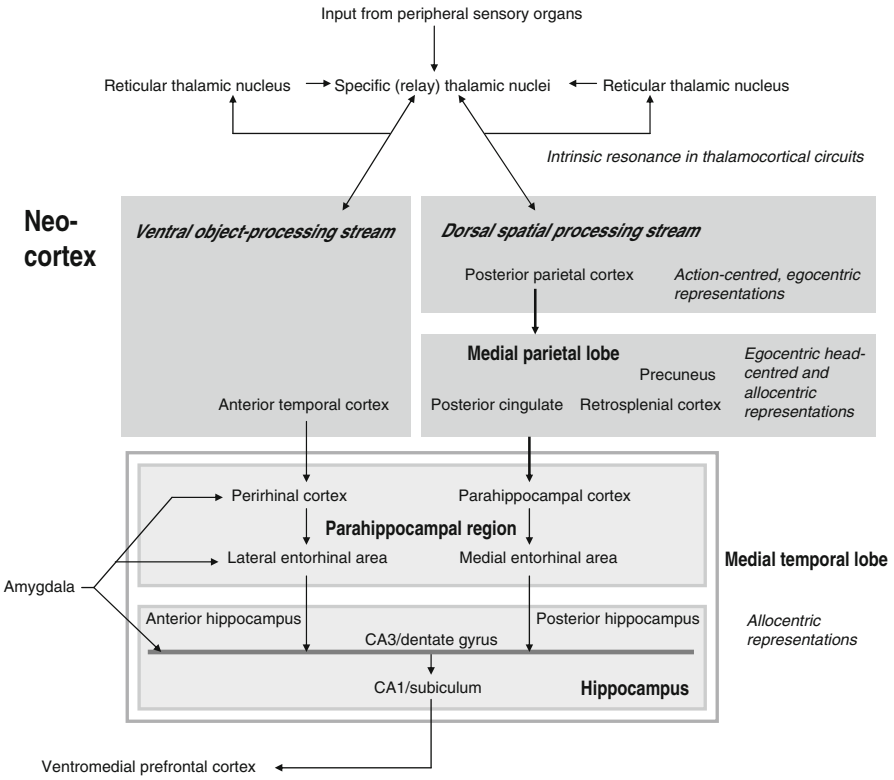

Fig. 3.1 Peripheral sensory information constrains intrinsic resonance processes in the thalamocortical system. Information processed in dorsal parts of the thalamoneocortical system, representing stimuli in action-oriented frames of reference, influences the formation of activity patterns in posterior (*dorsal*) parts of CA3 via medial parietal cortices, parahippocampal cortex, and medial entorhinal cortex. Information processed in ventral parts of the thalamoneocortical system (ventral object-processing stream) influences activity patterns in anterior (*ventral*) parts of CA3 via perirhinal and lateral entorhinal cortices – regions that are concurrently modulated by input from the basolateral amygdala. Arbitrary association patterns rapidly forming at θ rhythms in CA3 may have the information content of discrete epochs of unitary conscious experience and are temporarily stored as event (i.e., episodic) memories. Activity patterns formed in CA3 influence processes in CA1 that may serve to classify the location or situation presently occupied by the subject within its wider spatial or social environment (Behrendt 2010). The medial prefrontal cortex may encode emotional or habitual behavior modes that can be engaged in response to such contextual information

γ rhythms over the neocortex, intralaminar thalamic nuclei can facilitate the synchronization of γ reverberations in specific thalamocortical circuits that are activated by sensory input and attentional mechanisms. It has been suggested that conscious experience is based on coherent 40-Hz coactivation of specific and nonspecific thalamocortical circuits. The content of consciousness would lie in specific thalamocortical circuits, whereas nonspecific thalamocortical circuits may ensure the

temporary binding of activated specific thalamocortical circuits toward the creation of a unitary conscious experience (Llinás and Paré 1991; Llinás and Ribary 1993).

Cholinergic, noradrenergic, and serotonergic systems ascending from the brainstem to the thalamus globally facilitate or inhibit fast oscillatory and resonance capabilities of thalamic "relay" cells and modulate their responsiveness to afferent sensory input. Acetylcholine released in the thalamus from terminals of cholinergic brainstem nuclei induces membrane potential depolarization, characterized by subthreshold γ oscillations, and enhances both spontaneous and stimulus-evoked firing activity of relay cells. Effects of cholinergic arousal are mediated by activation of muscarinic receptors located on thalamic relay cells and γ-aminobutyric acidergic (GABAergic) interneurons (Francesconi et al. 1988; McCormick and Pape 1988). By mediating a reduction in the release of GABA in specific thalamic nuclei, activation of muscarinic receptors on interneurons plays an important role in increasing the efficacy of signal transmission in states of arousal and increased attention (Carden and Bickford 1999).

The impact of peripheral sensory information on resonance in the thalamocortical system is partly regulated by the reticular thalamic nucleus. The reticular thalamic nucleus forms a sheet along the outer surface of the thalamus and consists of GABAergic inhibitory neurons that receive collateral terminals from thalamocortical and reentrant corticothalamic projections. Reticular thalamic neurons, in turn, project in a topographically organized manner to specific ("relay") and nonspecific thalamic nuclei (Llinás and Ribary 1993). Cholinergic input from the brainstem inhibits spontaneous activity of GABAergic neurons in the reticular nucleus, contributing to disinhibition of thalamic relay cells at times of arousal. However, in response to certain patterns of sensory stimulation, reticular thalamic neurons can inhibit activity in specific thalamic nuclei during arousal (Villa 1990; Murphy et al. 1994). Stimulus-specific inhibition of thalamic relay cells may be mediated by activation of presynaptic nicotinic receptors on GABAergic terminals from reticular thalamic neurons. Reticular thalamic neurons densely express nicotinic receptors (particularly those with the α_7 subunit). Thus, while inhibition of GABAergic neurons in the thalamus mediated by muscarinic receptor activation may contribute to the global increase of relay cell activity during arousal, nicotinic facilitation of GABAergic transmission from the reticular thalamic nucleus may, at the same time, improve the signal-to-noise ratio of thalamic activity (Lena and Changeux 1997).

Dysfunction of the reticular thalamic nucleus may lead to loss of sensory-specific inhibition in specific thalamic nuclei. This may manifest particularly at times of arousal when thalamic relay cells exhibit increased spontaneous activity. Then, random activity may predominate over stimulus-specific inhibition, and relay cells may become recruited into thalamocortical reverberations without receiving adequate sensory input. Some abnormalities identified in studies of patients diagnosed with schizophrenia or animal models of schizophrenia, including dopaminergic and α_7 nicotinic receptor dysfunctions, may predispose to hallucinations at times of increased stress and anxiety by disrupting the balance between intrinsic activity of the thalamocortical system and constraints imposed by sensory input to the thalamus (Behrendt 2006; Behrendt and Young 2004). Peripheral sensory impairment

may constitute another cause for excessive noise in specific thalamic nuclei predisposing to pathological activation of thalamocortical circuits. This mechanism may contribute to musical hallucinations (see Chap. 11), the Charles Bonnet syndrome (see Chap. 6), late paraphrenia, and schizophrenia. Dysfunction of serotonergic raphe nuclei, as may be the case in peduncular hallucinosis, may also cause global disinhibition in specific thalamic nuclei (Behrendt and Young 2004).

3.3 Allocentric Representations and Episodic Memory

Synchronized thalamocortical γ oscillations likely play a role in the generation of conscious experience; however, it remains difficult to understand how widely distributed oscillatory processes can give rise to unified conscious experience of an external world ("binding problem"). The hippocampus, receiving major inputs from the entorhinal cortex, is in a unique position to rapidly integrate stimulus-related and contextual information processed in parietal and temporal association cortices. Superficial layer II of the entorhinal cortex projects, via the perforant path, to the granule cell layer of the dentate gyrus. Granule cells, in turn, send mossy fibers to hippocampal regions CA3 and CA2. Pyramidal neurons of CA3 (cornu ammonis region 3) are extensively interconnected via recurrent axon collaterals. CA3 is thought to form a single "autoassociation network" that displays "attractor dynamics" (Rolls 2007; for a full explanation see Chap. 4). The high degree of internal connectivity and effective synaptic plasticity enable the rapid formation of associations among individual elements of a patterned input reflecting sensory details processed in neocortical areas. The autoassociation network of CA3 stores "arbitrary associations" between object and place information as event memories for durations of seconds to minutes (Kesner 2007; Rolls 2007).

CA3 of the dorsal (posterior) hippocampus preferentially encodes spatial contextual information. Spatial information about the location of objects encoded in the parietal cortex enters the dorsal dentate-CA3 network via the medial entorhinal cortex (Kesner 2007). The posterior parietal cortex encodes sensory information in retinocentric and other egocentric reference frames for the purpose of guiding particular types of motor acts, such as saccadic eye movements, reaching, or grasping ("action-oriented spatial representations") (Colby and Goldberg 1999; Andersen and Buneo 2002). Regions in the medial parietal cortex integrate various feature representations activated in the posterior parietal cortex in order to encode, in egocentric head-centered coordinates, representations of locations or landmarks in the visible environment. Regions in the medial parietal cortex, in turn, are interconnected, via parahippocampal and medial entorhinal cortices, with the dorsal (posterior) hippocampus, which ties various visual feature units together, using "attractor dynamics" (see Chap. 4) to form an allocentric representation of the environment (i.e., a representation that appears fixed to the external environment) (Byrne et al. 2007).

The ventral (anterior) hippocampus is preferentially involved in the acquisition and retrieval of nonspatial memories (Ross and Eichenbaum 2006). The anterior

lateral temporal cortex, which forms part of the "ventral visual stream," forwards nonspatial visual information about objects via the perirhinal cortex and lateral entorhinal cortex to the anterior (ventral) hippocampus. The anterior lateral temporal cortex, which, in humans, also processes visual and nonvisual information about social and emotional cues as well as semantic components of language, acts as a "connectional hub" to the anterior hippocampus by way of perirhinal and entorhinal cortices (Kahn et al. 2008). CA3 of the anterior (ventral) hippocampus encodes event memories consisting of arbitrary associations between object/reward information and the "space out there" (allocentric space) (Rolls et al. 2005; Rolls and Xiang 2005). Information about rewards and punishers, represented in the amygdala and orbitofrontal cortex, reaches the anterior hippocampus via the perirhinal and lateral entorhinal cortices. Glutamatergic projections from the basolateral amygdala to superficial layers of the entorhinal cortex promote γ oscillations in the entorhinal cortex by rhythmically depolarizing pyramidal neurons, thereby enabling the integration of neocortical inputs in emotionally arousing situations and promoting the spread of neocortical activity to the hippocampus (Bauer et al. 2007).

During exploratory locomotion and paradoxical sleep, neurons in superficial layers of the entorhinal cortex and their projection targets in the hippocampus discharge synchronously at γ frequencies in relation to the phase of the θ cycle (Chrobak and Buzsáki 1998). Temporal convergence of information-bearing neocortical input to the hippocampus and local θ oscillations, sustained by cholinergic input from the medial septum, results in the encoding of event (episodic) memories. Synchronous γ firing in subsets of CA3 pyramidal neurons that are tuned to the θ rhythm is necessary for the temporary storage of information. Thus, hippocampal θ oscillations, which are selectively present in behavioral states of exploration and attentiveness (but also in paradoxical sleep), ensure the continuous gathering of information about the environment (Buzsáki 1996; Vertes 2005). VanRullen and Koch (2003) argued that θ oscillations, acting as a carrier for γ oscillations, provide the context for conscious memory recall. θ Oscillations may also be important for conscious perception, if we accept that conscious perception is closely intertwined with conscious recognition and event memory retrieval. During paradoxical sleep, θ and γ oscillations are highly synchronized between dentate gyrus and CA3, possibly reflecting the recombination of event memory fragments (Montgomery et al. 2008). This would be consistent with the suggestion that reproduced sequences of patterned ensemble firing in the hippocampus during paradoxical sleep represent reactivated episodic memory traces that form the content of dream states (Louie and Wilson 2001).

Acetylcholine in the thalamus may cooperate with acetylcholine in the hippocampus in enabling neural processes that underlie conscious perception. Cholinergic mechanisms enhance memory encoding by increasing θ oscillations in the hippocampal formation (Hasselmo 2006). In addition, cholinergic input from the medial septum facilitates the encoding of new information in CA3 via activation of nicotinic receptors. Activation of nicotinic receptors in CA3 enhances excitatory synaptic input from the entorhinal cortex and dentate gyrus, while activation of (presynaptic) muscarinic receptors in CA3 suppresses excitatory

transmission at recurrent connections between pyramidal cells (Hasselmo 2006). Thus, acetylcholine enables the encoding of new information in part by activating muscarinic receptors and suppressing feedback excitation within the autoassociation network of CA3. Conversely, lower levels of acetylcholine would encourage CA3 to settle on a previously learned event code (Burgess et al. 2001).

Rapid-event memory formation in the autoassociation network of CA3, integrating nonspatial information about landmarks or objects with information about their spatial context, may underlie externalized conscious experience (Behrendt 2010). Identifying consciousness with event memory formation in CA3 is consistent with Zeman's (2001, p. 1281) conclusion that "rather than guiding action from moment to moment, consciousness serves its biological purpose on a longer, more reflective, time scale." The world of our experience – subjective and dreamlike as it may be – appears to be "fixed" to the external physical world. The world of phenomenal space and time seems to be "out there" and contains objects that seem to be "out there," even though this world exists only "in our mind." What we conceptualize as "self" stems from others' attitudes and intentions toward us; it is our reflection in the social situation, which is essentially an aspect of the world that we see around us. Thus, consciousness, including evolutionarily more recent self-awareness, is allocentric. Even if the world of our experience is not constrained by peripheral sensory stimulation, as is the case in dream imagery or hallucinations, it is still externalized, that is, it still appears to be fixed to an external world. The highest-level encoder of allocentric information is the hippocampus, and if we take into account the ability of CA3 to form activity patterns that *bind* information from diverse cortical sensory processing areas into a coherent whole, then the hypothesis arises that consciousness is an emergent property of CA3 attractor dynamics and that dysfunctional regulation of neuronal activity and "parasitic attractor" dynamics in CA3 could be responsible for hallucinatory experiences.

3.4 Schizophrenic Psychosis and Hippocampal Hyperactivity

Schizophrenia is associated with GABAergic hypofunction in the hippocampus, especially in regions CA3 and CA2. GABAergic hypofunction in patients diagnosed with schizophrenia predominantly affects fast-spiking interneurons (basket cells), which contain parvalbumin and synapse onto perisomatic aspects of hippocampal pyramidal cells (Zhang and Reynolds 2002; Benes et al. 2007; Lisman et al. 2008). Decreased functionality of fast-spiking interneurons leads to a reduction of GABA-mediated inhibitory postsynaptic potentials in pyramidal cells and, hence, disinhibition of these cells. Deficient GABAergic transmission, in turn, may be a consequence of NMDA-receptor hypofunction in the hippocampus. Fast-spiking interneurons use NMDA receptors to "sense" the level of activity in surrounding pyramidal neurons (by responding to extracellular glutamate) in order to adjust the synthesis and release of GABA. Malfunctioning NMDA receptors would

be relatively insensitive to glutamate levels in the surrounding milieu, which would lead to downregulation of GABA synthesis (Coyle 2006; Lisman et al. 2008). NMDA-receptor hypofunction, resulting in deficient GABA release from fast-spiking interneurons and, hence, disinhibition of hippocampal pyramidal cells, has been implicated in schizophrenia. Similarly, NMDA-receptor antagonists may induce psychotic experiences, such as hallucinations, in healthy subjects by reducing the output of fast-spiking GABAergic interneurons and thereby increasing pyramidal cell activity (Lisman et al. 2008).

The decrease in GABAergic tone in the hippocampus may be an indirect consequence of elevated excitatory input from the basolateral amygdala (Gisabella et al. 2009). The basolateral nucleus of the amygdala provides strong excitatory input directly to CA3 and CA2. In a rat model of schizophrenia, excessive glutamatergic input from the basolateral amygdala to regions CA3 and CA2 causes excitotoxic reductions in GABAergic interneuron density (especially affecting fast-firing basket cells), mirroring postmortem findings of reduced GABAergic interneuron functionality in CA3 and CA2 in patients diagnosed with schizophrenia (Berretta et al. 2004). Reductions in GABA-mediated inhibitory postsynaptic potentials in pyramidal neurons of CA3 occur in association with an increase in hippocampal "long-term potentiation" (Gisabella et al. 2009). Thus, increased responsiveness of the amygdala may contribute to excessive formation of memories for the environmental context of aversive stimulation and, by implication, dysfunctional conscious experiences in the form of hallucinations. Psychotic episodes in patients diagnosed with schizophrenia are often preceded or accompanied by syndromatic or subsyndromatic social phobia characterized by intense apprehensions, generalized across all social encounters, about being criticized, negatively evaluated, or rejected by others (Michail and Birchwood 2009). In neuroimaging studies, patients with social phobia show hyperresponsivity of the amygdala, especially on the left, to others' angry or contemptuous emotional expressions (Stein et al. 2002; Phan et al. 2006).

Electrical stimulation of the human medial temporal lobe, especially in the region of the amygdala and hippocampus, can elicit complex visual hallucinations (see Chap. 6) and sometimes auditory hallucinations (Vignal et al. 2007; see also Chaps. 8–10). Direct stimulation of the amygdala can elicit feelings of fear and anxiety, as well as complex hallucinations. Brain lesions in or near the amygdala are associated with schizophrenia-like psychoses (Fudge and Emiliano 2003). Although hippocampal volume is often reduced in patients diagnosed with schizophrenia, metabolic activity in the hippocampus, as measured by neuroimaging, is often increased, indicating an excess of excitatory neuronal activity. Hyperactivity of the left hippocampus and parahippocampal gyrus is associated with a *tendency*, in these patients, to experience hallucinations and delusions (Liddle et al. 2000; Heckers 2001). *Actual experience* of auditory (Shergill et al. 2000) or visual hallucinations is accompanied by hippocampal activation as demonstrated in fMRI studies, along with activations in higher-order neocortical sensory processing areas (Oertel et al. 2007). These findings agree with the hypothesis that hippocampal hyperactivity might underlie hallucinations and other positive symptoms in patients diagnosed with schizophrenia (Liddle et al. 2000; Heckers 2001). Antipsychotic treatment with risperidone was

shown to reduce regional cerebral metabolism in the left hippocampus in association with a gradual reduction in hallucinations and delusions, "consistent with the hypothesis that reduction in aberrant hippocampal firing is a prerequisite for subsequent resolution of reality distortion" (Liddle et al. 2000, p. 406).

Patients diagnosed with schizophrenia, particularly those with "disorganized schizophrenia" (characterized by fleeting and fragmentary hallucinations and prominent thought disorder), are impaired in Gestalt tasks that require perceptual grouping of visual stimuli. In rats, blocking neural activity in one hippocampus induced coactivation, at γ frequencies, of pyramidal cells in the contralateral hippocampus that initially fired independently (Olypher et al. 2006). As a result, the ability of rats to subgroup distal spatial stimuli and segregate them from irrelevant local stimuli was impaired, preventing these rats from effectively avoiding regions of the room where footshock was administered. Coactivation, at γ frequencies, of initially uncoupled hippocampal pyramidal neurons amounts to a failure to segregate cell assemblies encoding unrelated representations. Disorganization of spike timing between cells would provide the basis on which "a pathological steady and stable state of activity" can emerge through γ synchronization: a "parasitic attractor" "that does not reflect reality" but a hallucination instead (Olypher et al. 2006, p. 166).

3.5 Conclusions

Normal perception, dreaming, and hallucinations are equivalent because even normal perception in wakefulness is fundamentally a state of hallucinations, one however that is constrained by external physical reality. Although Kant (1781) was not the first idealist, he can be credited with first recognizing idealism as the appropriate philosophical framework for understanding the nature of the perceived world and its phenomena and, at the same time, recognizing the embeddedness of the phenomenal world in a shared physical world that lies beyond subjective experience. The adaptive state of wakefulness depends on sensory information about changes taking place in the physical world, but we do not see, hear, feel, or smell physical reality itself. Instead, physical reality constrains the internal and fundamentally subjective process of conscious experience.

Activation of thalamic relay cells during arousal is normally balanced by sensory-specific and attention-specific inhibitory input from neurons in the reticular thalamic nucleus. The reticular thalamic nucleus, in turn, is under cholinergic control by the mesencephalic reticular formation and basal forebrain nuclei. In patients diagnosed with schizophrenia, deficient nicotinic activation of reticular thalamic neurons during arousal may lead to a loss of specific inhibition and random activity in specific thalamic nuclei. This would mask sensory input to the thalamus and weaken its impact on thalamocortical self-organization, resulting in impaired γ response synchronization to sensory stimulation. Thalamic relay cells could be recruited into "large functional states" involved in conscious experience without regard for the actual pattern of sensory input. Inhibition of the reticular thalamic

nucleus and disinhibition in specific thalamic nuclei may also result from dopaminergic hyperactivity, as in schizophrenia, or exogenous NMDA-receptor antagonists, such as phencyclidine (Behrendt and Young 2004).

Patterns of resonant thalamocortical activity, representing sensory information in egocentric or action-centered frameworks, provide the dynamic substrate from which the hippocampus rapidly constructs allocentric environmental representations that serve mnemonic functions and self-localization. The CA3 autoassociation network, forming unitary activity patterns at θ intervals, integrates information about objects and their spatial context into allocentric representations of the environment. Unitary conscious experiences, referring to *discrete* epochs of conscious experience (VanRullen and Koch 2003), may be an emergent property of unitary activity patterns formed through attractor dynamics in CA3 (Behrendt 2010). Regarding the stream of consciousness as a sequence of higher-order symbols that characterize unique states in CA3 formed through attractor dynamics agrees not only with Kant's idealism but also Chalmers' (1996) argument that consciousness is imbued with nonphysical properties (and therefore cannot make a difference to the trajectory of behavior). Hallucinations may not differ from normal conscious perception in terms of their intricate relationship with episodic memory formation and recall.

Increased excitability in CA3 may cause hallucinations in through the formation of parasitic attractors. Alternatively, pathophysiological processes that predispose to patterns of thalamocortical activity that are underconstrained by peripheral sensory input could be responsible for hallucinations. Ultimately, much of the thalamocortical system, processing external sensory input, interacts with hippocampal region CA3 in producing view-dependent allocentric representations that manifest as discrete epochs of conscious experience. The precise may be phenomenology of hallucinations. The presence of visual hallucinations, alongside auditory hallucinations, in patients diagnosed with disorganized schizophrenia may indicate pathologically increased hippocampal activity, due to GABAergic hypofunction, whereas hallucinations occurring exclusively in the auditory modality in patients diagnosed with paranoid schizophrenia may indicate underconstrained thalamocortical that, of abnormal reticular thalamic nucleus function, is excessively sensitive to attentional.

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Chapter 4
A Network Model of Hallucinations

Rutger Goekoop and Jasper Looijestijn

4.1 Introduction

The study of hallucinations is complicated by the huge number of factors that determine the occurrence and phenomenological characteristics of these phenomena. Until recently, this has made it impossible to develop a "global view" of the events that govern their existence. Recent breakthroughs in network science allow for a graphical representation and modeling of large numbers of interacting factors (Barabasi 2003; Barabasi et al. 2011), which may bring such a global view within reach. In this chapter, we will summarize a number of theoretical issues that are required for a basic understanding of network models. Finally, a network model of hallucinations is presented that aims to integrate a substantial number of clinical and research findings pertaining to the origin and phenomenological expression of hallucinations.

4.2 General Network Models

By the mid-twentieth century, network science began to take shape as a separate discipline, thanks to Paul Erdős (1913–1996) and many other brilliant physicists and mathematicians. In the 1950s, biological organisms were generally considered to be too complex to be described in terms of mathematical formulas. That all changed during the 1960s, when computers became available that allowed for complex

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simulations of anything ranging from molecules to cells, organs, individuals, and markets. Classical network theory was born, which earned a serious reputation when it produced successful explanations and descriptions of complex phenomena such as the crystallization of atoms, phase transitions in matter, and navigation (e.g., the traveling-salesman problem). And yet it would take until the 1990s before a number of important discoveries would allow for a revolution in network science to take place, the consequences of which are only beginning to be felt in modern medicine and the current neurosciences.

A network is a mathematical concept that describes interactions between agents that can be identified separately in space (Watts and Strogatz 1998). These agents may themselves be in a certain state, which can be transferred from one agent to another in the course of time. It was Albert Einstein (1879–1955) who first remarked that all natural phenomena can be described in terms of events (states) that take place in space and time (Russell 2011). Since the addition of "scale" as a final descriptor, the central thesis has become that *states can interact with one another on different spatial and temporal scales*. This type of representation is so general that it allows most natural phenomena to be described in terms of networks.

The graphic representation of a network is called a network graph (see Box 4.1). Network graphs contain "nodes" and "links," which together determine network *structure*. States traveling between the nodes along the links in the course of time reflect network *function*. Classical network theory was based on the assumption that nodes were randomly connected to other nodes. Biological systems turn out to violate this rule completely, and are best represented by networks in which many nodes have relatively few connections, whereas the remaining nodes have many connections. Those richly connected nodes are called "hubs." Hubs connect many different nodes within the network, thus forming clusters of tightly interconnected nodes that are called "modules." Hubs interconnect the modules, which themselves can serve as nodes to form superclusters at ever higher levels of spatial organization. Viewed this way, life can be characterized as an endless variation of multimodular-hierarchic network structures which collectively display a so-called small-world topology (see Box 4.1).

Box 4.1 Small-World Network Structures

Nearly all biological systems, including collections of interacting genes, proteins, organelles, cells, tissues, organs, and individuals, can be described in terms of a "small-world" network topology. Such a network structure is characterized by the presence of hubs (see main text) that form clusters, which themselves are connected by hubs into ever larger networks, thus creating a multimodular-hierarchic structure (see Fig. 4.1). In such structures, states can

(continued)

Box 4.1 (continued)

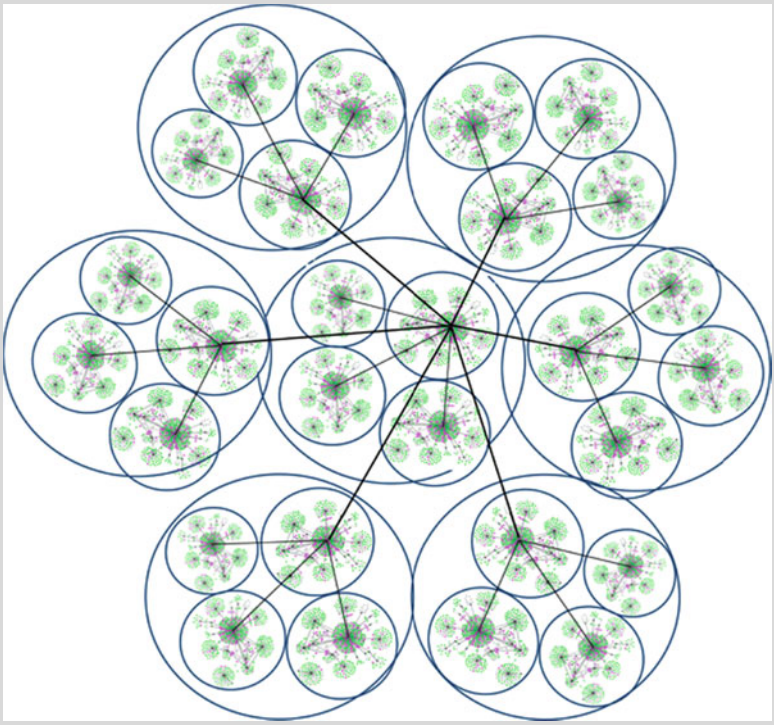

Fig. 4.1 Network graph showing an example of a "small-world" network structure. Hubs (i.e., high-degree nodes) connect clusters of lesser-degree nodes into superclusters (*marked by circles*) and so on. This hierarchical network structure is called "scale-free" or "fractal-like" since a similar structure can be found in nature at all spatial-scale levels of organization, including networks of genes, proteins, metabolites, organelles, neurons, brain areas, social networks, and markets

travel from one node to any other node in the network along very short routes. It turns out that every human being is part of various communities and hierarchies and connected to any other human being through an average of only six degrees of acquaintance (or six degrees of separation). In other words, the average "path length" of small-world networks is low. Because of the short distances between the nodes, such networks are called "small-world" networks (see Fig. 4.1), after the expression "It's a small world after all" (uttered, e.g., after meeting a total stranger who turns out to be an acquaintance of your best friend). In social systems, small-world networks promote the dissipation of information across a group of cooperating individuals. In neural networks, they help to optimize the transfer of information at minimal "costs" (i.e., connections).

4.3 Neural Network Models

4.3.1 Attractor Network Models

Neural networks are special types of biological networks. Like most biological systems, they have a multimodular, hierarchic network structure that displays a small-world topology (Bassett et al. 2006; Meunier et al. 2010). This network layout allows for maximum efficiency of information transfer and processing at minimal costs (expressed in terms of the number of links being used). The study of hallucinations by means of network theory involves the examination of (pathological) changes in neural network structure and function at various spatial and temporal scales, varying from micrometers to decimeters, and milliseconds to years. Such studies are nearly impossible to perform in living human beings. To overcome this obstacle, computer models of neural networks have been created that incorporate findings from different fields of study, including postmortem, in vitro, and animal research. In such models, it is possible to manipulate any parameter of interest and to examine the effects of such manipulations on network structure and function. Currently, "attractor network models" are among the most sophisticated models used for such purposes (Brunel and Wang 2001; see also Fig. 4.3). An attractor network consists of a network of neurons (e.g., pyramidal cells in the primary visual cortex) that receive dendritic inputs from an external location (e.g., the retina) and produce output via axonal connections that travel to another attractor network (e.g., the visual association cortex). Neurons within this attractor network have excitatory collaterals that feed back to their dendritic connections (collateral excitation) as well as to inhibitory interneurons that – on average – suppress the activity in networks lying outside of the attractor network (collateral inhibition) (Brunel and Wang 2001). Thus the excitatory and inhibitory collaterals form positive and negative feedback loops, which operate via N-methyl-D-aspartic acid (NMDA) and gamma-aminobutyric acid (GABA) receptors, respectively. From this basic layout, the brain is able to generate the multitude of visual representations of its environment that are required to fulfill the needs of its owner.

4.3.2 The Attractor State

When dendritic input enters the attractor network, neural activity reinforces itself by means of its positive feedback loop, thus aiding itself to persist even after the original stimulus has ceased (Rolls and Deco 2011; Chumbley et al. 2008). Meanwhile, the negative feedback loop suppresses the activity of neurons located (on average) outside of the attractor network. Collectively, the positive and negative feedback loops regulate the "persistence" of network activity within the attractor network (Brunel and Wang 2001). It has been shown that the application of an external stimulus to an attractor network can induce sustained and stimulus-specific neural activity within the network (Wu et al. 2008). Dendritic input pertaining to a particular stimulus

selects a subset of neurons that together enter a "preferential state" that is specific to that particular stimulus. Such preferential states are called "attractor states" (see Box 4.2). It turns out that attractor states are among the best candidates for the neural correlates of subjective experience as currently known to neuroscientists. Although definitive proof is still required, specific smells, tastes, sounds, and visual experiences are thought to be encoded by stimulus-specific attractor states. Additionally, thoughts, feelings, rule-based decision making, and memory states have all been linked to activity within specific attractor networks (Braun and Mattia 2010).

Attractor networks can assume two different stable states. One of those states is the attractor state itself, which can develop when the network has received dendritic input. This "active state" (or "persistent state") is characterized by high-frequency firing rates of neurons within the network, which are difficult to disrupt by alternative dendritic input (distracting stimuli). Another stable state develops when attractor networks are not receiving any dendritic input. Under such circumstances, attractor networks enter a so-called resting state, characterized by low-frequency, random-spiking activity as a result of spontaneous depolarizations of neurons within the attractor network (Eliasmith 2007; Rolls 2010). In the resting state, attractor networks are freely roaming their state spaces. They may switch between active and resting states, depending on the amount of "energy" applied to them. Such energy typically takes the form of novel dendritic input or of spontaneous noise fluctuations generated within the network itself.

Box 4.2 Network Function and State Space

Each node within a network can be in a certain *state* (often 0 or 1, but states may vary along continuous scales). Those states are transferred from one node to another along the links in the course of time. The temporal evolution of those states in the network is referred to as network *function*. Just as network *structure* is usually represented by a graph, network function can be depicted as a "state space" (Wuensche 2011). State space is a Euclidian space, characterized by a multidimensional coordinate system with perpendicular axes that represent the states of the nodes or clusters present within the network. In time, the network "travels" through its state space and leaves behind a "state-space trajectory," reflecting its past behavior (see Fig. 4.2a). By recording changes in the states of nodes at different moments in time, the behavior of the entire network across infinite time can be described using just a single image.

After a certain period of time, each network will enter a state that it has encountered before. For instance, a simple network with $n=3$ nodes (or clusters) may cycle from state-space coordinates (0 0 0) to (1 1 1) to (1 1 0) and back to (0 0 0). Thus a loop of a certain size has been made in state space from one particular (macro) state back onto itself, through a series of intermediate states. That loop is called a "state cycle," and the point, line,

(continued)

Box 4.2 (continued)

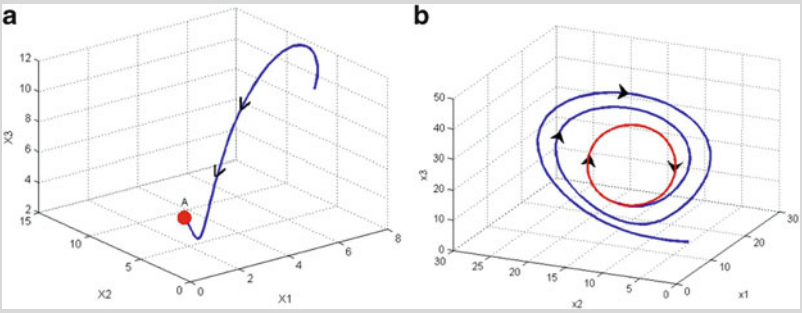

Fig. 4.2 State space trajectories, see box text (Reproduced from Eliasmith (2007). with permission)

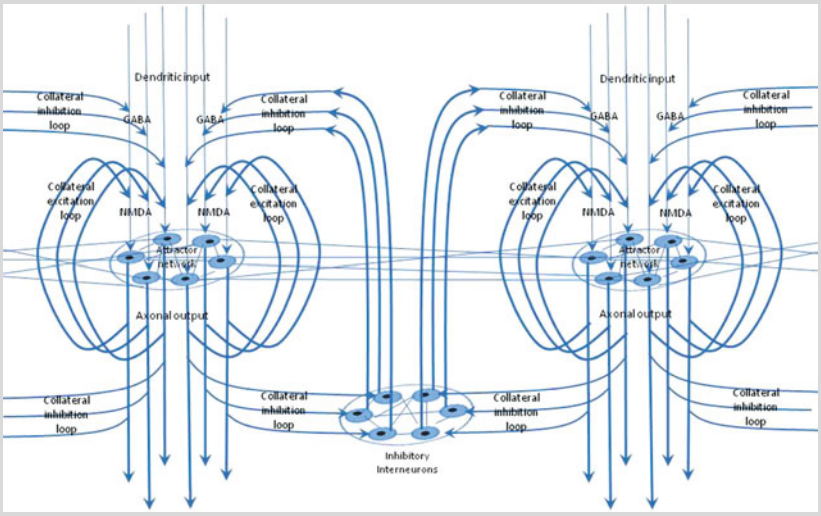

Fig. 4.3 The network structure of an attractor network, showing two attractor networks that are connected into a larger network. Dendritic input selects a subpopulation of neurons that forms the attractor network for that particular stimulus. Excitatory (NMDA-related) output loops back onto the dendritic input connections, causing a self-perpetuation of attractor activity. Excitatory output also connects to inhibitory (GABAergic) interneurons, which loop back to the dendritic input connections of all surrounding neurons. Thus attractor networks compete for activity by promoting the persistence of their own attractor states and suppressing activity in neighboring attractor networks

surface, or volume in state space that has been circled is called the "attractor" (see Fig. 4.2b). The term "attractor" was chosen because irrespective of the initial state of a network at any point in time, it will eventually enter a cycle of states that orbit the attractor at hand (see Fig. 4.3).

4.3.3 Signal-to-Noise Processing

Any influence that has the potential to affect attractor states can be referred to as "input" or "energy." With respect to a particular attractor network, two different sources of input can be identified. "Extrinsic input" refers to dendritic input originating from networks outside the attractor network. Such input constitutes either high- or low-frequency neural activity, corresponding to the active or resting states of upstream attractor networks. "Intrinsic input" is generated by spontaneous spiking activity of the neurons within the attractor network itself (Brunel and Wang 2001; Chumbley et al. 2008). Both sources of input can provide the energy needed to generate new attractor states or to disrupt existing ones. Attractor states constantly reinforce their own existence (as well as the "signal" they confer) through positive feedback while suppressing their surrounding states through collateral inhibition (see Fig. 4.4). Hence, attractor states are in a constant state of mutual competition (Rabinovich et al. 2001). As a result, robust signals are selected out of a sea of noise, which is called "signal-to-noise processing" (Rolls et al. 2008). This process allows organisms to separate distracting stimuli (noise) from meaningful signals, which is a major precondition for survival. Malfunctions of signal-to-noise processing have long been considered a candidate mechanism for the mediation of hallucinations and delusions.

4.3.4 Bottom-Up and Top-Down Processing of Information

Recent studies have shown that the human brain as a whole has a scale-free (i.e., fractal-like), multimodular, hierarchic network structure that displays small-world characteristics (Bassett et al. 2006; Meunier et al. 2010). Such a network structure enables the extraction of information from sensory input at an unprecedented level. At a small spatial scale, the primary visual system contains stimulus-dedicated neural networks that respond selectively to isolated perceptual stimuli such as direction, speed, color, movement, and texture (Horton and Adams 2005). Repeated encounters with similar isolated stimuli (e.g., yellow color, furry texture, vertical black stripes) will cause the networks that correspond with those percepts to strengthen their mutual connections to form a global ("tiger") network and a corresponding attractor state. This takes place according to the principle of "neurons that fire together, wire together," a process that involves the long-term potentiation of signal transduction at the level of individual synapses (Malenka and Bear 2004). Thus higher-order "associative" stimulus representations are generated from lower-level network activity. Such representations are formed in most association cortices (Bullmore and Sporns 2009). The combined states of those associative networks are in turn sampled by means of dendritic connections that converge onto an attractor network of hub neurons located in even higher-order association cortices (A and B in Fig. 4.4) (Zamora-Lopez et al. 2010; Kaiser et al. 2010). This process of associating

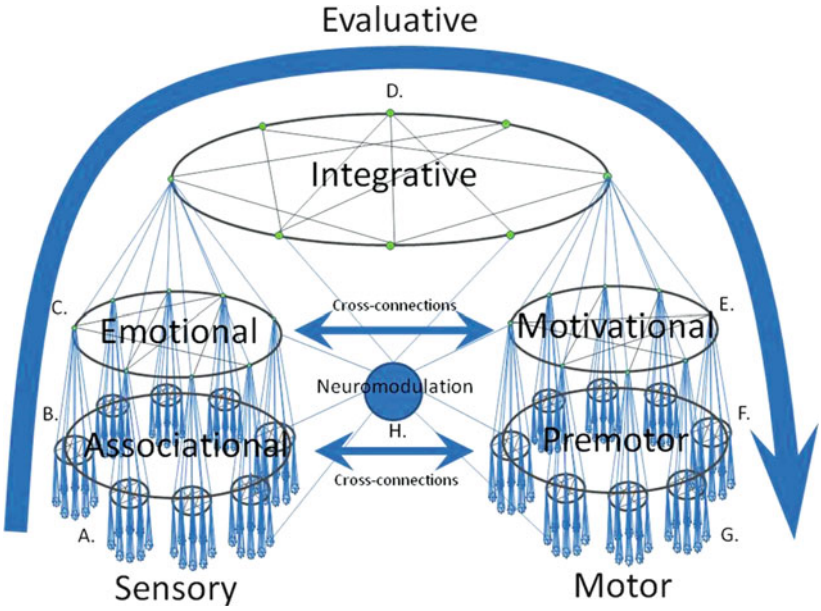

Fig. 4.4 A simplified model of the scale-free (i.e., "fractal-like") structure of the human brain and the flow of information through its neuronal architecture. As a result of sensory stimulation, stimulus-specific neural columns (*A*) enter attractor states that are associated into larger-scale networks through the process of long-term potentiation. Those states are integrated by means of dendritic connections that converge onto hubs, and they are transferred to higher-order stimulus-specific networks in sensory association cortices (*B*). The higher-order representations from multiple sensory modalities (not shown) are further integrated and transferred to emotional centers for evaluation (*C*). Combined sensory and emotional information is transferred to even higher-level integrative networks (such as the limbic system and prefrontal cortex) (*D*). Subsequently, attractor states of higher-order centers affect lower-level (sensory), motivational (*E*), and premotor (*F*) areas, and finally primary motor cortex (*G*) to elicit responses in individual muscle fibers. Thus the general flow of information involves a stimulus-evaluation-response loop, or "sensorimotor" loop. Cross-connections exist between the various levels of information processing to create stimulus–response loops of varying lengths. This allows for fast reflexive responses based on minimal sensory information in stressful situations, and iteratively processed, slower responses in more quiet situations. Information transfer in all loops is biased by neuromodulatory systems, including the noradrenergic, cholinergic, dopaminergic, and serotonergic systems (H). See main text for further details

and integrating information creates hierarchies of increasingly complex multimodal representations that are passed on to the limbic system and prefrontal cortex for further information processing (C and D in Fig. 4.4) (Freeman 1999).

At the highest level of information processing, the state spaces of all lower-level domains are bound together by a network of large-scale hubs to create a single multimodal representation of the organism's environment (Varela et al. 2001). Such a representation includes information from multiple sensory, emotional, motivational, premotor, and linguistic domains (including thoughts and feelings), and is processed

in the medial prefrontal cortex, which is one of the largest hub regions of the human brain (D in Fig. 4.4) (Bullmore and Sporns 2009). This multimodal form of processing is often referred to as "cognition" and is thought to be experienced consciously as the "sense of self" (Tononi 2005). The states of these high-level areas are subsequently transferred to motivational and premotor areas (E and F in Fig. 4.4), from which action-related information determines the states of lower-level motor areas and eventually pyramidal cells (G in Fig. 4.4), which elicit stimulus-directed contractions in individual muscle fibers. Thus a sensorimotor loop is completed in which lower-level attractor states may dominate higher-level states (referred to as "bottom-up processing of information"), while higher-level states may dominate lower-level states (i.e., "top-down processing"). Higher-level states have their own relative autonomy and may exert control on lower-level processing stages by inhibiting brain activity in these areas. The failure of top-down control and the subsequent disinhibition of lower-level perceptive areas has been associated with the occurrence of hallucinations (see below).

4.3.5 Neuromodulation

Neuromodulatory neurotransmitter systems (such as the dopaminergic, noradrenergic, cholinergic, and serotonergic systems) can interfere in basic neural signaling by adjusting the degree of NMDA-related excitation or GABAergic inhibition within the attractor networks (Rolls et al. 2008; Loh et al. 2007). This may affect signal-to-noise ratios within neural networks along the entire length of the sensorimotor loop within the human brain (see Fig. 4.3) (Beck and Kastner 2009). Thus neuromodulatory systems are involved in biasing the competition between attractor states, allowing for a balancing of top-down and bottom-up control routes (Beck and Kastner 2009). As an example, the presence of a high-energy (i.e., "clear") tiger attractor within the visual cortex of an organism can induce specialized attractor states of the amygdala (signal). Such states in turn induce activity within the noradrenergic system, which connects back to the visual cortex. Here noradrenalin increases the signal-to-noise ratios of attractor networks by increasing both NMDA-receptor activity and GABAergic inhibition (Hu et al. 2007; Tully and Bolshakov 2010). As a result, noise is suppressed, while the attractor states are sustained for longer periods of time. This process is known as "attentional biasing" (Browning et al. 2010). In a behavioral sense, such shifts of balance in neural activity render organisms more prone to certain stimuli and actions in specific situations. In stressful situations, this translates into a heightened state of alertness, focus, and attention with respect to the sensory and evaluative parts of information processing, and into an increase in motivation and dexterity with respect to the motor and executive parts. This allows organisms to better spot minute stimuli, such as subtle clues as to the presence of a predator, and to quickly mobilize evasive or aggressive action (Bishop 2008). In contrast, when clear stimuli are lacking (e.g., when a tiger is hiding between the yellow leaves of a bush on a dark autumn night), the signal-to-noise ratios are shifted in favor of

signal detection at the cost of noise suppression. That process, called "neural adaptation," is thought to be the combined effect of receptor sensitization and neuromodulation on the signal-to-noise ratios of lower-level perceptive networks (Clifford et al. 2007). As the potential costs of false-negative decisions in the case of predators and other threats may be high (to the extent of impending death), the network is biased slightly toward false-positive decisions (Dolgov and McBeath 2005).

4.4 Hallucinations in Network Terms

Since attractors represent specific subjective experiences, hallucinations are thought to reflect the presence of attractor states in the absence of an external source (Loh et al. 2007; Blom 2010). In what follows, we will discuss some of the many factors that can be held responsible for the production of such "false-positive" attractor states.

4.4.1 A Network Model of Sensory Deprivation

In some famous experiments of sensory deprivation, healthy subjects were brought into a state of almost complete disconnection from the external world by submerging them in flotation tanks containing salty water at body temperature. They were deprived of any patterned sources of light and sound and were instructed to float around weightlessly to avoid the corrective influences of gravity. Within 8 h, all of those subjects were hallucinating (Lilly 1956; Walters et al. 1964). The emergence of hallucinations in normal subjects under such extreme circumstances can be explained by means of the dynamics of attractor networks. Due to the absence of external stimuli, attractor networks enter their resting states. The absence of external stimuli prevents the use of collateral inhibition as a mechanism to suppress noise generated by extrinsic or intrinsic input to the attractor networks. Meanwhile, neural adaptation to the low stimulus intensities further reduces the number of GABAergic inhibitory currents and decreases the firing thresholds of neurons within attractor networks. As a result, these neurons become disinhibited, and attractor networks will switch more easily from their resting states to their active states (Behrendt and Young 2004). Collectively, those factors create a supersensitive network in which only a small amount of energy is required to trigger a false-positive attractor state. In the absence of any external input, such energy is provided by noise, either from the random-spiking activity of neurons within the attractor network itself (i.e., "intrinsic input") or from the dendritic input by other (disinhibited) attractor networks (i.e., "extrinsic input") (Deco et al. 2009). Depending on the types of network in which the attractors occur, sensory deprivation may yield different types of hallucination. Thus visual networks may generate images (see Chap. 6), whereas auditory networks may generate voices (see Chaps. 8–10), music (see Chap. 11), and other sounds.

Sensory deprivation can be aggravated by diminished sensory functioning (e.g., deafness or blindness) as well as social deprivation (e.g., loneliness in the elderly, which may entail paranoid delusions and hallucinations) (Pierre 2010; Teunisse et al. 1996). Stress and anxiety states during sensory or social deprivation may further enhance a network's sensitivity through the noradrenergic enhancement of NMDA signaling. The reason why many hallucinations and delusions involve situations of a frightening or threatening nature would seem to be that perceptive networks are biased toward the false-positive detection of predators and other threats. The increased sensitivity of attractor networks under sensory or socially deprived and stressful circumstances may be sufficient to turn that bias into a persistent attractor state (Dolgov and McBeath 2005; Van Os 2009).

4.4.2 A Network Model of Hallucinations

In more pathological cases, hallucinations can occur under normal circumstances. In such cases, individual differences in the structure and/or function of attractor networks can be held responsible for their mediation. As a general rule, such differences ultimately affect the levels of excitation, inhibition, and/or neuromodulation that govern the activity of attractor networks. With respect to the nature of such changes, various important clues have emerged from studies in patients diagnosed with schizophrenia (Rolls et al. 2008). One of the most solid findings is a decrease in the activity of the NMDA receptor, which is a primary predisposing factor for psychosis (see also Chap. 3). In addition, deficits in GABAergic inhibitory function have been established in patients diagnosed with schizophrenia, as well as elevated ratios of the activity of D2- versus D1-dopamine receptors (the receptor subtypes against which most antipsychotic agents are targeted). Finally, electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies show decreased signal-to-noise ratios in patients diagnosed with schizophrenia.

Collectively, those findings allow for the following conceptualization of hallucinations. A decrease in NMDA conductance and self-reinforcing collateral excitation produces labile attractor states that can be disrupted more easily by noise.[1] Meanwhile, reduced GABAergic activity reduces noise suppression, making it easier for networks to enter attractor states. Increased D2- versus D1-receptor activity amplifies the effects caused by the NMDA and GABA deficiencies, as shown by simulation studies that report shallower basins of attraction in the energy landscape in both resting and active states (see Box 4.3) (Rolls and Deco 2011). Under such conditions, a small amount of energy in the form of intrinsic or extrinsic input (see above) is capable of inducing false-positive attractor states, which are easily

[1] Such labile attractor states may well explain some of the cognitive symptoms in patients diagnosed with schizophrenia, including distractability, loss of concentration, and impaired working memory.

disrupted, and alternate with resting-state activity. The corresponding network activity is characterized by fast alternations between high-frequency (active) and low-frequency (resting) states (Loh et al. 2007; Winterer and Weinberger 2004). That process is analogous to a ping-pong ball that moves erratically from one valley in an energy landscape to another (see Box 4.3). The erratic switching between high- and low-frequency active and resting states, respectively, may well explain the huge variability ("noise") in the signals of EEG and fMRI recordings of brain activity in patients diagnosed with schizophrenia. In a behavioral sense, that may translate into the subjective experience of hallucinations (intrinsic noise) or of illusions perceived in synchrony with external stimuli (extrinsic noise) such as auditory pareidolias (e.g., hearing voices in the hissing of a radiator tube).

The above explanations form a general model of alterations in network function that can explain the final common pathway in the mediation of various types of misperception. The key parameters in this model are the excitation, inhibition, and modulation of attractor states. Those parameters can be affected by an array of different processes. Chemical substances such as psychoactive drugs and medication can interfere directly with the neurochemistry that underlies the functioning of attractor networks (Skosnik et al. 2006; Ehrlichman et al. 2009; see also Chap. 22). Such substances alter the connections, weights, and/or firing thresholds of neural networks that eventually affect attractor persistence and formation. With the aid of computer simulations, it is possible to identify drug targets that predict the effects of psychoactive drugs on subjective experiences and to test their efficacy as part of future – actual – treatments. Thus it has been shown that NMDA agonists and D1-receptor agonists are capable of improving attractor stability (thereby having the potential to reduce negative symptoms), whereas D2-receptor antagonists are capable of reducing the formation of false-positive attractors (thereby reducing hallucinations and other positive symptoms) (Rolls et al. 2008). Apart from such neurochemical changes at microlevel, macrolevel structural changes can alter the function of attractor networks and produce hallucinations. Such changes, referred to as "connectivity changes," will be discussed below.

Box 4.3 The Concept of Information

The resting state of an attractor network defines the largest volume of state space that the network can occupy. In that state, the network is freely roaming its state space. Dendritic input leads to a reduction of the total number of possible states of the network, causing the network to occupy a more confined volume of state space (i.e., the attractor). As a corollary, we may think of perception (or any other form of "measurement") as a deterministic process characterized by the "pruning of possibilities." That reduction of potential states is what defines the concept of "in-formation" in information theory: the number of possible states that is lost as a result of external input is equivalent

(continued)

Box 4.3 (continued)

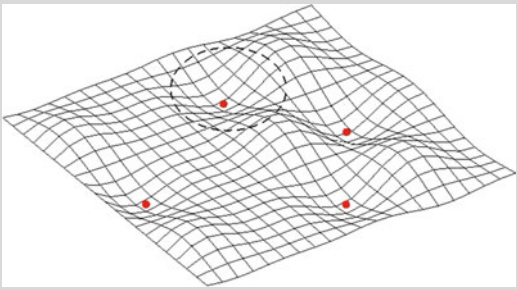

Fig. 4.5 Example of an "energy landscape." Signals or noise can provide the energy necessary to push networks from one stable attractor state (low-energy valley) into another. Those valleys are the active and resting states of attractor networks. A single network may harbor different low-energy attractor states, depending on the input to the network. This is represented by multiple valleys in the energy landscape (as depicted by the circle) (Reproduced from Eliasmith (2007) with permission)

to the amount of information gained as a result of the input (Heylighen and Joslyn 2001). The constraint that a particular stimulus context imposes on the occupied volume of state space of an attractor network can be linked directly to the degree of order (attractor state) or disorder (free-roaming state) that is allowed to exist within the state space. This has allowed researchers to connect the concept of information directly to changes in network entropy (Heylighen and Joslyn 2001). Since entropy itself is related to the amount of free energy contained in the network, "information transfer" can be understood as a complex flow of energy through network systems (Friston 2010). This signifies how fundamental the act of information transfer is in both physical and biological terms. The two stable states of each attractor network (the active and resting states) can be seen as two valleys in a landscape, where each valley represents a low-energy state (see Fig. 4.5). A ping-pong ball may leave one valley and enter a next, depending on the amount of energy applied to it. Likewise, an attractor network may switch between its resting and active states, depending on the amount of energy (signal or noise) applied to it. Simulation studies have shown that low levels of NMDA and GABA (e.g., in patients diagnosed with schizophrenia) increase the shallowness of the energy valleys. As a consequence, less energy (noise) is needed to induce false-positive attractor states (e.g., hallucinations). Shallow basins of attraction also mean that attractor states can disrupt more easily, thus producing a disorganized phenotype for hallucinations.

4.4.3 Structure-Function Relationships

A confusing aspect of network neuroscience is the distinction between structural and functional connectivity. In this chapter, we refer to network *structure* as that part of a network that can be described using a network graph, and to network *function* as that part of a network that can be described in terms of its state space. The brain has a distinct physical structure of anatomical connections that support the exchange of states (i.e., function) between spatially distributed nodes and clusters. It is thought that the functional connections between different brain areas (e.g., as measured by EEG or fMRI) closely follow the structural connections, but this is not always the case (Deco et al. 2011). The difference between structural and functional connections in the brain is analogous to the difference between the World Wide Web (which is a network of copper wires and glass-fiber cables that connects computers worldwide) and the Internet (which is a network of interconnected .HTML pages). This leads to a difference between structural connectivity (for which network graphs and state spaces can be created) and functional connectivity (for which different graphs and state spaces can be created) (Bullmore and Sporns 2009). In discussing the effects of changes in network structure upon network function, we will therefore commence with discussing changes in structural connectivity and then move on to changes in functional connectivity in patients diagnosed with schizophrenia.

4.4.4 Structural Connectivity

In studies of gray-matter density among patients diagnosed with schizophrenia, the most consistent finding is a loss of gray-matter density in the middle and bilateral superior temporal gyri (Nenadic et al. 2010; García-Martí et al. 2008; Glahn et al. 2008; Hulshoff Pol and Kahn 2008). Such alterations have varying correlations with the severity of hallucinations (Nenadic et al. 2010; García-Martí et al. 2008). In white-matter connectivity studies, a loss of connectivity has been found between frontal regions and medial and superior temporal areas in patients with verbal auditory hallucinations (Kubicki et al. 2007; Shergill et al. 2007). Neuroscientists are now able to combine such findings and to incorporate them into network topologies. As we saw, the human brain can be said to possess small-world characteristics, with "small-worldness" being defined as the ratio of average clustering and average path length (see Box 4.1). In network terms, a loss of gray matter can be considered a loss of network nodes (i.e., attractor networks) that reduces the possibilities for local clustering. Likewise, a loss of anatomical connectivity can be considered a loss of network links. Such a loss may affect the efficiency with which information travels through the anatomical network. In patients diagnosed with schizophrenia, reduced small-worldness has repeatedly been observed in graphs showing the structural connectivity of their brains. They show a longer path length, a reduced probability of frontal high-degree hubs, and the emergence of novel, nonfrontal

hubs (Bassett et al. 2008; Van den Heuvel et al. 2010). Those network abnormalities correlate with the severity of positive as well as negative symptoms (Rotarska-Jagiela et al. 2009).

The small-world, fractal-like topology of the human brain makes it ideally fit for extracting relevant information from the external world, ranging from the tiniest bits to a global, integrated whole. Small-world networks are characterized by nonrandomness of connectivity patterns, resulting in clear hub-like structures. Small-worldness is associated with a highly efficient transfer of information (because information travels over relatively small distances), an optimal balance between functional segregation and integration (allowing for constant recombinations of subnetworks to accomplish varying tasks and the formulation of creative solutions to novel problems), and unprecedented levels of integration of information, allowing for abstract representations of the environment. A disruption of small-worldness can therefore be expected to lead to a reduction in these abilities. Specifically, the increase in average path length can produce a general slowing down of information transfer, which may explain some of the cognitive and negative symptoms found in patients diagnosed with schizophrenia. A loss of clusters will reduce the number of attractor states that are available to a patient, reducing the efficacy of stimulus discrimination. Phenotypically, a loss of stimulus discrimination may well underlie the phenomenon of "jumping to conclusions," i.e., the drawing of conclusions on the basis of little or no evidence. Since clusters represent attractor states and alternative explanations, only few alternative explanations for a given event are available for consideration. This may feed paranoid interpretations of experienced events.[2] A loss of clusters may also reduce possibilities for the recombination of attractor states to generate creative solutions to novel problems, causing patients to persist in certain (maladaptive) coping strategies. Additionally, a loss of clusters reduces the number of possibilities for collateral inhibition by alternative (i.e., competing) attractor states, which may promote the formation of false-positive attractor states. This may induce hallucinations in a way similar to that in sensory deprivation. Increased randomness of anatomical connections (a possible result of the excessive pruning of synapses (Hoffman and McGlashan 2001)) may lead to the experience of bizarre delusions (e.g., the conviction that a thermonuclear power plant resides within one's belly).

[2] Jumping to conclusions (for instance, "My grandmother came by the other day." "My car broke down the same day." "She sabotaged it.") may well result from an overly sensitive form of "pattern completion," i.e., attractor networks entering their full attractor states as a result of minimal dendritic input. Such oversensitivity may be due to a hyperconnectivity between neurons within a single attractor network, leading to an "overrecruitment" of neurons receiving dendritic input. A likely cause of such hyperconnectivity is increased D2-versus-D1-receptor activity, which is capable of enhancing long-term potentiation and the formation of associative ties between networks that would otherwise remain separated. As a result of such an increased connectivity between attractor networks, smaller clusters with a relatively high degree of specialization will be replaced by larger clusters with a more generalistic function. That may well explain the overall decrease in clustering, as well as the emergence of novel high-degree hubs, found in patients diagnosed with schizophrenia.

Finally, a loss of small-worldness may reduce a patient's capacities for integration, abstraction, and overview (Van den Heuvel et al. 2010). Specifically, a reduced number of high-level frontal hubs may entail a reduction of the capacity to integrate high-level abstract information, allowing patients to miss out on the "global picture," to disregard corrective clues, and to take expressions literally (i.e., concretisms). The dissolution of higher-order (prefrontal) clusters reduces the amount of top-down control, causing a disinhibition of lower-level sensory attractor networks that may result in the production of hallucinations (Bassett et al. 2008).

4.4.5 Functional Connectivity

Functional connectivity can be examined during active, resting, and sleeping states. Generally speaking, functional connectivity studies of patients diagnosed with schizophrenia show changes in network topology that are similar to those in anatomical connectivity. Only recently have more sophisticated analyses of network topology (such as small-worldness) been performed in functional-connectivity studies. These studies show that healthy human brain function, like the physical network structure that supports it, is characterized by a small-world structure (Bullmore and Sporns 2009; Van den Heuvel et al. 2008). Analogously, a decrease in small-worldness is observed in functional connectivity studies of patients diagnosed with schizophrenia, which shows a loss of high-degree (frontal) hubs and reduced local clustering (Liu et al. 2008; Demirci et al. 2009; Yu et al. 2011; Guye et al. 2010; Rubinov et al. 2009; Lynall et al. 2010). Those deficits correlate negatively with behavioral performances on verbal-fluency tasks (Lynall et al. 2010) and positively with the duration of illness (Liu et al. 2008). Patients also show reduced functional connectivity between the prefrontal cortex and the temporal lobe (Wolf et al. 2007; Pettersson-Yeo et al. 2011). The severity of positive symptoms correlates positively with the degree of functional disconnectivity of frontotemporal and auditory networks (Vercammen et al. 2010; Gavrilescu et al. 2010; Rotarska-Jagiela et al. 2010), which is in keeping with the assumption that a loss of prefrontal function results in a disinhibition of attractor states in the temporal lobe and the production of verbal auditory hallucinations (Allen et al. 2008). Indeed, functional MRI studies have reliably shown an increase of activity in auditory networks accompanying the subjective experience of such hallucinations (Stephan et al. 2009).

When the brain as a whole enters its resting state (i.e., eyes closed but awake), characteristic regions are activated which are associated with mind-wandering and musing (Deco et al. 2011). Patients diagnosed with schizophrenia show an increase of functional connectivity between various regions of their resting-state network that is associated with the severity of positive symptoms (Garrity et al. 2007; Whitfield-Gabrieli et al. 2009). Such overactivity of the resting-state network may be due to a low NMDA-receptor conductance, which prevents high-frequency (i.e., active-state)

activity to take over from low-frequency resting-state activity. This may prevent patients from switching between active and resting states, thus forcing them to remain in the resting state for prolonged periods of time. As a result, patients tend to be more focused on their inner experiences and to be less open to external corrections of their behavior (Bagby et al. 2005). Such perceptual and/or social disconnection may lead to positive symptoms through the process described above for sensory deprivation. Many patients indeed report that they experience an increase in hallucinatory experiences when they are alone and engaged in a resting state (see also Chaps. 8, 11, and 28). In such situations, a switch to a more active state (by talking to other people, e.g., or whistling) may reduce the occurrence of hallucinations.

During sleep, the functional architecture of the human brain moves closer toward a veritable small-world structure (Ferri et al. 2008). Hence a loss of small-worldness can have profound effects on the quality of sleep. Patients diagnosed with schizophrenia often suffer from a lack of deep sleep, which may have debilitating effects on their daily functioning (Sarkar et al. 2010). Such sleep disturbances occur regularly in psychotic patients without any form of psychoactive medication, which may well point in the direction of a fundamental inability to switch between the sleep-stage equivalents of active and resting attractor states (i.e., rapid eye movement (REM) sleep and deep sleep). During REM sleep, the free-roaming state of the default network is thought to induce attractor states that constitute the source of dreams (Ghosh et al. 2008; Sämann et al. 2011). Low NMDA and GABA conductance may induce inconsistent dreams and an inability to enter a deep-sleep stage. As a result, patients may have the experience that they have not slept at all, whereas the nursing staff report that they have been asleep all night. Impaired switching between REM sleep and the waking resting state may well explain the dynamics of hypnagogic and hypnopompic hallucinations occurring during the transitional periods between waking and sleeping (Ben-Aaron 2003), while abnormally persistent attractors generated during the REM phase can be experienced consciously during the waking state as hallucinations.

4.5 An Integrated View

Network theory offers a comprehensive view of the pathogenesis of hallucinations by examining the mutual relationships between networks of biochemical agents, structural and functional connectivity, subjective symptoms, and social functioning. Figure 4.6 shows an example of various coupled graphs for patients experiencing hallucinations. Ultimately, the whole network can be described dynamically in terms of its various state spaces. When such models become increasingly detailed, computer simulations may well be able to predict which brain areas should be targeted to reduce specific symptom dimensions – such as the intensity, severity, frequency, and duration of hallucinations – and help to reduce the personal and social consequences of such symptoms.

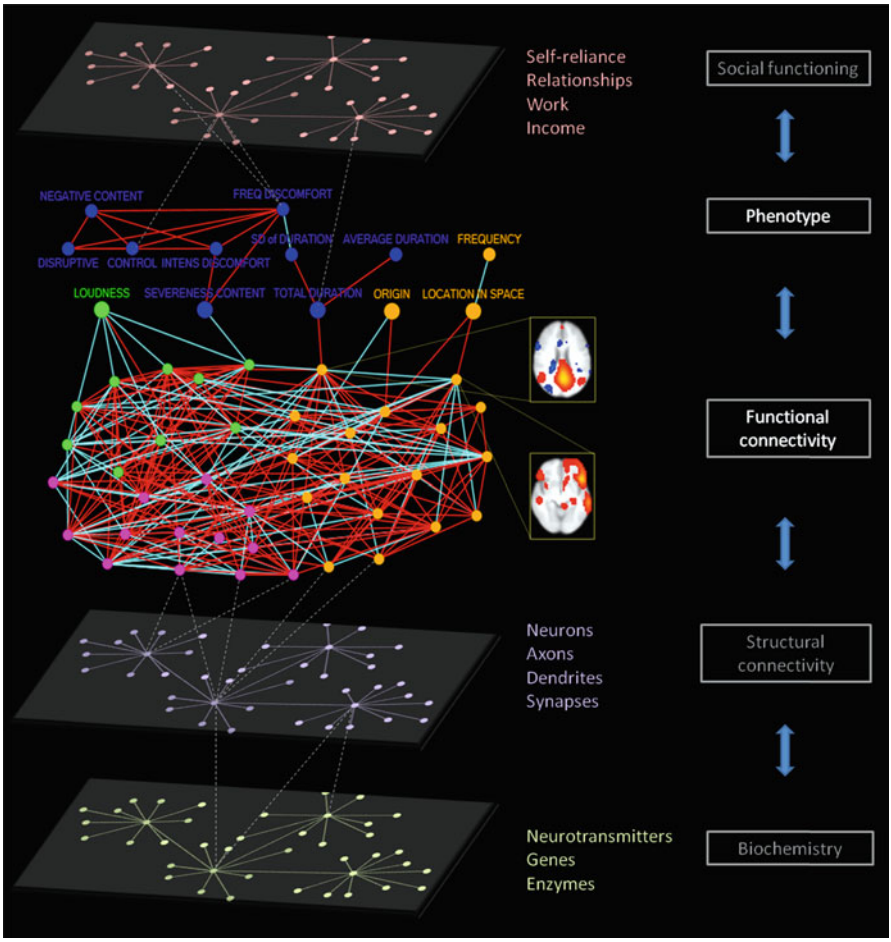

Fig. 4.6 Coupled network graphs of functional connectivity in relation to a network structure of symptoms of patients who experience verbal auditory hallucinations (Looijestijn et al., data in preparation). Measured data are shown in color. Functional connectivity: network of neurophysiological data (independent components of functional magnetic resonance signal). Phenotype: subjective symptoms as rated with the aid of a questionnaire (PSYRATS) and registered hallucination timings during magnetic resonance imaging. Hypothetical additional levels of organization are shown in gray and can be added to the model at later stages. Based on knowledge of the relationships between the various factors that relate to the origin and phenomenological expression of hallucinations, therapeutic intervention foci can be predicted at each level of network organization (e.g., medication, transcranial magnetic stimulation, psychotherapy, work, etc.)

4.6 Conclusion

In this chapter, we reviewed a number of biochemical and neurophysiological changes that accompany the experience of hallucinations. Collectively, those changes constitute a multitude of factors that give rise to a colorful palette of subjective experiences.

Network theory offers a way to integrate those findings in an unprecedented way, by offering a common terminology and methodology to describe relationships between events on different spatial and temporal scales. The specification of network models that incorporate the key players in the production of hallucinations allows researchers to make predictions with respect to specific targets for treatment. At a small spatial scale, new molecular targets are already being identified. At a larger spatial scale, network simulations may allow for a more specific targeting of brain areas using techniques that alter brain function, such as transcranial magnetic stimulation (see Chap. 25), electrocortical stimulation, and deep brain stimulation. With the progression of knowledge and the use of integrative science, it is hoped that a bigger arsenal of treatment options will become available for hallucinations and other psychotic symptoms in the foreseeable future.

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Chapter 5
The Construction of Hallucination: History and Epistemology

German E. Berrios and Ivana S. Marková

5.1 Introduction

Whether due to epistemological opaqueness or flawed conceptualization, little is known about the phenomena currently called "hallucinations." Given that only the second option is susceptible to remedial work, it is proposed in this chapter that a reanalysis be undertaken of the historical process that gave rise to the "received" view. Unpacking the reasons and assumptions informing such a process should allow for a fresh approach and hopefully for the development of management routines that might help those who want to be rid of hallucinatory experiences.

5.2 The Received View

The received view has given rise to much unproductive correlational research: To the nineteenth century surveyal and neuropathological work, the twentieth century added electroencephalography (EEG), brain cartography, electrode stimulation, sensory deprivation studies, neurochemical, neuroimaging, and genetic studies. Regardless of the technique employed, this research limited itself to linking proxy variables representing putative "changes" in the brain to proxy variables representing

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aspects of hallucinatory experiences. Often enough, the correlations thereby obtained have been furtively converted into "cause-effect" accounts.[1]

In all likelihood, this unproductiveness has resulted from the epistemological incoherence that characterizes the received view. Throughout this time, the latter has been masked by the sauntering plausibility of the received view and by costly academic investment. The said incoherence is but a reflection of tensions and contradictions generated by identifiable primary and secondary antinomies: the former built into the received view at the time of its construction; the latter added to alleviate the tensions caused by the primary antinomies.

5.2.1 Primary and Secondary Antinomies

The primary antinomies relate to four epistemological issues: (1) representation versus nonrepresentation,[2] (2) perception versus nonperception,[3] (3) unitary versus multiple, and (4) "organic" versus "psychiatric."[4] Esquirol (1817) gambled on the view that hallucinatory experiences were perceptual events, tokens of a unitary concept, best accommodated by a representational epistemology, and explained by either organic or psychological accounts. The definitional instability that has affected the concept of hallucination ever since can be explained by the choice of contradictory antinomies. This came to a head in 1855 when an (inconclusive) debate on the nature of hallucinations erupted at the *Association Médico-Psychologique* in Paris (Ey 1935) (see below).

To relieve these tensions, secondary antinomies were added during the second half of the nineteenth century: (a) true versus pseudo (or pale) hallucinations,[5] (b) hallucinations with and without insight, (c) hallucinations in the sane and in the insane,[6] (d) voice hallucinations versus auditory and other sense modality

[1]The literature on hallucinations in the main European vernaculars is absolutely enormous, and it would be unnecessary and inimical to list only some of them. Suffice it to say that the best-quality historical and conceptual work is still to be found in French (e.g., Quercy 1930; Paulus 1941; Ey 1973; Lanteri Laura 1991).

[2]The term representation is used here in its philosophical sense (Bernheimer 1961; Cummins 1989; Sterelny 1990; Ibarra and Mormann 2000; Clapin 2002, etc.).

[3]Perception is used here in both its philosophical and psychological sense. The literature on this theme is also vast (e.g., Merleau-Ponty 1945; Allport 1955; Hamlyn 1957, 1961; Armstrong 1961; Gibson 1966; Carterette and Friedman 1974; Dicker 1980; Yolton 1984, 1996; Fish 2009).

[4]This antinomy concerns the issue of whether hallucinations result from changes in the brain or from psychogenic mechanisms. Traditionally it has been traced back to the contrast that was established between the hallucinations affecting the German patient Nicolai and the French patient Berbiguier (for references and details, see Berrios 1990).

[5]For a full history of this concept, see Berrios and Dening (1996).

[6]On hallucinations with and without insight and on the debate on hallucinations in the same, see Gurney (1885) and Parish (1897).

hallucinations, (e) relevant versus nonrelevant hallucinatory content, (f) dream versus nondream view of the nature of hallucinations,[7] and (g) strict versus broad definition of hallucination (with the broad view including premonitions and visionarism; synesthesia; eidetic imagery; palinacusis and palinopsia; hypnagogic states; obsessional, negative, reflex, and extracampine hallucinations; oneiric states and image-related mental automatism; autoscopy; Charles Bonnet syndrome; formication and Ekbom states; écho de la pensée; unilateral hallucinations).[8]

The fact that there is little conceptual debate on the nature of hallucinations is less due to the coherence of the received view than to the fact that it has been adopted hook, line, and sinker by biological psychiatry which remains the predominant approach. In other words, hallucinations (regardless of sense modality) are considered as direct expressions of perturbations of brain regions related to the perceptual system.[9] To understand the infertility of the received view, the moment and circumstances of its construction must be analyzed.

5.2.2 The Construction of the Received View

Reports of phenomena redolent of hallucinatory experiences can be found in the literature of the ages. In earlier times, these reports seem to have been (a) socially and culturally integrated, particularly within certain religious contexts, and (b) considered to carry portentous messages concerning the life of the individual or its ancestors (Berrios 1996). The fact that on occasions hallucinatory experiences may have also been considered as manifestations of lunacy, madness, or insanity does not affect the appropriateness of the above claim. For reasons which need further historical elucidation, during the eighteenth century, hallucinatory experiences began to be included in the nosological listings of the time.[10] These attempts at medicalizing some hallucinatory experiences were *not* driven by the belief that they might constitute "symptoms of madness" (the notion of "mental symptom" is a nineteenth-century construct) but expressed the different belief that on occasions hallucinatory experiences might constitute independent "diseases." When thus considered, the predominant view was that hallucinatory experiences resulted not from pathological changes in the faculty of perception but of imagination.

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[7] Maury (1865) remains the best classical source on this issue.

[8] On each of these concepts, the reader will find a raft of references. Ey (1973) remains an important source in this regard.

[9] For a variety of presentations of this view, see Mourgue (1932), West (1962), and Aleman and Larøi (2008), etc.

[10] Reports of "hallucinatory experiences" can be frequently found in eighteenth-century nosologies sometimes as "hallucination" and sometimes under a different name (e.g., Boissier de Sauvages 1772). In all cases, each is considered as a separate disease and certainly not as "symptoms" considered as part of a "disease." This is because the concept of mental symptoms was only constructed during the nineteenth century (Berrios and Markova 2006; Markova and Berrios 2009)

The socioeconomic and epistemological context of the early nineteenth century encouraged the adoption by medicine of the so-called anatomo-clinical model of disease. The latter model, together with factors such as associationism (Locke's psychology),[11] representationalism (part of Cartesian dualism), and romantic philanthropy (including mental hospital building, penal reform, and abolitionism) participated in the medicalization of madness.

Both the epistemological and psychological versions of associationism redefined understanding as "analysis" and encouraged the breaking up of wholes into their constituent "units." Representationalism, in turn, defined knowledge as the organized accumulation of internal and private representations of reality. Although there were various versions of representationalism, according to the most popular, the knower was sure of the existence of the representation itself (e.g., in Descartes), but knowledge of the quality of the relationship between representation and reality itself was inferred rather than captured by intuition. Very conveniently to later empirical research into hallucinations, the new physiology of the senses was also based on the epistemology of representationalism.

The philanthropic movement contributed to insanity legislation and to the building of mental hospitals. The latter acted as repositories for mental patients with similar complaints and allowed both long-term observation of their complaints and the possibility of undertaking correlational autopsies. Lastly, the anatomo-clinical model of disease encouraged the belief that madness was a composite of symptoms and signs, and that the latter resulted from disturbances in specific brain sites (Berrios and Freeman 1991).

5.2.3 Background Factors

"Alienism" is the name of the discipline and trade that resulted from the medicalization of madness. By the 1880s, such a discipline included a body of medical and paramedical staff specialized in madness, rites of passage (examinations), specialized databases (journals and textbooks), venues (hospitals, institutes, societal headquarters), and organized communicational exchanges (associations and congresses) (Berrios and Freeman 1991). By the turn of the century, alienism became psychiatry. The alienist differentiated himself from other medical practitioners and other social agents by developing a specialized language (psychopathology), a theoretical syntagma, and supporting rhetorical devices. The descriptive language of madness needed to be constructed anew, and the syntagma combined borrowings from the medical sciences and from the philosophy of mind, psychology, and the burgeoning human sciences.

[11] For an analysis of the relationship between associationism and psychiatry, and full references, see Berrios (1988).

This Janus-like conceptual profile allowed alienists to participate both in the world of medicine and in the social management of madness. To implement the latter, alienists carved for themselves a role in the social, legal, ethical, and political world of the nineteenth century. Their double conceptual profile was based both on the natural sciences and on the developing human sciences. Thus, the epistemology of psychiatry has been hybrid from its inception. In the event, the objects of inquiry that alienists constructed for themselves were hybrid too (Berrios and Marková 2002). However, alienists tried from the start to create the impression that there was no difference between their objects of inquiry and those of the rest of medicine. This may have resulted from the fact that some were genuinely unaware of the hybrid nature of mental symptoms and disorders; others, however, may have done so for self-serving reasons. Whatever the explanation, the historical fact is that the concept of "hallucination" was constructed against this ambivalent context.

Esquirol (1817) both coined the generic name "hallucination" and tooled a unitary concept to embrace, irrespective of sense modality, all hallucinatory experiences: "If a man has the inner *conviction* of truly experiencing a sensation for which there is no external object, he is in a hallucinated state, he is a visionary." And: "Hallucinations of eyesight have been called visions but this term is appropriate only for that sensory modality. One cannot talk about 'auditory visions', 'taste visions', or 'olfactory visions'? … The latter phenomena, however, share with vision the same mechanisms and are seen in the same diseases. A generic term is needed for all. I *propose* the word hallucination." (our Italics). There is no space in this chapter to unpack Esquirol's reasons for expressing this view. The issue to remember is that before 1817 there were only "hallucinatory experiences" resulting from a pathology of imagination, and after this date, and irrespective of sense modality, they were reconceptualized as tokens of the same underlying phenomenon.

5.3 The 1855 Debate

In 1855, a debate broke out at the *Société Médico-Psychologique* on the nature of hallucinations. In the session of the 26th of February, Alfred Maury challenged remarks by Delasiauve and Moreau on a putative association between hallucinations and mystic states. The untidy debate that ensued lingered on until April 1856. The philosophical aspects of the matter in hand encouraged the participation of nonclinicians such as Maury, Bouchez, Peisse, and Garnier, particularly in relation to the questions of whether (a) hallucinations might be seen in the normal; (b) sensation, image, and hallucination formed a continuum; and (c) hallucinations, dreams, and ecstatic trances were similar states. Nonmedical participants also wanted to know whether hallucinations might have a "psychological" origin. By the end of May 1856, the debate had ended inconclusively in spite of efforts by Baillarger, Michéa, and Parchappe to draw some useful conclusions (Berrios 1996).

5.3.1 The Aftermath

By the end of the nineteenth century, opposite factions in the hallucination debate had made their positions clear: On the one hand, there were the alienists (by then, called psychiatrists or experts in psychological medicine) who supported the received view that hallucinations were a pathological and unitary disturbance of regions of the brain associated with perception; and on the other, there was a growing group of nonmedical academics and amateurs interested in psychical research who believed that hallucinations were frequent in the general population and were increasingly calling into question the received view by suggesting that hallucinations may have a psychological origin and on occasions carry a communicational meaning of sorts (Gurney 1885). Indeed, the interesting results of the Census of Hallucinations undertaken by the Society for Psychical Research during the 1880s seemed to support their view (Parish 1897). At the turn of the century, Freud threw yet another spanner in the wheels of the received view by introducing the concept of "negative hallucination" (first put forward by Bernheim) (Duparc 1992). To this day, the debate on hallucinations has been conducted along the tramlines set by these three approaches.

5.4 The Epistemology of Hallucinations

Fully to show the epistemological flaws of the received view would require a detailed analysis of all the primary and secondary antinomies. Lack of space precludes such an undertaking in this chapter; instead, only few of the polarities in question will be explored.

5.4.1 Representation Versus Nonrepresentation

The deepest antinomy embedded in the received view concerns the view that the hallucinatory experience is a sensation acting as a representation *manqué* (in the sense that in real or veridical perception, sensations are always vouchsafed by real external objects). The representational hypothesis of hallucinations has been particularly successful because (a) it identifies an easy explanatory locus (in other words, it makes the study of the "sensation manqué" the central theme in hallucinations research), and (b) it shares the same epistemological assumptions with sensory neurophysiology and neuropsychology, and hence, empirical research by means of the latter is bound to provide some support for the received view.

The representationist view of hallucinations provides reality (the noumena) with a permanent alibi by putting the blame on either of two components of the presentation: (1) the relationship between reality and its representation, or (2) the relationship between the subject and his inner representation. Hence, a

hallucinatory experience occurs either because (a) a representation presents itself to awareness without being vouchsafed by reality or (b) there is a failure in the subject's cognitive and emotional management of the representation.

Overemphasizing the explanatory power of the sensation manqué begs the question as to why hallucinations consisting of representations of nonperceptual material not vouchsafed by reality (e.g., hallucinatory emotions or hallucinatory volitions) do not seem to be reported in the clinical literature. This dearth of reports may of course be due to the fact that such phenomena do not "occur in nature." But it could also be that (if the representationalism view is correct) they do exist, but because the current definition of hallucination also operates under a perceptual constraint (i.e., that to be called "hallucination," a false representation must relate to material acquired by a sensory modality), then suspicious representations of a nonperceptual nature are made to fall outside the purview of the concept of hallucination.

In general terms, representationalism works better in association with the view that external reality is independent and fully constituted (realism in its many varieties) than in relation to constructivist epistemologies according to which man's cognition participates actively in the conformation of reality. For example, while for Kant phenomena are accessible to modulation by means of conceptions of understanding (i.e., categories; see also Chap. 1), noumena are cognitively unreachable.

According to the received view on hallucinations, representations (in general) are ontologically and epistemologically vouchsafed by reality itself and not by the subject who entertains them. This makes representations ideal loci for explanation in the sense that hallucinations can be described as representations manqué. This is because if the subject were to be allowed a major role in the vouchsafing (construction) of his own representations, then these would lose plausibility and power as potential loci of explanation. The naïve representationalism of the received view also excludes psychogenetic and cultural configurators from playing a central role in the construction of hallucinations.

To circumvent the rigidity of the received view, it may be necessary to return to nonrepresentational models according to which the relationship of the subject and his surrounding reality is conceived as direct, continuous, and unmediated. This purview was developed, for example, by the Scottish Philosophers of Common Sense to correct the epistemological difficulties posed by passive Lockean representationalism (Grave 1960; Yolton 1984). Following this lead, nonrepresentational models of hallucinations, such as Gibson's (1966), must be reclaimed.

5.4.2 Perception Versus Nonperception

The second antinomy built into the epistemology of the received view concerns the nature of the relationship between hallucinations and perception. The origin of such a "relationship" is likely to have been the observation that reports of hallucinatory experiences seem to indicate that the "content" of experience was an image, a sensation, or a perception. The issue here is why it has been assumed that those reports

entail *simpliciter* that the experiences in question are actually related to (or "caused" by) a pathological change in the perceptual system. The standard answer to this question is that there is plenty of clinical evidence that tinkering with the neuroanatomy, neurophysiology, and neuropharmacology of the perceptual system may trigger "perceptual" experiences which can be considered as similar to reported hallucinations. The evidential force of this reply, however, depends upon the assumption that such triggered perceptual experiences are identical to the hallucinatory experiences reported by subjects diagnosed with schizophrenia, mania, melancholia, obsessional disorder, hysteria, etc. This assumption is groundless and related to the belief that "organic" and "psychiatric" hallucinations are the same phenomenon (see below).

The perceptual nature of psychiatric hallucinations is called into question by the fact that the statement "S is experiencing an image" cannot be meaningfully differentiated from the statement "S believes that he is experiencing an image" (i.e., that S is having a perceptual delusion). A short digression into the historical background may throw light on this issue. The meaning of "perception" (*catalepsis* in Greek and *perceptio* in Latin) has changed in the West. Originally used to refer to the action of grabbing, collecting, and bringing things into oneself, it was later used in a metaphorical sense to refer to learning, i.e., to carrying information from the external world into the mind. At this stage, the nature of this information was *not* sensorial. The association between perception and sensation only starts with Descartes who uses the term to refer to the action of obtaining information about the world via the collection of sensations. From then on, perception was to carry two epistemological meanings: (a) a *general* meaning of getting to know the world in general (e.g., via intuition – which obviates intermediaries and representations), and (b) a *sensorial* meaning according to which such knowledge is exclusively obtained via sense-data (Locke's primary ideas, Condillac, etc.) (Hamlyn 1961).

The general and sensorial meanings of the term "perception" are often confused, and this may (partly) explain the problem at hand. While it would be perfectly in order to accept that hallucinations are related to the "general" meaning of perception (i.e., gaining information about the world, *simpliciter*), it might not be correct to state that hallucinations are causally or explanatorily related to "sensory" perception. A working compromise would be to state that (a) organic hallucinations may be the result of an impairment of the sensory perceptual system and (b) psychiatric hallucinations are related to a dysfunction of the general system of perceptual apprehension of the world, which would include intellectual, emotional, and volitional mechanisms as well as intuition. This compromise assumes that these two types of hallucination are different phenomena (see Sect. 5.4.4).

5.4.3 Unitary Versus Multiple

The third antinomy concerns the question of whether (a) all hallucinations are to be considered as the same phenomenon or (b) hallucinations differ (i.e., are different

phenomena) according to the sensory modality with which they are associated. A variation of (b) would be to consider hallucinations associated with public senses (vision, audition, and olfaction) as different from those associated with nonpublic senses (touch, taste, and coenesthesis). This is based on the observation that both groups seem to require different identificatory ascertainment (Berrios 1982).

The original unitary view built into Esquirol's definition has rarely been challenged. And yet there are interesting epistemological differences that show up the instability of the received view. According to the official epistemology of the latter and the current view of mental symptoms (e.g., DSM IV), hallucinations are self-contained objects whose recognition should not be based on context or history but on intrinsic attributes alone. Thus if a subject declares that he can see his grandmother sitting in a chair in front of him, the correct identification of the phenomenon ought to be carried out by ascertaining that the chair is empty and there is no one sitting on it. This method of consensual ascertainment can be accomplished vis-à-vis hallucinations predicated of objects sitting in the public domain. But it is otherwise in relation to nondistant senses. For example, if the subject were to report an itch in his right hand or a strange sensation inside his abdomen, the consensual ascertainment test no longer applies (see also Chap. 13). Indeed, the epistemology of the received view cannot differentiate for certain between a real and a hallucinated itch. In psychiatric practice, this epistemological discrepancy is concealed by the fact that hallucinations (like the rest of mental symptoms) are rarely if ever diagnosed on the bases of intrinsic attributes alone but against a clinical context constituted by other mental symptoms, history, assessment of personality, etc.

There is also the interesting issue raised by the received view and (DSM) definition of hallucination according to which "hallucination is a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ." This is interesting because hallucinations rarely occur against an absolute vacuum. The everyday world is populated by many objects, and in most cases hallucinatory experiences occur against a rich backdrop of stimuli. When the definition claims that the hallucination "occurs without external stimulation of the relevant sensory organ," it is likely to mean that a hallucination of a grandmother occurs when there is no grandmother sitting on the chair. But the subject's retinas are at that very moment being stimulated by the chair on which grandmother is supposed to be sitting and by a myriad of other background visual stimuli.

This analysis brings hallucinations very close to the definition of illusion because in both cases stimuli are being perceived in a distorted manner. Whether a reported perception is declared a hallucination or an illusion would depend, therefore, on the degree of distortion of the stimulus. A coat hanging behind a door "seen" as a man hiding is considered to be an illusion simply because their shapes are grossly similar. A chair "seen" as a grandmother is called a hallucination because their shapes are vastly different, and the claim that one is an illusion of the other would be considered as implausible. And yet, the question here is one of grades of differentiation between shapes, concepts, sounds, smells, etc., rather than there being *no* external stimulation.

5.4.4 "Organic" Versus "Psychiatric" Types

The issue here is whether, irrespective of putative cause, (a) *all* hallucinations are the same phenomenon, or (b) hallucinations seen in the context of neurological disease or experimental manipulation of the brain are radically different from the "hallucinations" observed in relation to psychiatric disorders. When Esquirol put together his original definition, rather wisely, he left the door open to the possibility that they might be different phenomena. Throughout the nineteenth century, alienists backed either poles of this antinomy, and this led to periods of predominance of one or the other. When the "neuropsychiatric view" of hallucinations predominated, alienists tended to be unitarians, i.e., it was believed that hallucinations were the same, regardless of putative cause. This view predominates at the moment and is sponsored by what can be called the third wave of neuropsychiatric or biological psychiatry. The problem with the unitarian view is that it may be misleading in regard to the nature and etiology of "psychiatric hallucinations." Hallucinatory experiences in patients diagnosed with obsessive-compulsive disorder, schizophrenia, melancholia, etc., may be fundamentally different, and this needs to be taken into account. For example, the musical hallucinations of funereal marches heard by a patient with melancholia and Cotard syndrome differ in every respect from the musical hallucinations of elderly subjects with tinnitus and hearing impairment (Berrios 1990a).

5.5 Toward a New Epistemology of Hallucinatory Experiences

5.5.1 The Cambridge Model

According to the Cambridge model (see Fig. 5.1), subjective mental symptoms are "hybrid" objects, i.e., entities constituted by both organic (neurobiological signaling) and semantic (an admixture of cultural, social, individual configurators conferring personal meaning to an experience) components. Little as yet is known about the respective roles of the organic components and semantic configurators (or indeed about their interrelationships), but this is liable to vary in regard to different mental symptoms. It is likely that the process of semantic or cultural configuration modifies both the gain and the specificity of the subjective experience associated with the neurobiological signal. The process can be said to start when signals issued out by dysfunctional or distressed brain addresses enter the patient's awareness and generate primitive experiences whose prelinguistic and preconceptual status makes them ineffable. In order to be communicated, such experiences need to be configured into mental and speech acts. Thus, from the start, mental symptoms are "hybrid objects," i.e., dense combinations of information issued out by both the cultural configurators and the proxies representing the neurobiological signal. Four pathways by means

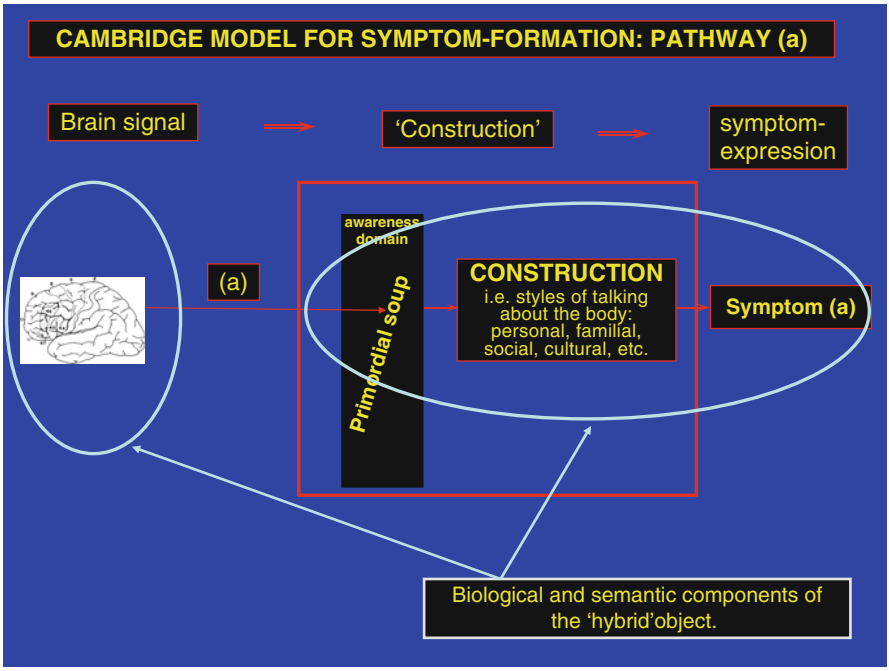

Fig. 5.1 Cambridge model of symptom formation (pathway a)

of which mental symptoms can be constructed have been proposed elsewhere (Berrios and Marková 2002, 2006).

According to pathway (a) patients construct subjective mental symptoms (e.g., hallucinations) on the basis of particular changes they experience in their mental state. Such changes in their awareness while mediated by neurobiological signaling may be in response to either internal (primary biological alteration) or external (perceived distress) stressors. The resulting inchoate, preconceptual and prelinguistic experiences have been called the "primordial soup." To integrate such experiences into the concert of his mind, the patient needs to provide them with meaning and articulate them into words. This configuratory process is achieved by means of personal, familial, and cultural templates (semantic components). Only then is the patient ready to communicate his experience via an utterance or behavioral gesture. It is important to remark that at this stage the "content" of the configured mental symptom may have little to do with the functional signature of the brain site that originated the signal in the first place. This means that the same biological signal may be configured into different mental symptoms, or that different brain signals may be configured into the same mental symptom.

Once the mental symptom has been configured, the subject may decide to complain, i.e., to report it to another person (e.g., a clinician). This dialogical interaction adds another stage to the process of configuration, for it entails conceptual haggling

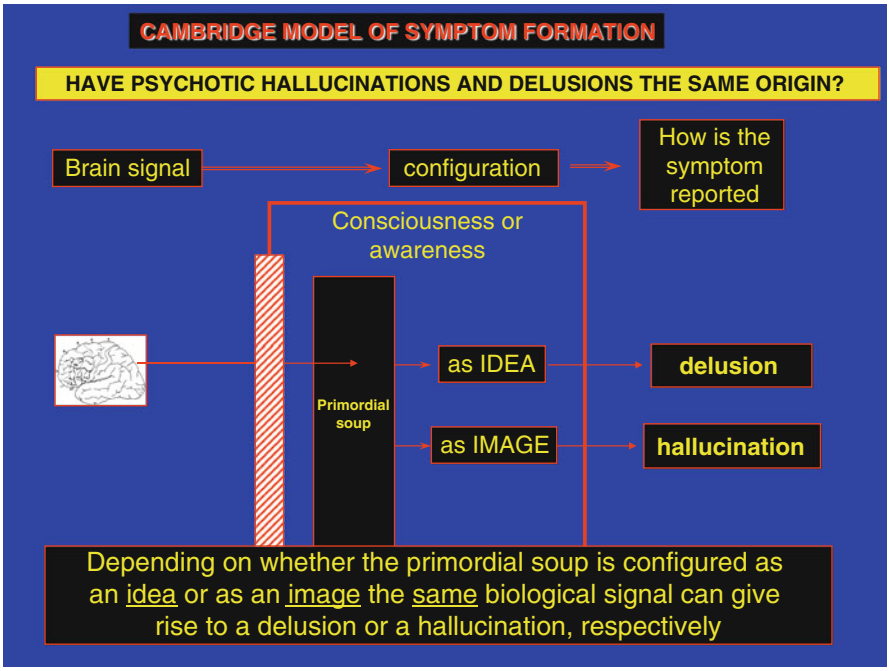

Fig. 5.2 Same origin of psychotic hallucinations and delusions

and negotiation. Clinicians do not behave like "phenomenological" amanuenses but as active negotiators. Against the context of a shared or different culture and influenced by the clinician's (diagnostic) view, each of these configured experiences is reshaped into what will become the final "mental symptom" (as recorded in the case notes).

There is no space in this chapter to deal with pathways (b) and (c). However, pathway (d) is interesting for it allows for the reconfiguration of a mental symptom already formed. Thus, mental symptoms configured via pathway (a) may undergo a secondary configuration based on specific representations and tropes that are of special importance to the individual. In this case, the neurobiological kernel built into the original mental symptom no longer plays any role as content and meaning are fully determined by the cultural configurators. It could be said that mental symptoms generated by pathway (d) correspond to those generically called "psychogenic" (as per dissociation, rerepresentation, etc.).

Against this background, one could then envisage a situation when the primordial soup (whatever its neuropsychological origin in the brain) could be putatively configured as an image or an idea or belief. If the former, the declaration by the subject would be deemed to be a hallucination; if the latter, a delusion (see Fig. 5.2). It is clear from this example that nonperceptual neurobiological signals can give rise to hallucinations and that perceptual signals may be configured as mental symptoms other than hallucinations.

5.5.2 Hybrid Objects

The concept of "hybrid object" includes components originating in the natural and social worlds. The proportional contribution of these two types of components and the manner of their combination and interaction require further research, and it is likely that such proportionality should be evaluated in relation to each hybrid object. In the case of "biological" objects (e.g., orchids or horses), describing and classifying are considered as overlapping operations in that both are meant to capture and release information about the objects classified. This is not the case in regard to ideal or abstract objects (e.g., virtues, revolutions, categories). Hybrid objects (particularly mental symptoms) are sui generis in this regard: (a) Their biological component may not in fact be informative at all, and (b) in spite of all the ongoing neuroscientific research, little is known about the "biological basis" of mental symptoms.

Although hybrid objects (e.g., hallucinations) may have biological and semantic components, their proportionality is yet to be determined, and hence any models developed to capture and classify them must take this into account. In general, however, it is likely that when it comes to psychiatric hallucinations, the semantic (cultural) component will be predominant to the extent that there will be little point in bothering with an analysis of their neurobiological kernel.

Comparing "hybrid objects" with physical and abstract objects throws further light on their nature, novelty, and usefulness. First of all, hybrid objects should not be considered as a mere combination of the other two. They represent the creative and configurative action of moral agents and hence are imbued with the emotional, volitional, and cognitive force that only persons can generate when confronted with a complex and (often) painful and perplexing experience (primordial soup). As dynamic responses, hybrid objects are fully consonant with personality and mental state. They are the expression of the manner in which beliefs, cultural codes, and views of the world get knitted together in response to a strange experience (see Figs. 5.3 and 5.4).

5.5.3 Consequences and Inferences

Although the Cambridge model still operates within a representational epistemology, it is able to do justice to (a) the existence of putative brain signaling constituting the kernel of mental symptoms (as dictated by the neuropsychiatric principle that mental disorders are disorders of the brain) and (b) to the operation of psychogenic and cultural factors. It offers a viable alternative to the received view of hallucinations, for it takes cultural configurators seriously. Instead of considering cultural modulation to be an "end-of-cascade" event with culture just coloring the "content" of the hallucination, the Cambridge model proposes that the cultural modulation occurs at the beginning of the cascade and hence it is drastic enough to

	CONCRETE	ABSTRACT	HYBRID
examples	orchids, dogs, gold	numbers, virtues, sacraments	works of art, maps mental symptoms
time	yes	no	yes
space	yes	no	yes
reducible without residuum	yes	no	no
epistemological approach	explanation	understanding	understanding
classification	Biological taxonomy	Artificial object	Artificial object
physical proxy variables	yes	no	yes
need for proxy variables	no	yes	yes
ontological origin	nature, evolution, god	man-made	man-made
relation to language	independent	dependent	dependent
semantic envelope	no	yes	yes
causally active	yes	yes?	yes

Fig. 5.3 Hybrid objects differentiated

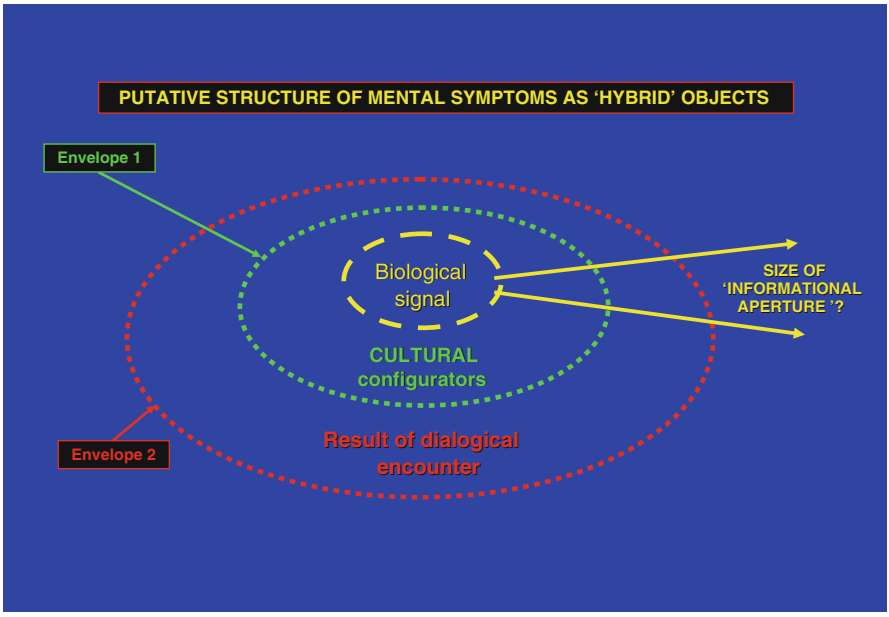

Fig. 5.4 Structure of hybrid objects

attenuate (and on occasions obliterate) the informational load of the biological signal.

As mentioned above, the Cambridge model allows for delusions and hallucinations (and for other mental symptoms) to share the same brain origin but to be differentiated in their form, meaning, content, and clinical import by the cultural configurators. In this respect, the biological signal would only provide the original trigger or force for a symptom to appear. What the symptom becomes must be considered as the total responsibility of the cultural and semantic configurators. This hybrid quality of the mental symptoms has important consequences for their brain localization and therapeutic management. But that is another story.

5.6 Conclusions

The current concept of hallucination was constructed during the early nineteenth century and carries epistemological assumptions belonging to this period. The received view has been useful to catalyze research but is proving infertile with each generation repeating the correlational research paradigm of the last except for making use of different research techniques. The same representational epistemology governs both conceptual and empirical research into hallucinations, and it is imposing severe constraints on both.

Deconstruction of the structure of the received view shows that it is supported by a raft of primary and secondary antinomies. The former were built into the concept at the moment of its inception; the latter were added throughout the nineteenth century to alleviate the tensions created by the original assumptions. The representational structure of the received view identifies the "representation" as the weakest point in the explanatory chain, both in its relationship to reality itself and to its management by the mind. Given the unknowable nature of reality, this is a pyrrhic victory. The fact that the nature of the representation itself cannot be fully ascertained means that declarations of entertaining an image in the mind's eye are conflated with declarations of believing that such an image is being entertained.

The relationship between hallucinations and perceptions is based on the fact that the images are part of the narrative of hallucinations. There is no reason to believe that this legitimizes the inference that (particularly psychiatric) hallucinations result from a pathology of the perceptual system. Likewise, hallucinations are unlikely to be a unitary phenomenon. Those linked to the distance and nondistance sense modalities are crucially differentiable, for consensual ascertainment is no longer available for the second group. The belief that hallucinations are the same phenomenon irrespective of etiology must also be revised. Organic hallucinations, i.e., those seen in relation to brain disease or experimental manipulation of the brain, may be related to perception in ways that psychiatric hallucinations are not.

An alternative hybrid model of hallucinations is proposed according to which what determines whether the experience is reported as an image or as a thought does

not depend upon the nature of the brain signal that triggers the experience but upon the cultural configurators that modulate its form and content.

Arguments have been offered to believe that a radical revision of the epistemology of hallucinations is long overdue. The new epistemology of hallucinations must first be formulated on the conceptual drawing board and should offer a clear alternative to the received view. This alternative view should escape the constraints imposed by the representationist, perceptual, and unitary antinomies. Many human beings entertain hallucinatory experiences, some report them, and some may want to be rid of them. For the sake of the latter group, psychiatrists should try to break new grounds in regard to the understanding of these extraordinary and little-understood phenomena.

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Part II
Hallucinatory Phenomena

Chapter 6
Visual Hallucinations

Daniel Collerton, Rob Dudley, and Urs Peter Mosimann

6.1 Introduction

Visual experiences of 'things that are not there' have, in different ways, been recorded throughout history. Thus night-time visual hallucinations of a figure accompanied by a sense of terror and paralysis currently classified as a hypnagogic or hypnopompic hallucination in the context of a parasomnia were previously construed as supernatural night hags, incubi or nightmares in Western cultures (Blom 2010), with equivalent kanashibari reported in Eastern cultures (Goswami et al. 2010; see also Chaps. 17 and 18). Over the same time span, people of many cultures have shown a marked willingness to induce hallucinations as a means of reaching spirit worlds through the use of a range of plants and venoms (Perry and Laws 2010). Even in these early periods, however, not all explanations were supernatural. In one of the most famous hallucinations in literature, Macbeth's vision of a dagger,

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Fig. 6.1 Charles Bonnet (1720–1792)

Shakespeare proposes a cortical explanation for hallucinations – 'or art thou but, A dagger of the mind, a false creation, Proceeding from the heat-oppressed brain?' (Macbeth, Act II Scene 1).

The shift from supernatural to scientific explanations became decisive with the European Enlightenment. In the eighteenth century, Charles Bonnet (1720–1792; see Fig. 6.1), a Swiss philosopher and scientist, reported the complex visual hallucinations experienced by his grandfather, Charles Lullin. '[He] sees from time to time, in front of him, figures of men, of women, of birds, of carriages, of buildings, et cetera. He sees these figures make various movements: getting closer, going away, fleeing, diminishing or increasing in size, appearing or disappearing; he sees the buildings rise in front of his eyes and a display of all the outside construction material.' An unequivocal physical (in this case bilateral cataracts) rather than a supernatural explanation was given together with a proposed neurological basis which would still stand scrutiny today: 'All of this appears to have a seat in that part of the brain involved with sight. It is not difficult to imagine physical causes, strong enough to shake sensitive bundles of fibres that will produce in the mind, the picture of various objects with as much veracity as if the objects themselves had stimulated the fibres' (Hedges 2007). Even in those still seeking supernatural explanations, for example, Sidgwick's mammoth survey of psychic experience in late Victorian Britain (Blom 2010), a scientific approach gradually took hold.

Table 6.1 Relative population frequency of common associates of formed (complex) visual hallucinations (Adapted from Collerton et al. 2005)

State	Relative frequency of visual hallucinations
Sleep-related hallucinations	100
Delirium	77
Nonpathological daytime hallucinations	33
Neurodegenerative disorders	28
Psychosis	22
Eye disease	20
Others (epilepsy, migraine, stroke, peduncular hallucinosis, narcolepsy, etc.)	5
Bereavement	1

Interest in clinical visual hallucinations slowly grew through the nineteenth and twentieth centuries. Charles Bonnet syndrome was named in the 1930s by the Swiss neurologist Georges de Morsier (1894–1982) (O'Farrell et al. 2010), and there was a gradual recognition of visual hallucinations in relatively rare neurological disorders, such as narcolepsy and peduncular hallucinosis, but also as core features of a much more common, albeit previously undiscovered, disorder – dementia with Lewy bodies. In psychosis, the historic focus on auditory hallucinations (and delusional beliefs) as core diagnostic characteristics overshadowed research on other modalities, with early interest in models of visual hallucinations in patients diagnosed with schizophrenia (Horowitz 1975) lapsing for a while.

By the start of the twenty-first century, however, four disorders – dementia, psychosis, delirium and eye disease – had become recognised as common associates of visual hallucinations (see Table 6.1). The hallucinatory consequences of physical or sensory deprivation and the flashbacks associated with psychological trauma also attracted increasing attention. Paralleling this clinical interest, but developing more slowly, was the recognition of visual hallucinations in nonpathological states, particularly on the borders of sleep (D'Agostino et al. 2010, see also Chap. 17) or following bereavements (Rees 1971; Alroe and McIntyre 1983).

However, research remained fragmented until the beginning of the twenty-first century, with most studies limited to a single disorder or mental state. Several factors have combined within the last decade to push these disparate fields together (Collerton and Mosimann 2010).

Firstly, developments in the understanding of normal visual processes in the latter decades of the twentieth century allowed the relationship of visual input and visual perception to be more clearly understood. The recognition that all visual perception is based upon generated internal models of the visual environment, rather than being a projection of visual input on the brain, provided a theoretical framework for integrating a range of hallucinations into disturbances within a single, albeit distributed and complex, system. Secondly, systematic comparisons of visual

hallucinations in separate disorders highlighted not only consistent similarities across these in, for example, phenomenology, but also regular differences in, as an instance, frequency. This data provided a focus for what models have to explain and a way of testing those that are developed. Finally, improvements in the accessibility of the scientific literature and in communication have made it much easier for research groups working in different fields to influence each other.

6.2 Defining Visual Hallucinations

The move away from visual perception as a simple analysis of visual input to the conception of subjective reality as an internal model which is checked by visual input is a double-edged sword for hallucination researchers. On the plus side, it easily allows the existence of hallucinations if the balance between model and input is tilted too far from the input. On the other hand though, it means that, conceptually, all perception is at least partially hallucinatory. The conundrum of defining veridical as opposed to hallucinatory perception remains unsolved. Within a constructive model of visual perception, there is no sharp boundary around any visual phenomenon. Perhaps as a consequence, many visual disturbances commonly co-exist with hallucinations in the same person, hence the pragmatic, though problematic, definition of hallucinations as seeing something that other people do not see. In experimental practice, this can be tested fairly reliably by comparing a stimulus with the self-report of an associated perception, but more difficulty arises in naturalistic settings when what is actually present in the visual environment is not easily measurable.

6.3 The Measurement of Visual Hallucinations

Setting aside these conceptual issues, there is no difficulty in describing an astonishing variety of visual experiences which occur in the absence of environmental equivalents (see Table 6.2). The reader with a special interest into the phenomenology of hallucinations may find further information in Blom's extensive catalogue (2010), with a briefer survey in ffytche et al. (2010). What is rather more challenging is to record and classify these experiences in a systematic, valid and reliable manner. Without privileged access to another person's perception and a means of relating this to the visual environment, distinguishing true hallucinations (where there is no environmental equivalent for the perception) from illusionary misperceptions (in which there is a partial equivalent) to visual re-experiences (in which veridical perceptions recur beyond the initial stimulus) can prove very difficult (see also Chap. 2). At present, there is no validated instrument for capturing all types of hallucinatory experiences, though reliable specific measures of, for example, complex object hallucinations do exist (Mosimann et al. 2008).

Table 6.2 Varieties of visual hallucinations (Adapted from ffytche et al. 2010; Blom 2010)

Unformed	Simple	Visual hallucinations with lowest degree of complexity. They include flashes, dots, spots or phosphenes (Greek phõs (light); phainein (to shine)), visual experience of a transient flash or spark of light
Intermediate (not clearly formed or unformed)	Geometric	Hallucinations characterised by lines, geometrical shapes, circles, patterns
	Teichopsia	Greek: teichos (wall) and opsis (seeing), usually seen as zigzag lines in one hemifield in the context of migraine
Formed	Complex	Phenomenologically rich and well-organised visual hallucinations, including people, animals or objects. May be lilliputian (small)
	Panoramic, scenic or landscape	The whole visual input is replaced by hallucinatory precepts
	Text	Words and figures
Partial (one aspect of the perception is hallucinatory)	Colour hallucination/illusion	
	Hyperchromatopsia	Greek; Huper (to exceed certain boundaries), chrõma (colour) and opsis (seeing). Colours are perceived as exceptionally vivid and brilliant
	Face hallucination/illusion	
	Facial intermetamorphosis	Latin: inter (between); metamorphoun (to change one's shape) Misperception of an individual with the belief that the person has been transformed
	Prosopometamorphopsia	Greek: prosõpon (face, expression, part, mask); metamorphoun (to change the form); opsis (seeing), i.e. seeing faces in altered forms
Visual re-experiences (perception is re-experienced after the initial stimulus)	Visual perseveration	
	Trailing phenomenon	
	Palinopsia	Palin (again) opsis (seeing)
	Illusory visual spread	
	Positive afterimages	
	PTSD flashbacks	
	Flashbulb memories	
	Memory hallucination	
	Re-perceptive hallucination	

6.4 The Phenomenology of Visual Hallucinations

Though hallucinations come in many forms, it is not yet clear whether they cluster into a smaller number of core types, and if they do, where the edges lie between different types (ffytche 2005; Collerton and Mosimann 2010). Existing classificatory schemes use the content of the hallucination. Thus formed (sometimes called

complex) hallucinations of figures or objects are distinguished from unformed (or simple) hallucinations of unformed dots, shapes or flashes. Beyond the problem of how to classify intermediate forms (tessellations, for example), it is not clear that content is the only potential divider since different hallucinations are also associated with variations in duration, distinctiveness, distress and other associated sensory, cognitive and behavioural phenomena. As an instance, hallucinations in other modalities are variably present in the same person (uncommon in eye disease, but common in Lewy body disorders, psychosis and delirium), but multimodal hallucinations are rare, even in these cases (see also Chap. 18). In hallucination-prone individuals, both internal (alertness and fatigue) and external (lighting and visual environment) factors may influence occurrence. Even in highly hallucinating individuals, however, veridical perception tends to be the rule with individual hallucinations being brief and episodic.

Comparison of visual hallucinations across different normal states and clinical disorders has the potential to test different ways of dividing up hallucinatory experiences (Collerton et al. 2005). However, differences in methodology (resulting partially from the conceptual and measurement problems mentioned previously) make it hard at present to know the contribution of reporting biases to these apparent differences (Collerton and Mosimann 2010). When different disorders are assessed within a single study, results are much more similar than comparisons of different studies might suggest. Bearing this caveat in mind, we will briefly review the evidence base for hallucinations in the most common clinical and nonpathological states. More systematic surveys can be found in Collerton et al. (2005), Aleman and Larøi (2008), ffytche et al. (2010) and Larøi and Aleman (2010).

Just about everyone experiences a visual hallucination at some time (Ohayon 2000), usually for a nonclinical reason. Prominent amongst these nonpathological states are the hypnagogic and hypnopompic hallucinations which occur on the borders of sleep, bereavement hallucinations and hallucinations associated with deprivation; both extreme physical deprivation and prolonged visual deprivation. In total, nonpathological hallucinations, mainly sleep related, are roughly as common as pathological ones (Collerton et al. 2005).

Though there is relatively little comparative study of nonpathological states, sleep- and bereavement-related hallucinations tend to be of formed figures (c.f. the night hags mentioned earlier), and are often fleeting and indistinct (D'Agostino et al. 2010). Similarly, reports of hallucinated figures are reported in physical extremis (Ryan 1995). In contrast, sensory deprivation is more commonly associated with unformed hallucinations (Meppelink et al. 2010), suggesting more of a commonality with eye disease in which unformed hallucinations also predominate.

Hallucinogens are a group of substances that have the potential to alter consciousness and to evoke phenomena such as hallucinations, illusions and other sensory distortions (Nichols 2004, see also Chap. 22). As an example, Albert Hofmann (1906–2008), the discoverer and inadvertent first user of lysergic acid diethylamide (LSD), described his initial experiences as follows: 'At home I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found

Table 6.3 Examples of the visual effects of hallucinogenic substances adapted from Blom 2010

Substance	Chemical properties	Possible visual experience
Serotonin receptor agonists		
Lysergic acid diethylamide (LSD)	Ergoline alkaloid, partial 5-hydroxytryptamine (5-HT2) agonist	Out-of-body experience, animation of extracorporeal world, sparkling, phosphenes, teleopsia, metamorphosis
Mescaline	Phenethylamine alkaloid from peyote cacti; 5-HT agonist	More vivid perception, kaleidoscopic hallucinations, kinesthetic hallucination
Psilocybin	Tryptamine alkaloid from mushrooms	Distorted vision, geometric complex visual hallucinations, complex scenes or forms
Bufotenine	Tryptamine alkaloid, from toad skin and eggs	Simple geometric visual hallucinations, increased intensity of colours
Acetylcholine receptor antagonists		
Atropa belladonna; Datura; Herba apollinaris; Mandragora officinarum	Tropane alkaloid, acetylcholine receptor antagonist, night shade plant	Vivid dreams, some illusions and complex hallucinations, but also anticholinergic side effects
Cannabinoids		
Tetrahydrocannabinol (THC); Dronabinol	Anandamide neurotransmitter, cannabinoid receptor agonists	Subtle changes of sensory acuity. In high doses it may be associated with illusions and hallucinations, possibly in conjunction with thought disorder

the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours.' The number of potentially hallucinogenic plants is large, and the list of their visual effects is long (see Table 6.3). Systemic effects, for example mydriasis, blurred vision, tachycardia, vertigo, dry throat, constipation and urinary retention with anticholinergic compounds limit usage. Dosage with plant compounds is challenging, and in overdose, psychedelics, particularly those with anticholinergic properties, can easily lead to delirium, stupor or death. The shift to synthetic hallucinogens, typified by LSD, initially appeared to open up the possibility of direct research into the pharmacological mechanisms of hallucinations, but discovery of the long-term disadvantages of hallucinogens, including visual flashbacks, visual snow and hallucinogen-induced persistent perception disorder (HPPD) in predisposed adults, combined to produce an abrupt stop to initial enthusiasm. Now, indirect studies based on case reports, or treatment studies for existing hallucinations, tend to predominate.

Hallucinations in eye disease are highly variable within and across people (ffytche and Howard 1999; ffytche 2009; ffytche 2010) and range from flashes, dots and other unformed experiences, to perceptual distortions and re-experiences, through to hallucinations of figures and objects, and ending with perceptions of

whole landscapes. As an instance, A.B. – a person with macular degeneration – described her hallucination as '…a huge, vast canyon. I had to step over the edge to get to my seat. I have seen large churches with gravestones inside and everything was larger than life, but doors appeared shorter. The rooms just carried on, and I have to walk through things to get around – like a bath or a wall.'

There is an inverse relationship between complexity and frequency (Collerton and Mosimann 2010). Thus simple dots and flashes are almost invariable, whilst complex scenes are rare. The nomenclature of simple to complex hallucinations and the phenomenology of hallucinations implies a continuum in these experiences, but it is not clear whether this is so.

Turning to neurodegenerative disorders, the strong association of figure and object hallucinations with dementia with Lewy bodies initially obscured the range of other visual experiences that patients report. To illustrate, P.J. – a person with dementia with Lewy bodies – reported his experiences as follows: 'Every night I would see a man and a young child standing in the corner of the room staring at me… it was really queer. They would move but not come any closer to me and didn't say anything… they both had on old-fashioned clothing, like Victorian style with cloaks on.' Though still the archetypal hallucination is of a figure, less formed hallucinations and perceptual distortions are very common (Mosimann et al. 2006). As with other disorders, hallucinations are associated with increased distress and disability and poorer outcome (Mosimann and Collerton 2010).

People with psychosis report a broad range of odd or anomalous experiences both as triggers for delusional interpretations and as psychotic phenomena in their own right (Garety et al. 2001). As an example, K.F. – a person with psychosis – reported that 'I saw a man hanging from a noose in a tree – the man is dead.' Even before the person has made the transition to a psychosis, there may be evidence of subtle anomalous visual experiences which are not necessarily disturbing. People often report odd or unusual experiences such as greater intensity of colours and sounds (Bell et al. 2006; Freeman and Fowler 2009) more akin to optical distortions and illusions than hallucinations.

Where people have made the transition to overt psychosis, the prevalence of visual hallucinations is high (Bracha et al. 1989) and associated with greater levels of distress and impairment (Mueser et al. 1990). Most visions are of figures. The remaining visions are either unformed or of animals or objects (Gauntlett-Gilbert and Kuipers 2003, 2005). Visions are not usually accompanied by voices, though the majority hear voices at other times. Fused visual and auditory experiences in which, for example, the person sees lips moving on an otherwise normal, real face at the same time as hearing a voice are relatively rare (Hoffman and Varanko 2006).

The extent to which psychosis and hallucinations are independent is under review. The classic belief that hallucinations are, by definition, psychotic symptoms (though not necessarily as part of a psychotic disorder) has been countered by the perspective that they can be nonpathological, though usually infrequent, phenomena which become part of a psychotic syndrome through cognitive and emotional biases towards distress. The physiological overlap between visual hallucinations in

psychosis and other disorders, for example, the role of cholinergic function (Hussain 1971; Patel et al. 2010), is starting to be investigated.

The final member of the big four hallucinatory disorders is delirium, an extremely common but poorly understood disorder (Fearing and Inouye 2009). In contrast to other disorders, there is little systematic evidence on the form of visual hallucinations in delirium, in large part because of the practical difficulties in doing research with actively delirious participants (a problem also found with acutely hallucinating people with psychosis and dementing disorders). However, it does seem that the phenomenology of hallucinations in delirium is more akin to that seen in dementing illnesses, whilst the interpretation and emotional reaction is more akin to that seen in psychosis.

6.5 Mechanisms of Visual Hallucinations

Any model of how people can see things that are not there has to be based on how people see things that are there. Early conceptualisations of vision emphasised a bottom-up abstraction of perception from an increasingly abstract and global analysis of visual input. Thus, perceptions of objects were abstracted from shapes which were built from lines and angles which were in turn recognised from patterns of excitation in primary visual cortex.

In contrast, current generative models see perception as an internal, sparse, functional, predictive, dynamic representation of the visual input that the brain would receive if that model were correct (Heerkeren et al. 2008). Hence, what is seen is the least unlikely match between predicted and actual visual input (Friston 2002). This moves the emphasis in vision away from input from the eye as the determinant of perception towards input as the means of checking or limiting the perceptual representation. This shift in model is associated with a parallel development in neuroscience towards investigating a distributed visual processing system which incorporates not only posterior visual areas, but also frontal attentional cortex, brainstem and thalamic regulatory mechanisms, as well as interconnecting tracts.

However, as might be expected from the continuing discussion on the existence of distinct visual hallucinatory syndromes, there is no established consensus on the mechanisms within this distributed system which may underlie these visual experiences. Different groups working on the pathogenesis of visual hallucinations variably stress the importance of disturbances in frontal, visual, regulatory and connective systems (Horowitz 1975; Manford and Andermann 1998; Pelaez 2000; Lee et al. 2003; Collerton and Perry 2004; Behrendt and Young 2004; Collerton et al. 2005; ffytche 2008).

The causes of visual hallucinations are not yet firmly established. In eye disease, for example, the extent of visual loss is a consistent risk factor, but other factors such as age, cognitive status and gender are inconsistent (ffytche 2009; Graham et al. 2011). Specifically, the factors which account for the variations in hallucinatory phenomenology from one person to another are very poorly understood, and it remains unclear why similar levels of visual impairment do not always lead to visual

hallucinations. Neuroimaging indicates that those areas active in hallucinations are also those that are active in sense perceptions of similar stimuli. Conversely, if the ability to perceive or image something is lost through damage to the brain visual systems, so is the ability to hallucinate that image. Clear eye pathology suggesting a primary role for loss of visual input supported by the relatively high frequency of unformed hallucinations in both eye disease and visual deprivation, and the similarity in content of the hallucinations seen in eye disease and following serotonin receptor agonists, places the emphasis on posterior, primarily visual, areas (ffytche 2007, 2010).

Cholinergic, and to a lesser extent, dopaminergic function is a key neuropathological concomitant of visual hallucinations in dementia with Lewy bodies. Unlike eye disease, dementia with Lewy bodies has a distributed pathology with consistent damage to frontal and secondary visual cortices. Putting this together with distributed models of veridical visual perception which highlight similar brain areas, with the cognitive characteristics of dementia with Lewy bodies and with evidence that cholinergic manipulation both induces and abolishes figure and object hallucinations heightens the emphasis on interactive models of visual hallucinations (Collerton et al. 2005). Unlike previous models which emphasised single areas of dysfunction, albeit within complex systems (Manford and Andermann 1998), these interacting models propose a number of interacting impairments, none of which in itself is sufficient to cause hallucinations. Thus the Perception and Attention Deficit (PAD) model (Collerton et al. 2005) stipulates combined dysfunctions in attentional and perceptual processes, and Diedrich et al.'s (2005, 2009) Activation, Input and Modulation (AIM) disturbance model proposes simultaneous shifts in external perception and internal image generation.

Subsequent research has confirmed that co-existing impairments in central top-down attentional/generational processes and in bottom-up perceptual processes do lead to a greatly increased chance of visual hallucinations (Ramírez-Ruiz et al. 2007; Ozer et al. 2007; Barnes and Boubert 2008; Imamura et al. 2008; Meppelink et al. 2008). However, just as in veridical perception, the nature of the dysfunctional interaction has remained elusive (Bronnick et al. 2011). Imaging has identified consistent dysfunction in posterior and ventral visual areas, but equivalent findings in more frontal attentional cortex have been less reliable (Diederich et al. 2009; Sanchez-Castaneda et al. 2010).

Research into Lewy body disorders also led to a renewed interest in the dream intrusion hypothesis which was initially proposed as an explanation for psychotic and sleep-associated hallucinations (D'Agostino et al. 2010), although this time it was the association with sleep disturbance and rapid eye movement sleep behaviour disorder rather than phenomenological similarities between dreams and hallucinations which sparked interest (Arnulf et al. 2000; Barnes et al. 2010). As in other areas, however, the association between disturbed dreams and disturbed perception appears more to reflect the fortuitous disruption of anatomically close but separable systems (Collerton and Perry 2011).

Current models of psychotic symptoms emphasise the importance of anomalous visual experiences both in and of themselves and as key drivers in the development of delusional beliefs (Garety et al. 2001). However, in many cases, there is a notable

absence of peripheral sensory or central perceptual impairments, suggesting either a heightened role for the influence of generative processes on the experience of visual hallucinations (perhaps in the context of image memories from the previous traumatic experiences which are common in psychosis) or for an anomalous interpretation of mundane experiences. For example, some people report seeing shadows in the corner of the eye. Normally dismissed as an insignificant transient illusion, the person with psychosis may interpret it as a ghost or vampire.

Despite the difference between age of onset of hallucinations in psychosis (usually in late adolescence or early adulthood) and other disorders (usually well into later life), transition to a full psychosis with distressing voices, visual hallucinations and delusions is associated with the same factors which increase the risk of hallucinations in other disorders. Thus, many people report that the onset of psychosis is associated with sleep disturbance, stress, social withdrawal and isolation, as well as with substance misuse. Whilst the use of hallucinogens is not a frequent factor, the sustained use of strong cannabis or amphetamine use seems to be frequent in the emergence of psychotic symptoms including visual hallucinations. Imaging (Oertel et al. 2007), though less extensive than in eye disease or dementia, also seems to indicate a relationship between the content of the hallucination and the activity of relevant brain areas.

Moving away from the mechanisms generating the hallucinatory experience, wider research in psychosis, aimed at understanding the psychological mechanisms which drive abnormal perceptions and interpretations, and the distress which flows from these, has led to a focus not only on the hallucinatory mechanisms themselves but also on an interest in the emotional and behavioural impact of these experiences.

Analogies from the experience of auditory hallucinations suggest that it is not the hallucination per se which drives distress (Andrews et al. 2007; Birchwood 2003; Collerton and Dudley 2004), but the interpretation of the hallucination as a threat (Dudley et al. in press) and subsequent behavioural response to that interpretation which is key.

The mechanisms underlying hallucinations in delirium are very poorly understood, but what evidence there is does suggest similar risk factors to those seen in dementia (Brown et al. 2009).

6.6 Visual Hallucinations: An Integrative Model?

There still remain many areas of less than perfect knowledge where visual hallucinations are concerned, but it now seems accepted that hallucinations are not phenomena that stand separate from normal vision, nor from other visual disturbances. Both conceptually and in practice, there are no clear dividing lines between veridical perceptions and hallucinations.

Looking across disorders and states, the beginnings of more integrative, multidimensional models are emerging (Aleman and Larøi 2008; see also Chaps. 2 and 3). Disturbances in several parts of the distributed visual system can all cause a transitory

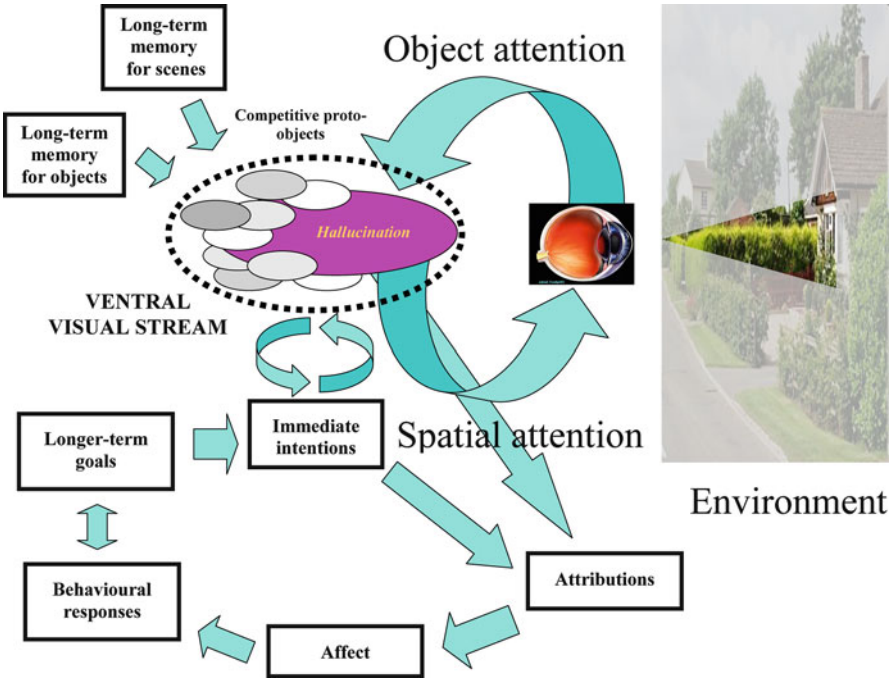

Fig. 6.2 An integrative model of hallucinations

disturbance in perception such that a perception including a hallucinatory element is a better predictor of visual input than is a wholly veridical perception.

From eye disease and sensory deprivation comes evidence on the effects of reducing or eliminating visual input; from neurodegenerative disorders and delirium comes data on the effects of distributed disturbances in brain function, particularly on attentional and top-down processes; from psychosis come models of emotional disturbance, psychological development and maintenance mechanisms. Putting these together, a tentative model can be sketched (see Fig. 6.2). In this model, spatial and object attentions shape sensory input which then interacts with expectancies biased by long-term memories of visual contexts and immediate intentions to increase the chance of a hallucinatory perception. This perception is then not disconfirmed since sensory input is, in itself, impaired. The content of the hallucination and the intentional context in which it occurs then trigger emotional and behavioural reactions which may lead to longer-term goals (for example, to avoid similar experiences in the future), which then feed into emotional reactions, if they do recur.

A number of consequences flow from this model.

Firstly, to test it is not trivial. Not only are many components of the model underspecified and hard to measure, but evaluation of it depends upon the accurate simultaneous measurement of dynamic perception, processing and stimulus during the

occurrence of relatively rare, unpredictable, episodic phenomena. At present, our measurement of the static factors which increase the chance of hallucinations is much better than our measurement of the dynamic factors which lead to a specific hallucination. We do not understand enough of the temporal course of visual hallucinations and their relationship with thought, affect and behaviour. Serial investigations, including functional imaging of people at risk of hallucinations whilst they are and are not hallucinating would allow hypotheses to be tested, but as yet, the practical problems of capturing an unpredictable and transient experience with a very large machine have only rarely been surmounted (ffytche et al. 1998; Oertel et al. 2007).

Secondly, it suggests that there may well be a number of potential avenues for developing effective treatments (Larøi and Aleman 2010). Hallucinations appear to be inherently unstable – veridical perception is the default position even in those people who do hallucinate. Thus, targeting specific cognitive or biological risk factors either for the occurrence of hallucinations or for their disabling emotional consequences may be effective; though it is fair to say that, as yet, no truly effective interventions have been discovered. The co-existence of multiple impairments in eye function, sensory processing and cognition in the population group most at risk of hallucinations – i.e. the elderly – together with the limitations of medication use in older people (see also Chap. 24) does suggest that optimism should be tempered by caution.

Looking to the future, most of the tools that are needed for progress are at our hands already. Despite our imperfect definitions and measures of hallucinations, their consequences and the neural systems underlying them, we can do these things well enough to move forward. Systematically using the tools that we do have across hallucinations in different clinical and natural states will undoubtedly refine our existing understandings and open up new areas of investigation.

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Chapter 7
Synaesthesias

Devin Blair Terhune and Roi Cohen Kadosh

7.1 Introduction

Most people believe that everyone else experiences the world in a similar way to them. However, a small percentage of the population, individuals with synaesthesia, experiences various aspects of their environment in profoundly different ways from the rest of us. *Synaesthesia* (literally meaning 'joined sensation') is an unusual neurological condition in which a stimulus, such as the number *5*, the note *C*, or the feel of sandpaper, reliably and involuntarily elicits an *ancillary*, atypical experience, such as the colour red or the emotion of excitement, alongside the typical response (Ward and Mattingley 2006). For individuals with synaesthesia, numbers may trigger colours, tastes may elicit tactile perceptions, and months of the year may be distributed in space. A number of historical figures, such as Pythagoras (see Cytowic and Eagleman 2009), suspected of having synaesthesia, but the first documented case dates to 1812 (Jewanski et al. 2009), with the first systematic study of the phenomenon occurring later in the century (Galton 1883). In the parlance of contemporary research, the stimulus that elicits the synaesthetic response is referred to as the *inducer*, whereas the ancillary event, which may be affective, cognitive, or perceptual, is termed the *concurrent* (Grossenbacher and Lovelace 2001). In what follows, we summarize the methods by which synaesthesia is typically studied, its principal characteristics and relationship to other phenomena such as hallucinations, and how recent research has informed our understanding of its origins and mechanisms.

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7.2 Measuring Synaesthesia

Before turning to its principal characteristics, it is imperative to outline how synaesthesia is typically measured and authenticated. There is broad consensus amongst researchers that an individual's synaesthesia is genuine if it is involuntary, or *automatic*, and if the inducer-concurrent pairs are *consistent* over time (Ward and Mattingley 2006).

The criterion of automaticity can be easily measured using different selective attention tasks in which inducers are alternately paired with stimulus dimensions that are either congruent or incongruent with an individual's concurrents for the respective inducers. For example, if a synaesthete experiences the colour *red* for the letter *E*, one can measure how quickly the synaesthete is able to identify the actual colour of the letter when presenting the letter *E* coloured in red (congruent condition) as compared to the letter *E* coloured in blue (incongruent condition). It has been repeatedly demonstrated that synaesthetes exhibit interference effects, as indicated by slower response times or lower accuracy rates for incongruent than congruent inducer-concurrent pairs, whereas control participants do not (Dixon et al. 2000). Cumulatively, these results suggest that synaesthesia is resistant to control.

The criterion of consistency requires assessing the reliability of participants' inducer-concurrent pairs. This is typically done by indexing an individual's self-reported concurrents (e.g. colours) for a set of inducers (e.g. numbers) at two time points separated by a few weeks or months. Insofar as synaesthetes reliably display high consistency, this feature is widely regarded as a marker of genuine synaesthesia. As a result, consistency is typically used to verify synaesthesia and as an inclusion criterion for experimental research (Simner 2011).

Despite the clear utility and widespread use of these criteria, they are not without their limitations. First, non-synaesthetes who are trained to associate graphemes with colours display interference effects akin to those observed by some synaesthetes (Cohen Kadosh et al. 2005; Meier and Rothen 2009). Grapheme-colour synaesthesia (and corresponding interference effects) can also be induced in highly suggestible non-synaesthetes with a posthypnotic suggestion (Cohen Kadosh et al. 2009). Accordingly, interference effects alone may be insufficient to verify an individual's synaesthesia. Simner (2011) has similarly argued that inducer-concurrent consistency may be an erroneous identifying characteristic of synaesthesia whose use will invariably lead to the specious exclusion of real synaesthetes. It is unclear whether this argument will gain traction amongst researchers; it is likely that consistency testing will remain the gold standard for the identification of synaesthetes for some time.

7.3 Principal Characteristics

Although still uncommon, synaesthesia is not as rare as once believed. Recent research estimates the prevalence of synaesthesia in the general population to be approximately 4% with equivalent frequency of occurrence for men and women (Simner et al. 2006b). Synaesthesias include a diverse set of experiences that

although notably similar may not represent a uniform set of phenomena with shared characteristics.

7.3.1 Types of Synaesthesia

There are a wide variety of forms of atypical binding that can be classified as synaesthesia. To date, more than one hundred different forms have been identified (Cytowic and Eagleman 2009). In the most representative study to date, the most common form of synaesthesia (2.8%) was coloured days, in which days of the week elicit colour concurrents (Simner et al. 2006b). By contrast, grapheme-colour synaesthesia, the mostly commonly studied form of this condition, had a prevalence of 1.4% in two independent samples. Another study found the prevalence of mirror-touch synaesthesia, in which viewing another person being touched produces corresponding tactile hallucinations, to be 1.6% (Banissy et al. 2009).

A critical question is how the different forms of synaesthesia are related to one another. It is well known that having one form increases the likelihood of possessing another. For instance, as many as 50% of synaesthetes have two or more forms of synaesthesia (Cytowic and Eagleman 2009). Indeed, having another form of synaesthesia is often used as an argument that a non-prototypical form is indeed a true form of synaesthesia (Simner et al. 2006b). However, whether synaesthesias represent a unitary or a diverse set of similar phenomena remains poorly understood. Eagleman (2010) has recently presented data that bear on this question. Applying factor analysis to the forms of synaesthesia exhibited by a large sample of synaesthetes, he found that 21 different forms fell into six higher-order factors, each comprised of multiple forms: coloured sequence (e.g. number → colour), non-visual concurrents (e.g. sound → smell), coloured flavour, coloured music, coloured affect (conceptual) (e.g. emotion → colour), and coloured affect (physical) (e.g. touch → colour). An individual with any of the four forms within the coloured-sequence cluster has a high probability of having another form from within this cluster, but only a chance probability of having forms from other clusters. Notably, spatial-sequence synaesthesia, such as experiencing numbers as localized in space, was only weakly related to the other forms of synaesthesia and thereby appears to represent a distinct condition. Mapping the similarities and differences between these clusters will be an important area for future research.

7.3.2 Unity and Diversity

The principal feature that unites all forms of synaesthesia is the atypical binding of two normally distinct experiences, in which either an environmental (e.g. a sound) or endogenous (e.g. an aural image) stimulus produces an atypical ancillary experience (e.g. a colour photism [image or percept]). Most synaesthetes do not experience *conscious* bidirectional synaesthesia (e.g. digit ↔ colour), although a minority does (Cohen Kadosh et al. 2007; Cytowic and Eagleman 2009). Some

grapheme-colour synaesthetes do exhibit bidirectional synaesthesia *implicitly*, that is, colours are associated with particular numerical values, associations that influence behavioural response patterns even though the association does not breach conscious awareness (Gevers et al. 2010). One persistent finding is that the experience of colour, as a photism, is the most frequent synaesthetic concurrent, present in approximately 77% of synaesthetes (Simner et al. 2006b). A further piece of evidence for the unity of synaesthesia is the aforementioned finding that many synaesthetes reliably exhibit other forms of synaesthesia. Finally, it is notable that synaesthetes' inducer-concurrent pairs are often remarkably consistent (Ward and Mattingley 2006). Concordance in inducer-concurrent pair consistency across different forms of synaesthesia would provide further support for the claim that synaesthesias are different expressions of the same underlying phenomenon.

There are also a number of noteworthy similarities in the inducer-concurrent mappings of synaesthetes. For example, *0*, *O*, *1*, and *I* are commonly white, and *A* is often red (Barnett et al. 2008; Rich et al. 2005; Simner et al. 2005), although there is variegation in other grapheme-colour pairs across studies. Similar consistencies are present in sound-colour and in grapheme-luminance pairs. Recent data by Eagleman (2010) suggest that mappings across synaesthetes may be determined by low-level features of the stimuli (e.g. shape) and occur through associative mechanisms during development. Specifically, for many synaesthetes, it appears that novel graphemes are assigned similar colours as similarly shaped graphemes. In some cases, mappings are likely due to semantic associations (*A* is associated with *apples*, which are often associated with the colour red), but such an explanation can only account for a small number of mappings. Further, similarly shaped graphemes (e.g. *S* and *5*) have been found to elicit different concurrents, which may in part be determined by their semantic context (Dixon et al. 2006).

Despite the shared commonalities between and amongst different forms of synaesthesia, there exist equally important differences. The most salient divergence from uniformity amongst synaesthetes is perhaps Eagleman's (2010) finding of different higher-order clusters of synaesthesia. This set of results calls into question the idea that synaesthesia is a uniform condition. We anticipate that this will be the subject of a considerable amount of research in the future.

Diversity in the expression of synaesthesia is also present amongst individuals experiencing the same form. For example, grapheme-colour synaesthetes have been found to vary with regard to whether they experience concurrents spatially localized to the stimulus (*projectors*) or as endogenous representations (*associators*) (Dixon et al. 2004). These two subtypes display distinct behavioural response patterns (Dixon et al. 2004; Ward et al. 2007) as well as differences in grey and white matter volumes and connectivity in regions related to sensory processing and memory (Rouw and Scholte 2007, 2010). However, synaesthetes' associator-projector status may be unreliable (Edquist et al. 2006); it is somewhat unclear how individuals are best stratified on this dimension (see Van Leeuwen et al. 2010; Ward et al. 2007), and the two subtypes do not always display behavioural and neurophysiological differences (Gebuis et al. 2009; Rouw and Scholte 2007; Weiss and Fink 2009). Grapheme-colour synaesthetes may also vary in the extent to which low-level features of an inducer (e.g. colour contrast with background) influence concurrents, pointing to

possible *higher* (concurrents independent of stimulus features) and *lower* (concurrents influenced by stimulus features) subtypes of synaesthesia (Ramachandran and Hubbard 2001). The associator-projector and lower-higher dimensions appear to be orthogonal (Ward et al. 2007). It has also been shown that mirror-touch synaesthetes may be comprised of one subtype that experiences mirror-touch perceptions as looking through a mirror, and another that experiences these perceptions as though they were in the same position as the individual being touched (Banissy et al. 2009).

Ignoring heterogeneity amongst synaesthetes has important consequences. It may result in the failure to uncover important individual differences amongst synaesthetes as well as the failure to replicate findings across laboratories (Dixon and Smilek 2005). Notwithstanding these concerns, whether the aforementioned subgroups reflect discrete subtypes or positions on continua in an otherwise uniform population is an issue that can be empirically resolved and which warrants greater attention (Cohen Kadosh and Terhune 2011).

7.3.3 Relationship with Cross-Modal Mapping

Some findings presented in the preceding section point to commonalities between synaesthetes and non-synaesthetes. One explanation for this concordance is that these similarities reflect a latent continuum in which synaesthetes are positioned at an extreme end of a normal distribution. For instance, individuals without synaesthesia display colour-pitch, pitch-size, and letter-colour associations that closely match those found in synaesthetes (Ward et al. 2006). There are also similarities between the implicit representation of numbers in space in non-synaesthetes and their explicit representation in space amongst number-space synaesthetes (Cohen Kadosh and Henik 2007). However, synaesthetes' experiences of atypical binding are of much greater magnitude and exhibit greater specificity and consistency than the cross-modal mappings of non-synaesthetes. Perhaps the most fundamental difference is that synaesthetes are *conscious* of their condition. Further quantitative evidence that synaesthetes are a discrete group is garnered when the consistency of grapheme-colour pairs is plotted. Critically, synaesthetes and controls are nearly wholly distinct from one another, resulting in a bimodal distribution (Barnett et al. 2008; Ward and Simner 2005). This challenges a continuum account of synaesthesia and suggests that the synaesthesia phenotype represents a discrete category. Further studies are needed to resolve these conflicting views. It might be that some types of synaesthesia exhibit continua-like properties, whereas others reflect discrete categories of experience.

7.3.4 Correlates

Synaesthesia may confer abilities on an individual that have a positive or deleterious impact on cognition. These effects may be specific to an individual's form of synaesthesia or be independent of it, stemming from common underlying mechanisms.

The cognitive correlate of synaesthesia that has attracted the greatest attention is memory. Insofar as many synaesthetes have access to two channels by which a string of information can be encoded (e.g. a string of letters and a string of colours), they presumably have access to a greater number of retrieval cues and thereby may be expected to exhibit superior memory. There are a number of case studies of synaesthetes with extraordinary memory abilities (see for example Luria 1968), but few investigations of groups. Group studies point to heightened mnemonic abilities amongst synaesthetes, although there have been some mixed results (Rothen and Meier 2009, 2010; Yaro and Ward 2007). Moreover, synaesthetes' performances are well within the normal range. Superior memory for graphemes and colours may underlie greater grapheme-colour pair consistency in this population (Yaro and Ward 2007) and may contribute to the greater *range* of colours that synaesthetes can describe (Simner et al. 2005), which may, in turn, facilitate greater colour discrimination.

Experiencing the world in a profoundly different way is likely to impact how synaesthetes interact with others. Banissy and Ward (2007) found that mirror-touch synaesthetes exhibit greater empathy than control participants. This effect presumably arises from the tactile 'hallucinations' these synaesthetes experience whilst viewing other individuals being touched, although it is critical to ensure that this effect is restricted to this particular form of synaesthesia. A related finding is that more grapheme-colour synaesthetes than controls report *Mitempfindung*, a neurological condition in which tactile stimulation produces sensation in a different location from the stimulation (Burrack et al. 2006).

Less is known about the deleterious effects of synaesthesia on cognition. There is empirical evidence that synaesthetes display difficulties in mathematics and in mislocating sensory stimuli to the contralateral side of the body (*allochiria*, see also Chap. 13) relative to non-synaesthetes (Cytowic and Eagleman 2009; Rich et al. 2005; Ward et al. 2009). One hypothesis is that number-form synaesthetes may utilize inflexible spatial strategies during computations (Ward et al. 2009). Cytowic and Eagleman (2009) note how a number of these and other deficits observed in this population are associated with parietal lobe functioning and thus may indirectly implicate the parietal cortex in synaesthesia.

This brief review illustrates how poorly understood the cognitive profile of the synaesthete is and how ripe for investigation this subject matter is. It will be important for future researchers to dissociate the relationships between particular cognitive (dis)abilities and different forms of synaesthesia.

7.3.5 Relationship to Other Hallucinatory Phenomena

Insofar as the concurrents of some synaesthetes qualify as hallucinations, it is worth considering the relationship between synaesthesia and other hallucinatory phenomena. Some colour-taste synaesthetes experience the respective taste localized in the mouth, grapheme-colour projector synaesthetes experience colour photisms localized in space, and mirror-touch synaesthetes experience tactile hallucinations resembling

touch. These experiences can be regarded as hallucinations because they constitute perceptual experiences that do not have a corresponding stimulus in the environment. At the same time, it needs to be noted that they are only produced when exposed to an inducer (e.g. a taste, a number, etc.) and are thus qualitatively different from other hallucinations. By analogy, projector photisms would be comparable to visual hallucinations that occur *only*, and *reliably*, when another specific stimulus is presented. In addition, the majority of synaesthetes know that concurrents are produced by their unique cognitive apparatus and are not actually present in the environment. In this regard, synaesthetic hallucinations do not meet conservative criteria that require that an individual believes that her or his hallucination is a veridical perception.

It is plausible that synaesthesia may share mechanisms with multisensory hallucinations. A recent case study, using multiple electrophysiological and neuroimaging techniques in a patient diagnosed with schizophrenia who experienced auditory-visual hallucinations, found that he displayed reduced cortical thickness in multiple regions (e.g. the superior temporal gyrus, see Jardri et al. 2009), whereas synaesthetes display the converse pattern in other regions (see Sect. 7.4.2 below). Whilst the activation of the fusiform gyrus during multisensory hallucinations parallels its activation during synaesthesia (see Sect. 7.4.2), the former appears to serve a binding/integration function, whereas the latter is associated with grapheme and colour processing. Cytowic and Eagleman (2009) note how synaesthesia may be experienced in the context of release hallucinations. Similarly, cross-modal percepts akin to synaesthesia are sometimes reported during seizures in individuals with temporal lobe epilepsy and in a minority of individuals with concussions; although it is unclear whether these phenomena occur through similar mechanisms as synaesthesia (Cytowic and Eagleman 2009). The oft-cited fact that LSD and other psychedelic drugs (see also Chap. 22) can produce synaesthesia-like experiences (Nichols 2004) has received virtually no empirical attention, but it is important to note that many of the hallmark phenomenological properties of synaesthesia such as automaticity and consistency do not appear to be present in psychedelic hallucinations (see also Cytowic and Eagleman 2009). It is clear that many hallucinations arise from a disruption of monitoring functions in which an endogenous representation is misattributed to the environment or an environmental stimulus is misinterpreted. One potentially fruitful avenue for research in this area would be to consider whether projector synaesthesias and other forms with hallucinatory properties represent instances in which concurrents are misattributed to one's environment because of a source-monitoring deficit. At present, how synaesthesias and hallucinations may or may not be related has received such little attention that it is difficult to provide any firm conclusions regarding this relationship.

7.4 Mechanisms

A considerable amount of research on synaesthesia has been devoted to its mechanisms. In this section, we summarize work on the genetic and developmental origins of synaesthesia as well as its cognitive and neural mechanisms.

7.4.1 Genetic and Developmental Origins

When considering the genetic and developmental contributions to the incidence and phenomenology of synaesthesia it is imperative to distinguish between three types of variables: (1) those that determine whether one has synaesthesia; (2) those that determine one's form of synaesthesia; and (3) those that determine the characteristics of one's synaesthesia, such as inducer-concurrent pairs and localization of concurrents. Some evidence has been yielded for the variables underlying each of these features.

Early research by Galton (1883) suggested that synaesthesia runs in families. More recent research corroborates his results and indicates that synaesthesia is a heritable condition (Barnett et al. 2008; Baron-Cohen et al. 1996; Ward and Simner 2005). Familial studies have shown that around 40% of synaesthetes have a relative with synaesthesia (Barnett et al. 2008; Rich et al. 2005; Ward and Simner 2005). In contrast, case studies of monozygotic twin pairs have produced inconsistent results: in one case, both twins had synaesthesia (Hancock 2006), whereas in two other cases, only one twin had synaesthesia (Smilek et al. 2002, 2005). Smilek et al. (2005) speculated that discordance amongst monozygotic twins may result from genetic mutations or changes in brain morphology during development. The results of a whole-genome analysis of auditory-visual synaesthetes and their families yielded evidence for a link with chromosome 2q and suggestive links with other chromosomes, indicating that synaesthesia is a complex condition with genetic heterogeneity (Asher et al. 2009).

Data bearing on the heritability of the features of synaesthesia indicate that its phenomenological expression is not wholly constrained by the synaesthesia of one's relatives. Amongst a group of synaesthetes and family members with synaesthesia, only grapheme-colour synaesthesia was found in 73% of the families. However, the remaining families had members with different forms of synaesthesia, suggesting that a specific form is not inherited (Barnett et al. 2008; Ward et al. 2005), although it is plausible that one may inherit a predisposition for a particular higher-order cluster (Eagleman 2010, see Sect. 7.3.1). Barnett and colleagues also found that grapheme-colour pairs differed across family members and were comparable to those observed between unrelated synaesthetes. Finally, synaesthetes' associator-projector status did not appear to be inherited. Cumulatively, these results indicate that synaesthesia is heritable but that its form and phenomenological features are determined by other factors.

Synaesthesia is typically reported as having been experienced since early childhood and thus is generally considered a congenital condition. However, environmental influences during development appear to contribute to the phenomenology of synaesthesia. The clearest evidence is seen with inducer-concurrent pairs. As described above (see Sect. 7.3.2), low-level features and semantic properties of graphemes as well as syllable stress position of words (Simner et al. 2006a) appear to determine colour concurrents. Similar effects may be at play in sound-colour synaesthesia (Ward et al. 2006). However, patterns of inducer-concurrent pairs

exhibit considerable diversity and often appear to be idiosyncratically determined by features of an individuals' unique environment, such as through explicit exposure to coloured graphemes during childhood (see also Simner et al. 2009; Witthoft and Winawer 2006).

7.4.2 Cognitive and Neural Mechanisms

The mechanisms underlying synaesthesia have been a consistent source of debate and motivation for research. One point of contention amongst synaesthesia researchers is the extent to which synaesthesia requires attention. Synaesthesia was initially widely regarded as a sensory-perceptual phenomenon that occurred through low-level mechanisms and could be induced by exposure to stimulus properties (Ramachandran and Hubbard 2001). In contrast, recent research has emphasized the importance of conceptual representations for synaesthesia (Simner 2011) and indicates that attention is indeed necessary for synaesthesia (Rich and Mattingley 2010; Ward et al. 2010). As described above (see Sect. 7.3.2), the extent to which sensory or conceptual properties of inducers trigger synaesthetic experiences may vary across synaesthetes. Behavioural differences amongst grapheme-colour synaesthetes may emerge because of differential shifting of attention from one spatial reference frame to another, which will produce different attentional demands across synaesthetes (Ward et al. 2007).

There is broad consensus that synaesthesia results from the enhanced communication, or crosstalk, between cortical regions governing processing of the inducer and concurrent. However, the mechanism supporting crosstalk is the source of fervent debate. To date, two distinct, albeit not wholly competing, neurological accounts have been advanced to account for crosstalk.

The two-stage model of Hubbard (2007) proposes that excess structural connectivity between particular brain regions gives rise to their cross-activation during experience of an inducer but that binding processes in the parietal cortex produce a coherent synaesthetic experience (see Fig. 7.1). Functional neuroimaging studies have implicated the fusiform gyrus, including V4/V8, which is known to support colour, letter, and word processing, in various forms of synaesthesia (Barnett et al. 2008; Brang et al. 2010; Nunn et al. 2002; Rouw and Scholte 2007; Sperling et al. 2006). Grapheme-colour synaesthetes also appear to exhibit larger cortical volume than controls in the left and right anterior fusiform gyrus (Jancke et al. 2009) and the left intraparietal sulcus and right fusiform gyrus grey matter (Weiss and Fink 2009). Further support for the role of the parietal cortex in synaesthesia is gleaned from two studies that demonstrated that transcranial magnetic stimulation (see also Chap. 25) applied to the right parietal occipital junction transiently disrupted grapheme-colour synaesthesia (Esterman et al. 2006; Muggleton et al. 2007). Finally, increased structural connectivity in the left superior parietal cortex, the motor cortex, and the right inferior temporal cortices (adjacent to the fusiform gyrus) has been observed in grapheme-colour synaesthetes (Rouw and Scholte 2007, 2010). Cumulatively,

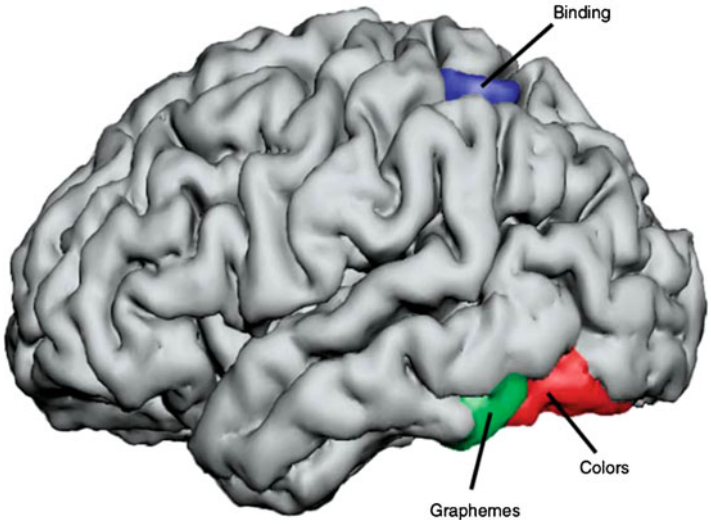

Fig. 7.1 The cortical regions implicated in the two-stage model of grapheme-colour synaesthesia (Hubbard 2007). Crosstalk between V4 (*red*) and the visual word form area in the fusiform gyrus (*green*), produced by excess anatomical connectivity, gives rise to the experience of colour during the presentation of graphemes. Grapheme-colour binding is further enabled by the intraparietal sulcus (*blue*) (Reprinted by permission from Macmillan Publishers Ltd: Nature Neuroscience (Hubbard 2007). Copyright 2007)

these results support Hubbard's (2007) model, but it should be noted that evidence supporting a *causal* link between hyperconnectivity and synaesthesia has not yet been found.

A second theory of synaesthesia (see Fig. 7.2) asserts that synaesthesia results from cortical disinhibition, in which functional neural pathways that are normally inhibited in the general population are disinhibited in synaesthetes (Cohen Kadosh and Henik 2007; Grossenbacher and Lovelace 2001). Insofar as neural pathways strengthen with repeated use, disinhibition could also give rise to hyperconnectivity, that is, excess connectivity may be a *consequence* rather than a *cause* of synaesthesia (Cohen Kadosh and Walsh 2008). The finding that synaesthesia can be transiently induced by suggestion further indicates that hyperconnectivity is not *necessary* for the occurrence of synaesthesia because the suggestion is unlikely to produce excess cortical connections so rapidly (Cohen Kadosh et al. 2009). A recent magnetoencephalography study of grapheme-colour synaesthesia found that the activation differences associated with synaesthesia in the posterior temporal lobe (grapheme region) preceded corresponding differences in V4 (colour region) by approximately 5 ms (Brang et al. 2010). This finding has been interpreted as challenging a disinhibition account, but the prior activation of the grapheme region is arguably consistent with feedback disinhibition.

A number of caveats regarding results bearing on the neural basis of synaesthesia are worth mentioning. First, many of the results concern grapheme-colour

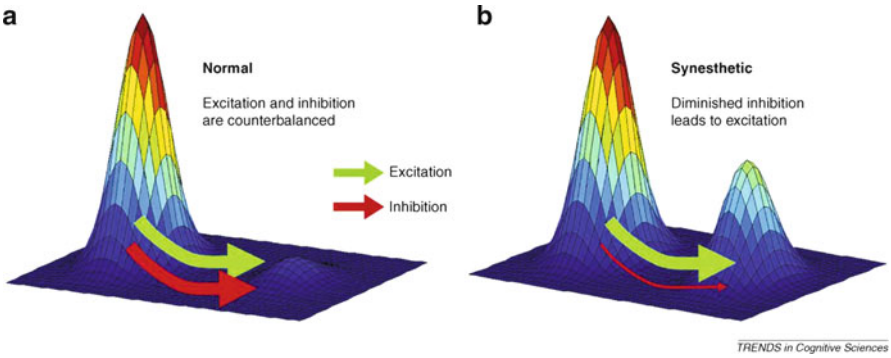

Fig. 7.2 Diagram of a proposed mechanism in the disinhibition model of synaesthesia. (**a**) When levels of excitation (*red*) and inhibition (*green*) are equivalent, crosstalk is disrupted. (**b**) Diminished inhibition from the region processing the inducer gives rise to the activation of the concurrent-selective region (Reprinted from Eagleman and Goodale (2009). With permission from Elsevier)

synaesthesia, and it is unclear whether they generalize to other forms of synaesthesia. As an example, a recent model of mirror-touch synaesthesia does not invoke a parietal binding mechanism but instead asserts parietal involvement in this form of synaesthesia through its modulation of processes supporting bodily representation and disembodiment (Banissy et al. 2009). Second, V4 activations are not always observed across studies, and some studies implicate left-hemisphere parietal regions whereas others observe right-hemisphere effects (see Hubbard 2007). Finally, it is imperative that caution be exerted when assuming that all forms of synaesthesia occur through uniform mechanisms (Cohen Kadosh and Walsh 2008). For instance, within-modality forms may be the product of excess structural connectivity facilitating increased cross-activation, whereas cross-modality forms may be produced more often through disinhibition.

7.5 Conclusions

In the preceding pages, we have reviewed recent research on the characteristics and mechanisms of synaesthesia. It is abundantly clear that considerable knowledge has been gained and theoretical accounts are becoming increasingly sophisticated. However, it is also evident that many questions remain unanswered and many fascinating avenues remain unexplored. We are confident that further investigation of the characteristics and mechanisms of synaesthesia will yield insights into the nature of other anomalous experiences as well as subjective experience itself.

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Chapter 8
Auditory Verbal Hallucinations, First-Person Accounts

Steven Scholtus and Christine Blanke

8.1 What It Is Like to Hear Voices

Steven Scholtus

All the time that I have been hearing voices, altogether some 25 years now, many people have asked me what it is like. It is not as complex as it seems. I hear voices in two different ways: within my head and outside my head. When I hear voices inside my head, it is as if someone is talking to me. There are male and female voices, loud and clear, easily distinguishable from my own thoughts, and sounding very realistic. That is why it is so easy to believe in telepathy. I can communicate with these voices, and they react to my thoughts. It is difficult to ignore them (Fig. 8.1).

Voices outside my head are easier to handle. They sound as if they are coming from a radio, placed somewhere in a high corner of the room. These voices sound very realistic, too, but the distance appears to be larger, which makes them less direct.

I have been hearing voices since 1986. At first I thought I was having a paranormal experience (many people who hear voices develop an interest in the occult). I was convinced that people were watching me, and that they wanted me dead for some reason. I heard voices all day long and developed a psychosis. I did not seek any mental health care, and the psychosis remitted spontaneously after 10 months. The years afterward, I was on the edge of a new psychotic episode, but I managed to finish my education (history) at an academic level. Then the second psychosis hit me, less severe than the first one, and yet it wreaked more havoc. This time I did seek help and was diagnosed with schizophrenia.

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Fig. 8.1 Steven Scholtus

Over the years I have developed various different explanations for the origins of my voices. In the beginning I thought that they stemmed from paranormal sources such as spirits or 'entities'. Later I learned about the neurobiological processes that govern them.

Learning to cope with voices has been a central theme in my life. This was, and still is, a process with ups and downs. An important aspect was learning to accept the presence of the voices. I assume that I will be hearing them all my life. My magic word for coping with them is *distraction*. I just try to continue whatever it is that I was doing before the voices started. I know that I should not listen to them too much, and that I should not let them upset me: no fighting against the voices, nor becoming attached to them, even at times when their messages are quite joyful.

I am convinced that the hearing of voices is a state of mind. I can 'set' my consciousness in a way that makes me very vulnerable to them. When I do so, I am always able to hear them. It is also easier to hear them when I am tired or a bit drowsy. In the early mornings and near the end of the day, when I am usually more drowsy, it costs much more effort not to give in to the hearing of voices. I have two options to avoid that: I can then either try to focus on some activity – such as playing the drums – or, alternatively, try to take a nap. Any intermediate states of mind, in which I am neither awake and focussed nor fully asleep, are the most dangerous to me, as they render me too vulnerable to the voices.

The voices have completely shaken up my life. A normal way of living, with a full-time job, a family, the raising of children, is no longer within my reach. And yet the voices have not only brought me bad things. I have learned who my real friends are, I have learned to really enjoy social contact, and I have met inspiring people. I would rather have been without the voices, but even in their presence I am able to enjoy my life.

8.2 A Delicate Balance

Christine Blanke

I heard a child crying. There was no one around, no parent or grandparent. I went looking for that child. But there was no child. So I went home, where I heard the child crying again. I looked everywhere, I didn't understand. When I went outside a second time, I heard my name called out in a soft and friendly tone. I saw no one who knew me, and again I heard that crying child. I saw no one who could have called out, which frightened me. I started running and kept yelling, 'Blue! Blue!' The crying child and the lady who had called my name were nowhere to be found (Fig. 8.2).

At the time I did not know that it was possible to hear voices or to see things that aren't there. Therefore, those voices represented real people to me. Or perhaps deceased people, I thought, whose spirits might be dwelling between heaven and earth. Perhaps they wanted to protect me, but I was not sure about that. Sometimes I wish that I could go back to that time, when I only heard a crying child and a friendly lady.

I started to work as a trainee. I made friends and took notice of all the injustice in this world. Perhaps for being so busy with other things, I hardly paid any attention to the gentle voices inside my head. Then other people came into my head, conveying evil messages. I also started to see blood in the streets, and arms, legs, and heads that had apparently been chopped off.

Whenever I hear voices I look behind me, mostly to the right. At times the voices have gotten very close to me, becoming massive. At other times they came into my body, and I felt their massiveness within me. I was in their power, but only when they were so close to me.

They will kill me! I look behind me. There is a gentleman walking behind me. I am positive that he is going to kill me. He is putting his hand into his pocket. I am sure that he will be taking out a gun. But no, it's his handkerchief (Fig. 8.3).

They tell me that I am ill. That I have schizophrenia, and what that is all about. When I look behind me, they call me suspicious, which means that I am ill. I do behave like someone who is ill. However, I never took the things they say too seriously. That may be the reason that I manage to live happily with my own reality.

Fig. 8.2 Christine Blanke

Fig. 8.3 *Droedel 53.* Red ink on paper (Copyright 2007 Christine Blanke)

It may be deviant. If I would find my own reality abnormal it would frighten me, and I would have a problem. Whenever I accept my deviant reality, I am fine.

I still hear them, they haven't changed at all. And yet they are not inside my intimate zone in the upper right corner anymore. Why do I care? They are a part of me. Or maybe the voices do belong to real people after all. In the shopping district you can hear the weirdest things, but not everything applies to me. That is what I have had to learn.

Voices are not thoughts! Thoughts have a vibrant quality to them. Rather monotonous. Thoughts may be compulsory too, and they may be in my way, but they are not voices. My voices sound unfamiliar to me. A male voice, a child that I do not know. I don't know any of these voices, and yet they sound like real people. The difference with real people of flesh and blood is that the voices utter only short phrases, using a lot of repetitions. My thoughts are audible inside my head, whereas the voices are audible in my ear.

Pills do help. I am convinced that they do. But when you are not ill, you don't need to take any pills. I have noticed that pills can expand my world, that they allow me to improve the way I make contact with other people. And yet I have always been sure that the pills I took were only a placebo. If you think hard enough that such tasteless candies can make you feel better, they will.

I create the world with my thoughts. I see and make up all kinds of beautiful things. That makes me happy. If the voices go on saying that I will be killed, then that is part of my world. It will not scare me anymore, or make me sad. I ignore them, or make jokes in order to take away the heaviness. Sometimes I can walk the streets full of giggles, because I was to be murdered again, and yet it didn't happen…again.

They think that I will fall.

But I won't.

Balance can be so delicate.

Chapter 9
Auditory Verbal Hallucinations

Kelly M.J. Diederen and Iris E.C. Sommer

9.1 Introduction

In 1971, in a village in the Philippines, a woman was found unconscious and fevered in a field where she had been plucking fruit. The woman later reported, "As I busied myself picking fresh fruit I felt as though a gush of strong wind passed by. Then all of a sudden I heard human voices crying, pleading, and asking not to be shot. Some were cursing. Then there was silence. A few minutes later the voices came again, agonizing groans of men about to die, writhing in pain. I started to run but I could not move my legs. I tried to shout but I couldn't. Then the world started to turn round; I did not know what happened next." According to the villagers, the woman's experiences were caused by spirits called *bahoy,* which haunt places where violent deaths have happened in the past (Jocano 1971).

While auditory verbal hallucinations (AVH) or "voices" are frequently attributed to possession by a spirit in non-Western societies (see also Chap. 18), in modern Western societies they are generally considered an aspect of disease (Al-Issa 1995). This contrasts with earlier Western accounts, in which powerful men were supposedly being guided by gods speaking to them. The Greek philosopher Socrates (470–399 BC), for instance, was reportedly aided by a voice to make important decisions, and in the nineteenth century Joan of Arc (1412–1431), the "Iron Maiden," was declared a Saint by the Catholic Church because she had heard the voice of God telling her how to liberate France from English domination.

AVH can occur in a wide variety of individuals, including patients with a neurological or neurodegenerative disease, patients with a psychiatric disorder, and

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healthy individuals in the general population (Aleman and Larøi 2008; Asaad and Shapiro 1986). Moreover, they can be induced by illicit substances such as cannabis, amphetamines, and cocaine, as well as by prescribed drugs and alcohol (Asaad and Shapiro 1986) – although it should be noted here that substance-induced hallucinations tend to occur most frequently in the visual modality. They have also been reported in association with progressive deafness (Slade and Bentall 1988). But irrespective of the context in which they occur, AVH often co-occur with hallucinations in any of the other sensory modalities, as well as with delusions and formal thought disorder (Asaad and Shapiro 1986; Sommer et al. 2010).

Over time, various different approaches have evolved to study AVH. Thus, a number of studies have investigated the prevalence rates of AVH in different subgroups and in the general population. Other studies have focused on distinguishing different subtypes of AVH, based on specific characteristics such as frequency, intensity, and content. In addition, specific characteristics of AVH have been compared among different groups of individuals to elucidate whether they should be considered phenomenologically similar or not. Finally, various theories have been proposed to account for the mediation of AVH in an etiological and pathophysiological sense. Each of these approaches will be discussed below.

9.2 Patients with a Neurological or Neurodegenerative Disorder

AVH tend to occur in the context of a number of neurological disorders, including epilepsy, brainstem pathology, brain tumors, cerebrovascular infarctions, migraine, and delirium (Asaad and Shapiro 1986; Brasic 1998; Brasic and Perry 1997). They can also occur in the context of neurodegenerative diseases such as Lewy body dementia, Parkinson's disease, and Alzheimer's disease (Bassiony and Lyketsos 2003; Inzelberg et al. 1998; McKeith et al. 1992).

Although various studies investigated the prevalence rates of hallucinations in patients with neurodegenerative disorders, only a handful of them focused exclusively on AVH. For instance, Inzelberg et al. (1998) reported that 37% of a group of patients with Parkinson's disease experienced hallucinations, that 29% of their sample experienced only visual hallucinations, and that 8% experienced visual as well as auditory verbal hallucinations. In agreement with this, Fénelon et al. (2000) showed that hallucinations were present in 39.8% of patients diagnosed with Parkinson's disease, while hallucinations in the auditory modality were experienced by 9.7%. Interestingly, cognitive impairment was more common among the hallucinating patients.

In an early study, Wolff and Curran (1935) found auditory hallucinations to occur in 41.5% of patients diagnosed with Alzheimer's disease. Almost 70 years later, Bassiony and Lyketsos (2003) reviewed all prior studies on Alzheimer's disease, and showed that the prevalence rates ranged from 4% to 76% for all types of hallucinations, and from 1% to 29% for auditory hallucinations. In addition, the authors

reported that hallucinations tended to persist over time, to recur throughout the disease process, and to be associated with negative consequences such as functional impairment and aggression.

From those studies, it can be concluded that although auditory hallucinations are relatively common in Parkinson's and Alzheimer's disease, visual hallucinations tend to occur more frequently in those patient groups. This is in sharp contrast with patients diagnosed with psychiatric disorders, in whom hallucinations of the auditory modality tend to be the most prevalent ones (Baethge et al. 2005).

9.3 Patients with a Psychiatric Disorder

AVH frequently occur in the context of bipolar disorder, major depressive disorder, borderline or schizotypal personality disorder, posttraumatic stress disorder, and dissociative identity disorder (Ross et al. 1990; Siegel 1984; Skaf et al. 2002). However, their prevalence is highest in patients diagnosed with schizophrenia, as defined by the DSM-IV-TR (American Psychiatric Association 2000).

A number of studies have investigated the prevalence rates of auditory hallucinations in psychiatric patients. For instance, the International Pilot Study of Schizophrenia (WHO 1973) recorded AVH in 74% of patients diagnosed with schizophrenia. In agreement with this, Sartorius et al. (1986) reported them to occur in 70% of their cases. However, Slade and Bentall (1988) reported a somewhat lower prevalence rate (60%).

In patients diagnosed with bipolar disorder, the frequency of hallucinations was established in 22.9% in patients with a mixed episode, 11.2% in those with a manic episode, and 10.5% in those with a depressive episode. Among the bipolar group presenting with hallucinations, 56.9% heard voices (Baethge et al. 2005). Among the patients diagnosed with a unipolar mood disorder, 5.9% reported hallucinations, and 40.6% of the latter group AVH (Baethge et al. 2005). Reviewing studies published between 1922 and 2007, Goodwin and Geddes (2007) showed that auditory hallucinations had been recorded in 18% of all patients diagnosed with bipolar disorder. Finally, Kingdon et al. (2010) found that 50% of the patients diagnosed with borderline personality disorder, 66% of those diagnosed with schizophrenia, and 90% of those with both diagnoses experienced auditory hallucinations. Among those, the auditory hallucinations were reported most frequently.

Some studies found sex differences associated with the prevalence rates for hallucinations in psychiatric patients. For instance, Marneros (1984) reported a significantly higher prevalence of auditory hallucinations among women (25%) than among men (15%) diagnosed with schizophrenia. Interestingly, the prevalence rates of hallucinations in their sample are much lower than generally reported (Sartorius et al. 1986; Slade and Bentall 1988; Wing 1974). This might be due to the fact that the authors only included patients who were hospitalized for the first time. Rector and Seeman (1992) showed that while 54% of the male participants in their study experienced auditory hallucinations, 78% of the female patients experienced them.

Cetingok et al. (1990) reported that hallucinations were more frequent among married Turkish women diagnosed with schizophrenia than among unmarried Turkish women, Turkish men, and Americans of either sex. However, another study of the prevalence rates of AVH in individuals diagnosed with schizophrenia did not report any sex differences (Mueser et al. 1990). As regards mood disorders, various studies showed a higher prevalence rate for hallucinations in women than men (Baethge et al. 2005; Bowman and Raymond 1931).

9.4 The General Population

Although AVH are often associated with pathological conditions, they also occur in healthy individuals in the general population (Sidgwick et al. 1894; Sommer et al. 2008a; Tien 1991; Van Os et al. 2000; see also Chap. 28). More than a century ago, Henry Sidgwick (1838–1900) et al. (1894) were the first to study hallucinations in the general population. In their sample of 17,000 individuals who were primarily of British descent, 9.9% claimed having experienced visual, tactile, or auditory hallucinations. AVH were reported by 3.6% of all respondents. Over a century later, Tien (1991) reported that visual, tactile, or auditory hallucinations occurred in 13% of all healthy individuals in the USA. The frequency of AVH varied with age, ranging from 1.5% to 3.2%. Roughly similar rates for AVH were found in New Zealand (3.4%) by Caspi et al. (2005) and in the Netherlands (2–4%) by Escher et al. (2005). A much higher prevalence rate (16%) was reported in a French study by Verdoux et al. (1998), which is in keeping with the findings of Léon Marillier (1862–1901), who collaborated with Sidgwick et al. in the nineteenth-century Census of Hallucinations, and reported a steeping prevalence rate of 20% for hallucinations (visual, auditory, or tactile) among the French (Sidgwick et al. 1894). The reported differences in prevalence rates are probably at least partially due to differences in study design and demographic characteristics of the cohorts under study (Linscott and Van Os 2010; Beavan et al. 2011).

While the prevalence rates of hallucinations are rather similar across population groups in Western countries, there are striking differences to be found among specific subgroups of those populations. For instance, 14% to 71% of college students in the USA report having experienced AVH at least once in their lives (Barrett and Etheridge 1992; Bentall and Slade 1985; Posey and Losch 1983), which is substantially more often than in the general population (Caspi et al. 2005; Escher et al. 2005; Sidgwick et al. 1894; Tien 1991; Verdoux et al. 1998). In concordance with the prevalence rates recorded in individuals with a psychiatric disorder, Young et al. (1986) found that female students had a significantly greater propensity to hallucinate than men. Likewise, in Tien's sample (Tien 1991), women reported more auditory and olfactory hallucinations, whereas visual hallucinations were reported slightly more frequently by men.

Prevalence rates for hallucinations would also seem to depend on ethnic and cultural differences. Jocano (1971), for instance, reported that 13.3% of the

individuals in a village in the Philippines experienced supernatural experiences which to us would qualify as auditory hallucinations. In addition, Johns et al. (2002) found a higher prevalence rate for hallucinatory experiences in subjects of the general Western population as compared to (originally) non-Western individuals living in the UK. Interestingly, subjects belonging to ethnic minorities reported fewer hallucinations when they were born abroad and had migrated later in life, as compared to those who were born in the UK. The exception was a Caribbean subgroup, where hallucinations were reported 2.5-fold more often than by Caucasian respondents.

9.4.1 A Continuum Hypothesis

As AVH can be experienced by psychiatric and neurological patients as well as by healthy individuals in the general population, a number of authors have argued that so-called clinical and nonclinical hallucinations are points on a continuum that do not differ qualitatively from each other (Aleman and Larøi 2008; Linscott and Van Os 2010; Strauss 1969; Van Os et al. 2000, 2009). As a corollary, they assume that AVH in clinical and nonclinical groups result from the same underlying mechanisms, and that the need for treatment depends primarily on the percipients' reaction to them rather than on the presence of AVH themselves. At present, it is insufficiently clear, however, whether AVH in clinical and nonclinical individuals can indeed be considered identical (David 2010; Lawrie et al. 2010; Linscott and Van Os 2010). Comparing the phenomenological characteristics of AVH in different groups may well help to shed light on this matter (David 2010; see also Chap. 23), although it should be borne in mind that this issue is ultimately a matter of conceptualization.

9.5 Phenomenology

A striking aspect of AVH is their variegated nature. While one person may hear a single voice giving friendly advice approximately once per hour, someone else may continuously hear multiple voices gossiping about him. This variable nature of AVH has been recognized for a long time and has led to the conception of numerous subclassifications. Starting from the assumption that phenomenological differences reflect differences in the underlying neurobiological mechanisms, those subclassifications may well be of aid in elucidating the neural underpinnings of AVH (Blom and Sommer 2010). In addition, it may well be that phenomenologically different AVH require different types of treatment. For instance, frequent AVH with a predominantly negative content often call for pharmacotherapeutic interventions, whereas less frequent AVH with a benevolent character may well respond to psychotherapy (see, e.g., Chap. 27 on the Coping-With-Voices Protocol).

9.5.1 Classifications

Although early classification studies generally define subgroups of hallucinations based on observation and clinical experience, contemporary studies predominantly use data-driven approaches to identify independent clusters of AVH characteristics. For instance, Haddock et al. (1999) identified three hallucination factors, comprising emotional characteristics (i.e., distress and negative content), physical characteristics (i.e., frequency, loudness, etc.), and a cognitive interpretation factor (i.e., beliefs about the voices, control, etc.). Stephane et al. (2003) reported two clusters of which the first included components such as control strategies, self attribution and repetitive content, and the second systematized content, high linguistic complexity, and a number of other components. Singh et al. (2003) identified two factors, which they called "reality of hallucinatory perception" and "immersion in the hallucination." Finally, Hayashi et al. (2004) identified four independent factors, consisting of "the intractable nature of the experience" (comprising negative voice content, negative patient responses, and uncontrollability of the voices), "delusional reality distortion," "influence," and "externality" (which was composed of perception of external or internal voices and their origins). Variations among the nature and number of factors identified are striking. They may well result from a number of factors, including the ethnicity of the participants, and the use of dissimilar interview scales (Carter et al. 1995; Chadwick and Birchwood 1994; Haddock et al. 1999). For a detailed overview of the classifications rendered by these studies, see Table 9.1.

9.6 Comparisons

9.6.1 Comparisons 1: Within-Subjects

Multiple studies have compared the characteristics of AVH among different groups of individuals and across different disease states. For instance, Larkin (1979) studied inpatients diagnosed with schizophrenia during the acute phases of their illness and during phases of remission. While during the acute phases, the hallucinatory content was reported to be predominantly threatening and isolating, and during phases of remission, it tended to be supportive directed at social interaction. Moreover, during phases of remission, patients were better able to exert control over their auditory hallucinations. Nayani and David (1996) showed that, over time, psychotic patients are likely to undergo a gradual shift from experiencing their voices in the extracorporeal world to experiencing them inside the head. Meanwhile, the complexity of those hallucinations tends to increase, in the sense of voices being added, dialogues becoming more extensive, and the relation between the experient and his voices becoming more intimate. Interestingly, the patients' levels of distress and their coping skills both improved over time.

Table 9.1 Overview of factor structures for auditory hallucinations

Study	Country	Studied sample	Interview scales	Analysis	Identified factors		
Haddock et al. (1999)	UK	71 Patients (schizophrenia/ schizoaffective disorder)	Psychotic symptom	Principal component analysis	(1) Emotional characteristics	(2) Physical characteristics	(3) Cognitive interpretation
			Rating scales (auditory hallucination subscale)		Distress	Loudness	Disruption
					Negative content	Frequency	Control
						Location	Beliefs about the voices
Stephane et al. (2003)	USA	30 Patients (schizophrenia/ schizoaffective disorder/ psychotic depression)	Semi-structured interview (unnamed)	Hierarchical cluster analysis	(1) Cluster 1	(2) Cluster 2	
					Control strategies	Systematized content	
					Self attribution	High linguistic complexity	
					Repetitive content	Conversation	
					Other hallucinations	Inner space location	
					Clear acoustics	Multiple voices	
					Low linguistic complexity	Attribution of voices to others	
					Words	Nosognosia	
					Outer space location	Episodic occurrence	
						Spontaneous occurrence	
						Linguistic complexity	
						Sentences	

(continued)

Table 9.1 (continued)

Study	Country	Studied sample	Interview scales	Analysis	Identified factors			
Singh et al. (2003)	India	75 Patients (schizophrenia)	Phenomenology of Hallucinations Scale	Principal component analysis	(1) Reality of hallucinatory perception	(2) Immersion in the hallucination		
					Reality (current)	Frequency		
					Reality (past)	Duration		
					Sensory intensity	Overt behavior		
						Control		
						Time		
						Content-affect		
Hayashi et al. (2004)	Japan	214 Patients (schizophrenia/ schizoaffective disorder)	Matsuzawa Assessment Schedule for Auditory Hallucinations	Principal component analysis	(1) Intractability	(2) Delusion	(3) Influence	(4) Externality
					Unpleasant feelings	Generalization of delusion	Ego disturbance	Voices speaking to patient
					Hostility of voices	Conviction	Audible thoughts	Conversation among voices
					Malevolent content	Unusualness of origin	Influence of voices	Outside location of origin
					Distress	Delusional explanation	Preoccupation	Perception through ears
					Recognition of failure coping	Illness	Imperative content	Voices from present figures
					Controllability of voices	Identification of origins		Outside
						Actualness		

9.6.2 Comparisons 2: Different Patient Groups

Lowe (1973) compared the characteristics of hallucinations in patients diagnosed with manic-depressive disorder, schizophrenia, and organic psychosis (i.e., resulting from a known physical disorder) and proposed to use them as discriminatory indicators for differential diagnosis because numerous differences could be found between them. By contrast, Junginger and Frame (1985) compared the AVH in patients diagnosed with schizophrenia and those with an affective disorder, and reported no significant differences at all. Cutting (1987) showed that while AVH occurred in 34% of patients diagnosed with schizophrenia, they occurred in only 18% of those with an organic psychosis. Moreover, unknown voices in the second or third person occurred in 22% of the group diagnosed with schizophrenia and in no more than 4% in the organic-psychosis group. Mitchell and Vierkant (1991) compared hallucinations among cocaine abusers and patients diagnosed with schizophrenia and showed that while command hallucinations were found in both groups, those in the schizophrenia group more frequently involved the harming or killing of others. Gonzalez et al. (2006) compared auditory hallucinations among groups of psychotic patients with persistent and sporadically occurring hallucinations. Pleasurable hallucinations were more frequent in the persistent hallucinators. Finally, Kingdon et al. (2010) observed that patients diagnosed with borderline personality disorder scored higher on the negative content of the voices and distress associated with them than patients diagnosed with schizophrenia (see also Chap. 10).

9.6.3 Comparisons 3: Psychiatric Patients and Healthy Individuals

The first study comparing AVH in psychotic and nonpsychotic voice hearers (Leudar et al. 1997) focused on pragmatic properties of AVH, such as the familiarity of the voices, the type of action demanded by those voices, and the degree of dialogical engagement of voices and voice hearers. Honig et al. (1998) reported that the form of hallucinatory experiences was not significantly different among patients diagnosed with schizophrenia or dissociative identity disorder on the one hand and healthy voice hearers on the other. However, in contrast to the patient groups, healthy voice hearers perceived their voices as predominantly positive: They were not alarmed or upset by their voices and felt in control of the experience. Daalman et al. (2011) studied the phenomenological characteristics of AVH in a substantial sample of psychotic and nonpsychotic individuals. Differences between the groups included the emotional valence of their content, the frequency of AVH, and the control subjects experienced over their AVH. An additional difference was that the onset of AVH tended to be at a younger age in the healthy subjects, which might well be due to a – as yet unknown – difference in the underlying mechanisms of origin. Other characteristics of the AVH, such as experienced location and loudness, perceived

reality, the number of voices, and personification (i.e., attribution to one or more actual persons), were similar in both groups.

9.6.4 Comparisons 4: Differences in Cultural and Ethnical Background

Other variables which may influence the characteristics of hallucinations are the individuals' cultural or ethnical background. For instance, Kent and Wahass (1996) found that while AVH tended to have religious and superstitious connotations in patients from Saudi Arabia, verbal instructions and a running commentary were more common in patients from the UK. The frequency and loudness of the AVH did not differ among the groups. Gecici et al. (2010) observed that auditory hallucinations were more frequent in patients diagnosed with schizophrenia from central Turkey than in those from western Turkey. In addition, voices ordering, conversing, commenting, and threatening, as well as voices from prophets and goblins, were more frequent in the group from central Turkey. To disentangle cultural and racial influences, Suhail and Cochrane (2002) compared Pakistani patients living in their home country with a sample of Pakistani immigrants in the UK, as well as to Caucasian patients of British origin. The patients living in Pakistan reported visual hallucinations of spirits or ghosts significantly more often than the two groups living in the UK. Moreover, auditory hallucinations were significantly less frequent in the Pakistan-dwelling group as compared to the other two groups.

9.7 Theoretical Frameworks

Yet another approach involves hypothesis-based studies of the theoretical frameworks proposed to account for them. Although numerous theories have been proposed (Aleman and Larøi 2008), most studies focus on either of four models.

The most influential model proposes that AVH are due to a failure to recognize self-generated inner speech, which entails the false belief that they stem from an external agent (Frith 1991; Frith and Done 1989). In support of this theory, patients diagnosed with schizophrenia were shown to have difficulties in identifying their own actions and thoughts, and to commonly misattribute self-generated behavior to an external source (Waters et al. 2010, see also Chap. 26). Further support comes from observed abnormalities in brain regions implicated in self-processing (Allen et al. 2007b). However, the tendency to misidentify inner speech appears to be related to positive symptoms in general rather than to AVH per se (Allen et al. 2007a).

A second model suggests that AVH may well result from aberrant activation of the primary auditory cortex (Lennox et al. 1999). Support for this hypothesis comes from a number of neuroimaging studies that show activation of the primary auditory cortex during the experience of AVH (Dierks et al. 1999; Jardri et al. 2010).

In addition, the perception of external verbal stimuli was shown to compete for the same neural resources as AVH (Dierks et al. 1999; Hubl et al. 2007; Jardri et al. 2010). In support of this hypothesis, Hunter et al. (2006) found increased spontaneous activity (i.e., in the absence of specific external stimulation) in the auditory cortex of healthy individuals.

A third model proposes that AVH result from the spontaneous recollection of memories, leading to the auditory reexperience of previously encoded information (Copolov et al. 2003; Waters et al. 2006). This hypothesis offers an explanation for the strong association between trauma and AVH (Read et al. 2005). Support for it comes from studies reporting the (de)activation in the hippocampus and parahippocampal gyri (involved in memory processes) during and preceding the onset of AVH (Copolov et al. 2003; Diederen et al. 2010; Hoffman et al. 2008; Silbersweig et al. 1995).

Finally, AVH have been hypothesized to result from the release of language activity in the right hemisphere, which is normally inhibited in the healthy brain (Sommer and Diederen 2009). Support for this theory comes from studies on language lateralization, which consistently show a decreased language lateralization in patients diagnosed with schizophrenia (Li et al. 2009; Sommer et al. 2001) and other psychiatric patients experiencing AVH (Sommer et al. 2007). In addition, neuroimaging studies investigating brain activity during AVH in patients with psychosis showed activation of the right homologues of the language areas (Diederen et al. 2010; Jardri et al. 2010; Sommer et al. 2008b).

Thus, at present, empirical support for all four models is present yet limited. Most likely not one but several, and perhaps all of the proposed mechanisms, play a role in their mediation.

9.8 To Conclude

This chapter provides an overview of the phenomenological characteristics and prevalence rates of AVH, and of the neurobiological mechanisms possibly underlying them. Studies of the prevalence rates of AVH show rather consistent results in healthy individuals as well as in individuals with psychiatric or neurological disorders. In contrast, investigations into the phenomenology of AVH yield highly heterogeneous results. This variability can perhaps be partially explained by the use of dissimilar interview scales and differences in the groups of participants under study. As a corollary, future studies may well benefit from the use of standardized methodologies. In addition, efforts to divide AVH into different types have not proved helpful, if only because the studies at hand have yielded different subclassifications. Investigations into the phenomenology of AVH may well benefit from focusing on specific symptoms rather than symptom clusters. Finally, hypothesis-based studies have shown that dysfunctions in a number of cognitive domains, including language, memory, self-monitoring, and auditory perception, are involved in the mediation of AVH. However, it is as yet unclear how dysfunctions in these domains

interact with each other, and how they contribute to the mediation of AVH. Therefore, a major challenge for future studies lies in integrating phenomenological and cognitive factors associated with AVH in order to obtain a more comprehensive understanding of their origin and expression.

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Chapter 10
Auditory Verbal Hallucinations in Patients with Borderline Personality Disorder

Christina W. Slotema and David G. Kingdon

10.1 Introduction

In 1938, the expression 'borderline' was coined to designate the overlap area of neurotic and psychotic symptoms (Stern 1938). The term is somewhat confusing and unsatisfactory – if only because patients diagnosed with schizophrenia or affective disorder can also experience symptoms belonging to this nosological twilight zone – but for the sake of clarity we will stick to the established term 'borderline personality disorder' (BPD) in this chapter. In contrast to the name, the concomitant concept does have significant clinical utility, being operationalized in terms of a combination of affective dysregulation, impulsive-behavorial dyscontrol, cognitive-perceptual symptoms (including suspiciousness, referential thinking, paranoid ideation, illusions, derealization, depersonalization, and 'hallucination-like symptoms'), as well as persistent personal invalidation (Skodol et al. 2002).

Since the 1940s, transient psychotic episodes are recognized as possible manifestations of BPD (Hoch and Polatin 1949), and during the 1980s, they were added to the diagnostic criteria for BPD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, APA 1987). Nevertheless, the current DSM criteria for BPD (DSM-IV-TR, APA 2000) fail to include auditory verbal hallucinations (AVH) and other types of hallucination, even though two studies (with admittedly small sample sizes) demonstrated their occurrence in 21% and 54% of the cases, respectively (George and Soloff 1986; Chopra and Beatson 1986). Moreover, clinical experience indicates that in these patients, the occurrence of AVH can result in suicidal or self-injurious behaviour due to their imperative nature or the burden they cause.

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Only few studies have systematically assessed the phenomenology and severity of AVH and other psychotic features occurring in the context of BPD. The reason for this is unclear, although it should be noted that the execution of such studies is complicated by the fact that a substantial number of patients diagnosed with BPD have a comorbid axis-I disorder associated with an increased risk for psychosis (i.e. mood disorder in 97% of the cases, and substance abuse in 62%; see Zanarini et al. 2004). Moreover, the interpretation of the results of earlier studies tends to be hampered by the use of such terms as 'psychotic' and 'psychotic-like' to designate cognitive rather than perceptual symptoms in patients diagnosed with BPD (Zanarini et al. 1990).

As the diagnostic criteria of BPD fail to account for the occurrence of longer-lasting hallucinations, clinicians and researchers often find themselves struggling for words when confronted with AVH experienced by patients thus diagnosed. Because of the contradiction in terms of a borderline patient experiencing AVH, those hallucinations tend to be explained in four different ways. First, they are conceptualized as 'pseudohallucinations'. The term as well as the concept were originally introduced by Friedrich Hagen (1814–1888) (Hagen 1868), and elaborated further by Victor Kandinsky (1849–1889) (Kandinsky 1885) and many others, which eventually resulted in an impressive number of terms and connotations (for an overview see Blom 2010) that all differ somewhat from Hagen's original version. As a result, true consensus is lacking, although there is some agreement that pseudohallucinations might be perceptions that are experienced inside the head, with preserved insight into their nature (Van der Zwaard and Polak 1999). This is consistent with a number of publications in which psychotic features occurring in the context of BPD are described as transient, affecting no more than one or two areas of life (such as work and family), atypical (possibly reality-based or totally fantastic in content) or not genuinely psychotic (Soloff 1979; Zanarini et al. 1990; Skodol et al. 2002), and in which they are described in terms of 'quasipsychotic thought' or 'hallucination-like symptoms'. Secondly, AVH experienced by patients diagnosed with BPD may be considered quite similar to those occurring in individuals without a psychiatric or neurological diagnosis. Daalman et al. (2011) compared the characteristics and ensuing distress of AVH experienced by individuals without a diagnosis with those in patients with a psychotic disorder, and found differences in the frequency of AVH and the emotional valence of their content, with higher scores for the patients diagnosed with a psychotic disorder. In addition, control over the voices was found to be higher in individuals without a diagnosis. In the third place, AVH occurring in the context of BPD are considered to lie on a continuum with those experienced by individuals without a diagnosis or diagnosed with schizophrenia, with the BPD group holding some sort of middle ground. And fourth, AVH are conceptualized as occurring across different psychiatric disorders, including BPD. So far, it is unknown whether the voices experienced by patients diagnosed with BPD comply with any of those explanations. We are aware of only two studies that investigated the phenomenology and ensuing distress of AVH in the context of BPD (Kingdon et al. 2010; Slotema et al. submitted). In this chapter, we present the results of those two studies, and discuss the consequences of their findings for the diagnosis and treatment of BPD patients.

10.2 Methods and Results

10.2.1 Methods

Details of the two studies are described in Kingdon et al. (2010) and Slotema et al. (submitted). Participants were included when they experienced AVH, and were diagnosed with BPD or schizophrenia. The Kingdon study added a third diagnostic group, consisting of patients diagnosed with BPD *and* schizophrenia, whereas the Slotema study also included patients with a schizoaffective disorder in the schizophrenia group. The Slotema study was matched for age and gender, and included only female patients. In both studies, the phenomenological characteristics of AVH and the ensuing distress were quantified on a five-point scale with the aid of the AVH-related items of the Psychotic Symptom Rating Scales (PSYRATS, Haddock et al. 1999). In the Slotema study, four additional questions were asked:

1. Do the voices comment on the thoughts and behaviour of the patient?
2. Does the patient experience thoughts being heard out loud?
3. Do the voices converse with other hallucinated voices?
4. Do the voices have an imperative character?

The Kingdon study used three additional questionnaires, i.e. the Beck Depression Inventory II (BDI, Beck et al. 1996), the Beck Anxiety Inventory (BAI, Beck et al. 1988), and the Childhood Trauma Questionnaire (CTQ, Bernstein 1998).

10.2.2 Results

Forty-eight patients diagnosed with BPD, 86 with schizophrenia or schizoaffective disorder, and 17 with BPD *and* schizophrenia were included in the two studies. Their demographic data are presented in Table 10.1.

The patients diagnosed with BPD experienced AVH for a mean duration of 17 years, the majority of them in a frequency of at least once per hour, and with a duration of various minutes or more per episode. More than half of them believed that the AVH originated from an internal source, and experienced them accordingly inside the head. The content of the voices was negative in the majority of the cases, the ensuing distress and disruption of life were high, and control over the voices was low. The mean scores on the items *frequency*, *duration*, *negative content*, and *controllability* are presented in Fig. 10.1.

No significant differences among the three groups of patients were found regarding the mean length of time during which AVH had been experienced, the frequency, duration, loudness, and perceived location of AVH (i.e. whether they were experienced inside or outside the head) or their perceived source (i.e. whether they were believed to originate from an internal or an external source). No significant group differences were found for their controllability (which, incidentally, tended to be low).

Table 10.1 Demographic information

	BPD	Schizophrenia	Both	*p* value
Kingdon et al. (2010)				
AVH present, *n* (%)	15 (46)	35 (59)	17 (90)	0.002
Age, mean (Sd)	32.9 (10.0)	40.2 (10.7)	32.5 (10.4)	0.002
Gender, female, *n* (%)	30 (91)	19 (32)	14 (74)	<0.001
n, % outpatients	21 (67)	16 (27)	12 (63)	<0.001
Slotema et al. (submitted)				
Schizoaffective disorder, *n* (%)	0	15 (29)		
AVH present, *n* (%)	33 (100)	51 (100)	–	ns
Age, mean (Sd)	33 (10.4)	37 (9.8)	–	ns
Gender, female, *n* (%)	33 (100)	51 (100)	–	ns
n, % outpatients	33 (100)	25 (93)	–	ns

BPD borderline personality disorder, *n* number of patients, *ns* not significant, *sd* standard deviation

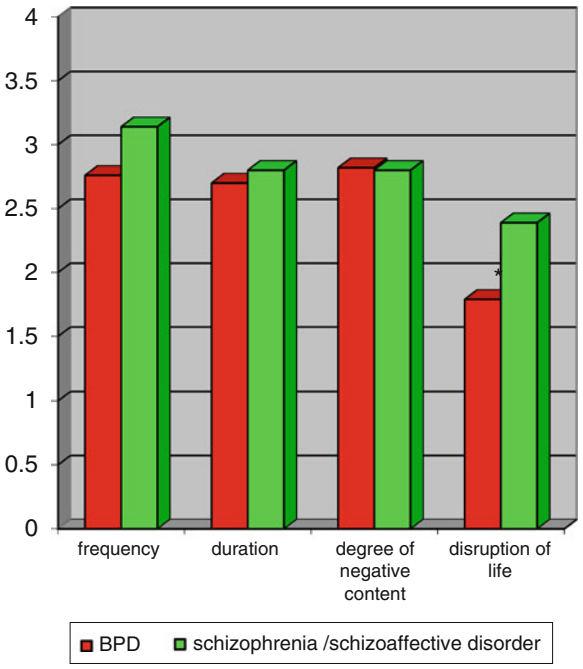

Fig. 10.1 Mean scores on the auditory-verbal-hallucinations-related items of the Psychotic Symptom Rating Scales (Adapted from Slotema et al. submitted)

The only differences were higher scores on the items *negative content* and *ensuing distress* for the BPD group in the Kingdon study, and a higher score on the item *disruption of life* for the schizophrenia group in the Slotema study. No differences were found in the proportion of patients experiencing AVH-related Schneiderian criteria (i.e. voices commenting on the thoughts and behaviour of the patient, thoughts being heard out loud, and voices conversing with other hallucinated voices) or in the proportion of patients experiencing voices with an imperative character.

In addition, the BPD group showed higher scores for depression and anxiety. Severe emotional abuse and severe sexual abuse were significantly more frequent in patients diagnosed with BPD. Logistic regression using the CTQ category found emotional abuse to be the key predictor of allocation-to-diagnostic-group, with sexual abuse only adding marginally to the variance.

10.3 Discussion

In this chapter, we present the first two studies in which the phenomenology of auditory verbal hallucinations (AVH), as well as the distress they may yield, were systematically investigated in patients diagnosed with borderline personality disorder (BPD). The results were compared with those in patients diagnosed with schizophrenia and schizoaffective disorder. In summary, the two studies failed to find any significant differences in the frequency, duration, perceived location, and loudness of AVH, or in the beliefs about their source. Patients diagnosed with BPD had a long history of experiencing AVH. The ensuing burden was high, and did not differ from that in the other diagnostic groups, except for the items 'distress' and 'negative content' (which were higher in the BPD group as found by Kingdon et al. (2010)), and a higher score for 'disruption of life' in the schizophrenia group as found by Slotema et al. (submitted). Severe emotional abuse and severe sexual abuse were reported significantly more often by patients diagnosed with BPD. In conclusion, the phenomenological characteristics of AVH and the ensuing distress in patients diagnosed with BPD do not differ from those in patients diagnosed with schizophrenia, as indicated foremost by the high frequency and long duration of AVH in both groups.

An interesting question might be whether these results can be explained by assuming that the patients diagnosed with BPD should in fact also have been diagnosed with schizophrenia. However, this possibility was ruled out by the strict inclusion criteria and the use of standardized interviews by trained psychiatrists. Evidence of the contrary was also found in the long histories of experiencing AVH in the BPD group. After so many years, it would be highly unlikely if those individuals would go on to develop schizophrenia after all.

Our results imply that the AVH experienced by patients diagnosed with BPD and by those with schizophrenia show many similarities, and only few differences. Therefore, we argue that terms such as 'pseudohallucination' and 'hallucination-like symptom' fail to do justice to the hearing of voices in the context of BPD. Using those terms – or terms of similar meaning – brings the risk of repudiating the AVH experienced by those patients, and of undertreating them, whereas our own two studies indicate that they fulfil all the criteria of hallucinations proper, and therefore deserve to be named and treated as such.

Although a direct comparison has never been performed, AVH occurring in the context of BPD appear to differ from those in individuals without a diagnosis, in the sense that the latter have lower scores on the items 'frequency' and 'duration', as well as on the scores indicating 'burden', as compared to patients diagnosed with a psychotic disorder (Daalman et al. 2011).

Another important question is whether our current diagnostic criteria for BPD and schizophrenia constitute an accurate reflection of clinical reality (Blom and Van Praag in press). Perhaps BPD and schizophrenia should be conceptualized as continuous disorders with a broad variety of clinical presentations, with 'pure schizophrenia' lying on one end of the spectrum, and 'pure BPD' on the other. The group diagnosed with schizophrenia as well as BPD is particularly challenging in clinical and scientific terms, but is usually excluded from treatment trials (Turkington et al. 2006). However, while our studies indicate that AVH occurring in the context of BPD or in the context of schizophrenia are quite similar, we would rather conceptualize AVH as nonspecific for any particular kind of psychiatric disorder, thus endorsing previous studies that have consistently demonstrated that hallucinations are found across different psychiatric disorders without having any diagnostically predictive value (Pierre 2010; Mott et al. 1965; Goodwin et al. 1971; Nayani and David 1996; Copolov et al. 2004).

As our results indicate that patients diagnosed with BPD can suffer from genuine AVH, it is important to consider all treatment strategies for this indication. Unfortunately, studies reporting on the treatment of AVH in patients diagnosed with BPD are rare. Those reporting on the effects of antipsychotic agents, and especially those using questionnaires to quantify those effects, are virtually nonexistent. Cognitive-behavioural therapy for psychotic symptoms (Kingdon and Turkington 2005, see also Chaps. 27 and 28) is used at a modest scale for patients diagnosed with BPD, but needs to be assessed alongside other psychological interventions such as dialectical behaviour therapy.

Our advice is that more attention be given to the occurrence of genuine AVH in borderline patients, as well as to the burden they may cause. In every patient diagnosed with BPD, therefore, caregivers should explore whether any AVH are experienced. Secondly, we argue that more research is needed to assess the prevalence of AVH and other psychotic symptoms in larger patient samples. Further research should preferentially focus on the phenomenological characteristics of other psychotic phenomena occurring in the context of BPD, and on the distress they may cause. In the third place, it would be interesting to learn whether the symptoms occurring in the contexts of BPD and psychotic disorders, which show so many similarities at a phenomenological level, also share a similar neurophysiology. But most importantly, the use of antipsychotic agents and psychotherapy should be explored in randomized controlled trials with questionnaires assessing their effects on the severity of psychotic features.

10.4 Conclusion

The phenomenological characteristics of auditory verbal hallucinations (AVH) do not differ significantly among patients diagnosed with borderline personality disorder (BPD) and those with schizophrenia. Both groups tend to have long histories of experiencing AVH, and to experience high levels of distress due to the voices they hear.

Therefore, in the treatment of BPD, more attention should be paid to AVH. This implies that those AVH should not be given a different name, as this may lead to misdiagnosis and consequently to insufficient medical care. Antipsychotic agents and cognitive behavioural therapy may well be proper treatment options, although this has not yet been properly investigated. More studies are needed to investigate other psychotic features that may occur in the context of BPD, and to assess the neurophysiological basis and therapeutic options for AVH.

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Chapter 11
Musical Hallucinations

Oliver W. Sacks and Jan Dirk Blom

11.1 Introduction

In 1846, the French alienist Jules Baillarger (1806–1891) published the first known medical account of musical hallucinations (Baillarger 1846). Since then no more than 150 studies on the subject have been published in the international literature, most of them involving case reports. Although the past century saw ten large epidemiological surveys of hallucinations in the general population, yielding prevalence rates for auditory hallucinations of around 4% (for an overview see Blom 2012), none of them discriminated between various types of auditory hallucination. As a consequence, it is not possible to extract any prevalence figures for musical hallucinations from them (Cole et al. 2002). This state of affairs would seem to reflect – and perhaps also sustain – the long-held opinion that musical hallucinations are rare, and for the most part irrelevant from a clinical point of view (Fig. 11.1).

And yet, working over the past 50 years with elderly patients living in hospitals and nursing homes, and in neurology clinics for patients with migraine, epilepsy, movement disorders, sleep disorders, and other conditions, I have been given many accounts of musical hallucinations from my patients (*the first person in this chapter will refer to one of the authors, O.S.*). After 1985, when I published case histories of two such patients in my book *The Man Who Mistook His Wife For A Hat*, (Sacks 1985) many readers wrote to me about their own musical hallucinations. I have thus had contact, in person or via correspondence, with hundreds of patients with musical hallucinations, and certain trends emerge from their accounts.

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Fig. 11.1 *Musical hallucinations II* (Artwork by Marten Blom, copyright 2011)

11.2 Phenomenological Characteristics

Although there is a wide range in the quality of individual musical hallucinations – sometimes they are soft, sometimes disturbingly loud; sometimes simple, sometimes complex – there are certain characteristics common to all of them. First and foremost, they are perceptual in quality and seem to emanate from an external source – in this way, they are distinct from all forms of imagery (even "earworms," the often annoying, repetitious musical imagery which most of us are prone to from time to time; see Sacks 2006). People with musical hallucinations will often search for an external source – a radio, a neighbor's television, and a band in the street – and only when they fail to find any such external source do they realize that the source must be in themselves. Thus they may speak of a tape recorder, a jukebox, or an iPod in the brain, something autonomous with a will of its own, something not felt to be a controllable, integral part of the self. That there should be something like this in one's head arouses bewilderment and, not infrequently, fear. The fear is that one is going mad, or perhaps that the phantom music may be a sign of a tumor, a stroke, or a dementia. Such fears often inhibit people from acknowledging that they have hallucinations; perhaps this is the reason why musical hallucinations have long been considered rare – although it is now realized that this is far from the case. It may require direct but gentle and discreet questioning to elicit the fact that hallucinations are occurring, and it may afford immense relief to patients (even if their hallucinations cannot be cured) to be assured, after careful questioning and examination and testing if appropriate, that there is no evidence of mental illness or progressive cerebral pathology.

Hallucinations share the subjective character (and much of the physiological character too) of perception, and they can intrude upon and even overwhelm perception; musical hallucinations (like tinnitus) can be so loud as to make it impossible to hear someone speak; imagery never rivals perception in this way.

Musical hallucinations usually appear suddenly, out of the blue; but sometimes, they may follow a tinnitus or an external noise (like the drone of a plane engine or a lawn mower), the hearing of real music, or verbal or other associations to a particular piece of music. Some people with musical hallucinations experience them virtually nonstop, while others hallucinate only intermittently. The hallucinated music is mostly familiar (though not always liked; thus, one of my patients hallucinated Nazi songs from his youth, which terrified him). It may be vocal or instrumental, classical or popular, but in almost all cases, it is music which was heard in the patient's early years such as children's songs, folk songs, hymns, arias, and advertising tunes (Warner and Aziz 2005; Sacks 2007; Coebergh et al. 2009). Very occasionally, patients may hear "meaningless phrases and patterns," as one of my correspondents, a gifted musician, put it.

Hallucinated music can be very detailed, so that every note in a piece, every instrument in an orchestra, is distinctly "heard." Such detail and accuracy may be astonishing, no least to the hallucinator, who may be relatively "unmusical" and scarcely able, normally, to hold a simple tune in his head, let alone an elaborate chorale or instrumental composition. Typically though, only a few bars, a segment, or a single theme is hallucinated – which may then be repeated, as with a stuck record, again and again. One patient of mine heard part of *O Come, All Ye Faithful* nineteen and a half times in 10 min (her husband timed this) and was tormented by never hearing the entire hymn. Hallucinatory music can wax slowly in intensity, and then slowly wane, but it may also come on suddenly full blast in midbar and then stop with equal suddenness (like a switch turned on and off, patients often comment).

Musical hallucinations may continue in their own way, irrespective of whether one attends to them consciously. Some patients may sing along with them; others ignore them – it makes no difference. And having their own autonomous mechanism, musical hallucinations can continue, pursue their own course, even if one is listening to or playing something else. Thus, Gordon B., an Australian violinist described in *Musicophilia* (Sacks 2007), sometimes hallucinates a piece of music while he is actually performing an entirely different piece at a concert.

The natural history of musical hallucination is usually one of spreading. A familiar tune, an old song, may start the process; this is likely to be joined, over the ensuing weeks, by another song, and then another, until a whole repertoire of hallucinatory music has been built up. And this repertoire itself tends to change – one tune will drop out, another will replace it. There is usually very little conscious control of musical hallucinations. One cannot voluntarily start or stop the hallucinations coming, though some people may be able, on occasion, to replace them with other hallucinated music. Thus one man who said he had "an intracranial jukebox" found that he could switch at will from one "record" to another, provided there was some similarity of style or rhythm, though he could not turn on or turn off the "jukebox" as a whole.

The assumption that musical hallucinations are rare is no longer tenable (Evers and Ellger 2004). Although they still seem to be rare in children, one boy I have seen, Michael, has had them since the age of 5 or 6. His music is nonstop and overwhelming, and often prevents him from focusing on anything else.

11.3 Classification and Differential Diagnosis

Musical hallucinations are conceptualized as auditory hallucinations characterized by songs, tunes, melodies, harmonics, rhythms, and/or timbres (Berrios 1990; Blom 2010). They can be perceived either unilaterally or bilaterally, and within the head or as if coming from the environment. Whether they should be classified as verbal or nonverbal auditory hallucinations depends on the presence or absence of any vocal elements. When they occur in the absence of any associated pathology other than hearing impairment, they are called idiopathic musical hallucinations (Pasquini and Cole 1997). When occurring in the presence of such pathology, they are called symptomatic musical hallucinations. Table 11.1 lists these types of musical hallucination, as well as various phenomena from which they should be distinguished.

Musical hallucinations should be distinguished, for example, from music "heard in" the background noise of engines, refrigerators, computer ventilators, and so on, a phenomenon known as auditory illusion or auditory pareidolia. The term musical palinacusis is reserved for the continued perception – or reperception – of music after some actual piece of music has stopped. A final phenomenon from which they should be distinguished is musical tinnitus (Vernon and Sanders 2001). Although the two may be indistinguishable in clinical practice, the latter term refers to musical

Table 11.1 Glossary of musical hallucinations and related phenomena (Adapted from Blom 2010)

Phenomenon	Characterization
Musical hallucination (musical hallucinosis, musical ear syndrome, auditory Charles Bonnet syndrome, Oliver Sacks' syndrome)	An auditory hallucination characterized by songs, tunes, melodies, harmonics, rhythms, and/or timbres
Idiopathic musical hallucination	A musical hallucination occurring in the absence of any type of associated pathology other than hearing loss
Symptomatic musical hallucination	A musical hallucination occurring in the presence of any type of associated pathology other than hearing loss
Auditory illusion (auditory pareidolia)	An auditory percept resulting from a misrepresentation or misinterpretation of random auditory stimuli, which may or may not have a musical quality
Musical illusion	A paradoxical auditory illusion created with the aid of actual musical sounds
Musical tinnitus	A musical hallucination with evolution from "ringing in the ears"
Musical palinacusis	The continued perception or reperception of an actual piece of music
Musical imagery	An imagined or remembered piece of music, having no perceptual characteristics
Earworm	A tune going round in the head, having no perceptual characteristics

hallucinations which evolved out of tinnitus or "ringing in the ears." The music experienced by Gordon B., who had suffered for more than 20 years from a tonal type of tinnitus before it changed into "the most horrific grinding," and then, a few weeks later, into a nonstop flow of musical phrases and patterns, constitutes an apt example of musical tinnitus.

11.4 Pathophysiology

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that musical hallucination, like actual musical perception, is associated with the activation of an extensive network involving many areas of the brain – auditory areas, motor cortex, visual areas, basal ganglia, brainstem, pons, tegmentum, cerebellum, hippocampi, amygdala, and, according to some, even the peripheral auditory system (Gordon 1999). Apparently, any of those regions – and probably many additional ones – are capable of mediating musical hallucinations (Stewart et al. 2006). The factors responsible for this would seem to be even more diverse. The musical network can be stimulated directly, on occasion, as by an irritable focus as in temporal lobe epilepsy, but what seems to occur in most cases of musical hallucination is a "release" of activity in the musical network when inhibition or constraints which are normally operative are weakened (Keshavan et al. 1992). The commonest cause of such a release is auditory deprivation or deafness. In this way, the musical hallucinations of the elderly deaf are analogous to the visual hallucinations of the blind (Charles Bonnet syndrome (CBS), see also Chap. 6). In both cases, it is as if the networks normally employed in musical or visual perception escape into a spontaneous and autonomous activity of their own if there is no longer adequate perception to constrain them. We therefore speak of such hallucinations as "release hallucinations."

But although the musical hallucinations of deafness and CBS hallucinations may be akin physiologically, they have striking differences phenomenologically, which reflect the very different nature of our visual worlds and our musical worlds – differences evident in the ways we perceive, recollect, or imagine them. We are not given an already-made, preassembled visual world; we have to construct our (own) visual world as best we can. This construction entails analysis and synthesis at many functional levels in the brain, starting with orientation receptors, perception of lines and angles and orientation, in the occipital cortex (see Chap. 2). At higher levels, in the inferotemporal cortex, the "elements" of visual perception are of a more complex sort, appropriate for the putting together and recognition of natural scenes, objects, animal and plant forms, and faces. But all of these visual objects have to be broken down and reassembled, whereas music is already made and assembled for us.

Visual hallucinations of the CBS type commonly include faces, but typically they are not familiar or recognizable. They may sometimes be deformed or

grotesque, with exaggerated eyes or teeth. The hallucinations of CBS often contain elements that change kaleidoscopically; they have the quality of bric-a-brac, of bits of images, continually taken apart and reassembled, by the early visual system, unconnected with the hippocampi or amygdala, unconnected to memory, intention, or emotion.

Musical hallucinations are quite different. With music, although there are separate functional systems for perceiving pitch, timbre, rhythm, etc., the musical networks of the brain work as a whole, and a piece of music cannot be significantly altered (in melodic contour or tempo or rhythm) without losing its musical identity – without, indeed, its ceasing to be music. We apprehend a piece of music as a whole. Whatever the initial process of musical perception and memory may be, once a piece of music is known, it is retained not as an assemblage of elements, but as a completed procedure or performance; music is performed by the mind/brain, whenever it is recollected; and this is also so when it surfaces spontaneously, as a hallucination.

Table 11.2 provides a list of risk factors for the mediation of musical hallucinations extracted from the literature. It should be noted, however, that some of those risk factors have been corroborated more thoroughly than others. Hearing impairment, tinnitus, and advanced age appear to be the most robust risk factors presently known. Female sex, on the other hand, may well be a spurious finding due to a historical underrepresentation of male hallucinators. Cerebral pathology in all its many forms is associated with an increased risk for musical hallucinosis, although here it should be noted that – the other way round – the prevalence of musical hallucinations among such cases is remarkably low, especially if we consider the vastness of the brain networks involved and the a priori chance of damage to those networks in the case of cerebral pathology.

Table 11.2 also features a number of psychiatric disorders. As suggested by some authors, musical hallucinations may well be more prevalent in the context of psychosis (Baba and Hamada 1999) or other psychiatric conditions (Hermesh et al. 2004). In fact, the literature boasts more than 30 such cases (Evers 2006). However, given the relatively high prevalence of those disorders it is as yet unclear whether the occurrence of musical hallucinations in the context of psychiatric disease is any higher than in the general population (Evers and Ellger 2004; Tuerlings et al. 2009). Our own clinical experience speaks against the assumption that psychosis predisposes to musical hallucinations, as does the largest study to date carried out among psychiatric patients. That study identified 5 individuals out of 128 (3.9%) as being familiar with musical hallucinations (Schakenraad et al. 2006), 3 of them being of advanced age and only 1 of them being diagnosed with a psychotic disorder. Finally, Table 11.2 features a number of drugs and illicit substances reportedly associated with musical hallucinations, as well as a group of miscellaneous issues, ranging from sensory deprivation, Hashimoto's encephalopathy, and cochlear implantation to electroconvulsive treatment, Lyme disease, and Behçet's disease, which are all in need of further investigation (Fig. 11.2).

Table 11.2 Risk factors for musical hallucinations, as derived from the literature

Hearing impairment
Tinnitus
Older age
Female sex (possibly)
Cerebral pathology
Epilepsy
Brain tumor
Stroke
Hemorrhage
Meningitis
Alzheimer's disease
Neurosyphilis
Localized atrophy
Traumatic lesion
Psychiatric disorder
Schizophrenia spectrum disorder
Bipolar disorder
Psychotic depression
Depression
Obsessive-compulsive disorder
Adaptation impairment
Personality disorder
ADHD
Cocaine dependence
Intoxication
Alcohol
Antidepressants
Opioids
Antibiotics
Beta-blockers
Quinine
Salicylates
Miscellaneous
Behçet's disease
Hashimoto's encephalopathy
Lyme disease
Electroconvulsive treatment
Cochlear implantation
Sensory deprivation

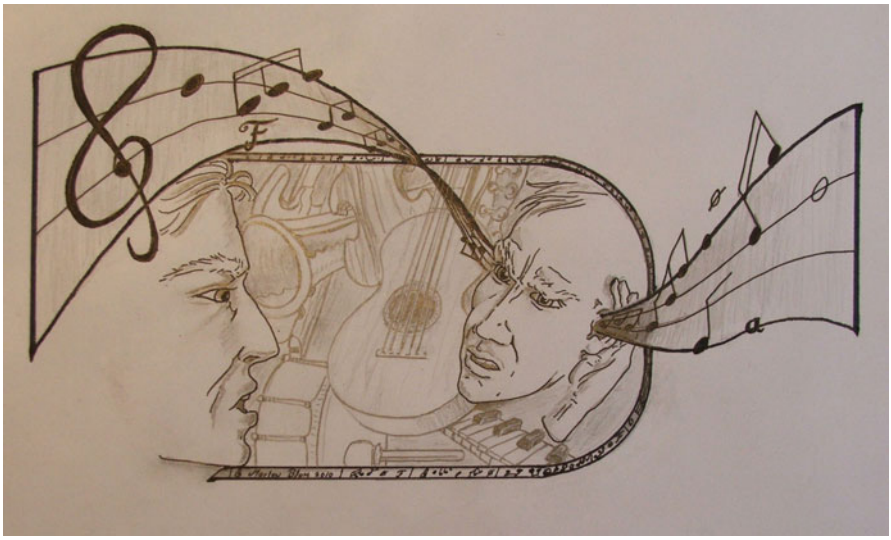

Fig. 11.2 *Musical hallucinations I* (Artwork by Marten Blom, copyright 2011)

11.5 Diagnosis and Treatment

Diagnosis hinges on proper history-taking, and, if necessary, auxiliary investigations such as blood testing, audiological evaluation, electroencephalography, and an MRI scan. If present, any underlying pathology should be treated first. The symptomatic treatment of musical hallucinations tends to consist of anticonvulsant, antidepressant, or antipsychotic drugs. In the literature, a few reports can be found on successful treatments with the anticonvulsants gabapentin (Holroyd and Sabeen 2008; Sacks 2007), carbamazepine (Gertz et al. 1996), and valproic acid (Coebergh et al. 2009), and with the antidepressant clomipramine (Matsui et al. 2003); however, none of these drugs have yet shown a broad usefulness, and perhaps the majority of cases are refractory to treatment. Nonpharmacological treatment may consist of simple reassurance (i.e., that musical hallucinations are certainly no sign of dementia or psychiatric illness), a hearing aid (for the hearing impaired and probably being more useful in cases of auditory pareidolia than in hallucinations proper), and the advice to engage in other activities that may divert attention. Most patients will discover for themselves that getting absorbed in such activities – conversation, physical activity, playing bridge, sometimes listening to real music – may drive their hallucinations into the background. But this may not always work, and some people may have musical hallucinations which are loud and intrusive, sometimes maddeningly so. At the current time, there are few if any reliable therapeutic approaches. With the passage of months or years, most people with musical hallucinations find ways of living with them, accommodating to them, so that what was initially felt as so alien and intrusive may become tolerable or even companionable. One lady, Sheryl C., whom

I followed for several years, became resigned to living with her musical hallucinations, and said, "It's *my* music, now. It's like I have a circuit in my head. I think I am landed with it forever." I asked another woman, June B., whether, after more than a decade, her hallucinated music had become important in her life in either a positive or a negative way. "If it went away," I asked, "would you be pleased or would you miss it?"

"Miss it," she answered at once. "I would miss the music. You see, it is now part of me."

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Chapter 12
Olfactory and Gustatory Hallucinations

Richard J. Stevenson and Robyn Langdon

12.1 Introduction

This chapter examines hallucinations in the chemical senses. Almost all of the literature, which is not abundant, concerns olfaction, with little coverage of taste and flavor – that is the integration of taste, smell, and somatosensation during eating (Rozin 1982). For this reason, most of the chapter will focus on olfaction.

Olfactory hallucinations (OHs) are smell experiences which occur in the absence of an appropriate stimulus (Greenberg 1995). OHs can occur in healthy people, as a primary symptom in the smell disorder phantosmia (see Table 12.1 for definitions of common chemosensory disorders) and as a secondary symptom in a range of disease states, notably psychotic disorders, temporal lobe epilepsy (TLE), brain injury, and migraine. Unlike hallucinations in other modalities, it does not appear possible to classify OHs into simple and complex forms. Most OHs involve the experience of odor objects (e.g., coffee) – there being no obvious parallel to seeing spots of light (simple visual hallucination) or angels (complex visual hallucination). The OH can also differ in other ways, in time course (brief to persistent) and location – being perceived as originating in the environment, arising from the self, but rarely from the mouth. The latter is surprising given that olfaction is a significant input into flavor perception via retronasal delivery (Rozin 1982). However, flavor hallucinations may be misreported as gustatory ones, just as flavor is typically misidentified as

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Table 12.1 Common chemosensory disorders and their definitions

Sensory modality	Name of disorder	Definition
Taste		
	Ageusia	Inability to perceive or detect tastes
	Hypogeusia	Reduced ability to perceive or detect tastes
	Dysgeusia	Altered taste perception, even with tastes absent
Smell		
	Anosmia	Inability to perceive or detect odors
	Hyposmia	Reduced ability to perceive or detect odors
	Parosmia (cacosmia, troposmia)	Distortion of smell, usually unpleasant
	Phantosmia	Long-lasting olfactory hallucination

"taste" – but this possibility has not been explored. The term gustatory hallucination (GH) refers to the experience of taste sensations, namely sweet, sour, bitter, umami (meaty), and salty, in the absence of an appropriate stimulus (Brasic 1998).

This chapter opens with a brief look at GHs, followed by a more extensive survey of OHs, examining their incidence, phenomenology, and correlates in healthy people, and then in conditions where they feature as primary or secondary symptoms. The latter half of the chapter diverges from previous reviews (Greenberg 1995, Stevenson 2009a; Velakoulis 2006) focusing on current and emerging theories of OHs.

12.2 Gustatory Hallucinations (GHs)

GHs occur in healthy people (Ohayon 2000), but they can also be a secondary symptom in brain tumors, TLE, migraine, drug misuse, and psychotic disorders (Brasic 1998). Detailed reports of GHs are rare, and of those known to the authors, involve experience of diffuse sensations of taste (unspecified but often unpleasant) either in the mouth or throat (see Chen et al. 2003; Hausser-Hauw and Bancaud 1987). Cases of highly localized GHs have also been reported (Daly (1958) describes a TLE patient who experienced a taste experienced between two teeth). The incidence of GHs has not been well established; although the TLE literature would suggest a figure far lower than for OHs, with Chen et al.'s (2003) data suggesting 0.5% and Hausser-Hauw and Bancaud (1987) 4.0%. A further factor that makes the study of GHs especially problematic, including establishing their incidence, is the confusion between a GH and a flavor hallucination. A "pure" GH involves the experience of just a taste (i.e., sweet, sour, salty, bitter, or umami), while a flavor hallucination involves orally located food- or drink-like experiences, which include gustatory, olfactory, and somatosensory components – that is the senses that compose flavor under normal perceptual conditions. The etiology of GHs has not been investigated. However, it would seem that at least for TLE, many of the brain structures known to

be involved in OHs may be abnormally active here as well (see Hausser-Hauw and Bancaud 1987).

12.3 Olfactory Hallucinations (OHs)

12.3.1 OHs in Healthy People

OHs are relatively common in healthy adults. Ohayon (2000), in a large-scale survey of hallucination frequency, found that for daytime hallucinations, OHs were the most frequent, second only to GHs. OHs were reported to have occurred at least once in 8.6% of the sample, with 0.9% having experienced multiple OHs in the preceding week. OHs may be more likely to occur in those healthy adults who score highly on measures of psychosis proneness (Kwapil et al. 1996).

12.3.2 OHs as a Primary Symptom

Phantosmia is a condition in which the primary presenting symptom is an OH. Leopold (2002) noted that incidence data is unavailable but observed that phantosmia may be more frequent in women, with a sudden mid-life onset. OHs in phantosmia may be unpleasant and enduring, lasting hours or days, and can be triggered by actual olfactory events. Both of these latter features seem to distinguish phantosmia from other types of OH discussed below, which tend to have no obvious trigger and whose time course is more akin to normal smelling. There are currently no established treatments for phantosmia, and the disease shows a relapsing and remitting presentation (Frasnelli et al. 2004).

A further condition in which OHs may feature prominently is olfactory reference syndrome. Here, patients may visit multiple medical specialists in the belief that they are emitting a foul body odor (Pryse-Phillips 1971). The key feature of this disorder is the unshakeable belief that one smells foul – even when tests reveal no underlying pathology. This may suggest a delusional condition rather than the presence of OHs, but this issue remains unresolved (see Phillips et al. 2006).

12.3.3 OHs as a Secondary Symptom

OHs have been documented as occurring in many conditions as a secondary symptom (Greenberg 1995). However, as symptom frequency varies between conditions, as with the literature devoted to it, we present independent sections for psychotic disorders, temporal lobe epilepsy (TLE), migraine, brain tumors, and injuries, along with a miscellanea section for rarer presentations.

12.3.3.1 Psychotic Disorders

Estimates of the incidence of OHs in the context of psychotic disorders vary from 1% to 35% (Kopala et al. 1994). Drawing from all such studies produces an incidence rate of around 14% (Stevenson et al. 2011) and one comparable to the 13% incidence rate obtained from the WHO-10 data set (Jablensky et al. 1992) and the 17% incidence rate estimated from Australian data (Langdon et al. 2011). While the WHO-10 data set indicates cross-cultural variation in this figure (with no obvious geographical pattern; Langdon et al. 2011), these incidence rates suggest that OHs are unusual but not rare in the context of psychotic disorders.

OHs in psychotic disorders may be more common in females (Kopala et al. 1994) and in patients who experience referential or control delusions (Langdon et al. 2011) as well as tactile hallucinations (Stevenson et al. 2011; Langdon et al. 2011). However, contrary to clinical lore (see Kwapil et al. 1996), the presence of OHs does not seem to be associated with worse symptomology or disease course (Stevenson et al. 2011). Early reports on OHs suggested principally negative experiences, with smoky, decay, body, and animal odors predominant (Bromberg and Schilder 1934; Rubert et al. 1961). We interviewed 51 people diagnosed with schizophrenia and a history of OHs to determine their phenomenology (Stevenson et al. 2011). Affectively negative experiences were dominant (51% of all reported OHs), but a significant minority were either neutral (19%) or positive (30%). Qualitatively, the OHs covered a broad range of smells, with some participants experiencing the same OH repeatedly. Although most OHs were localized as stemming from the environment, a minority were reported as emanating from the self, echoing other reports (e.g., Bromberg and Schilder 1934). Our study did not, however, reveal any bizarre smells, as have been observed before and which may be better characterized as delusions (e.g., "devil's breath" – see Greenberg 1995). As for time course, we found that OHs generally mimicked normal olfactory experience. The parallel with normal olfactory experience, as noted by other workers, included reports of engaging in appropriate behavior after experiencing the OH (Rubert et al. 1961). Insight varied and tended to be more common if the OH was unpleasant (Stevenson et al. 2011).

12.3.3.2 Temporal Lobe Epilepsy (TLE)

The presence of an OH prior to a seizure (or a migraine attack – see below) is referred to as an aura rather than a hallucination. Phenomenologically, epileptic olfactory auras closely resemble OHs reported in other conditions. Olfactory auras appear to be largely restricted to TLE (West and Doty 1995), and they (like other prodromal cues) tend to signal an approaching seizure. Incidence estimates of OHs in epilepsy vary from 1% to 30% (West and Doty 1995; Chen et al. 2003), with a mean across studies of around 9% – making them relatively rare. The actual incidence in TLE may be somewhat higher because early studies may have included patients whose seizure focus fell outside of the temporal lobe. Olfactory auras are

brief; they may be accompanied by other types of aura (epigastric auras and nausea may predominate; see Chen et al. 2003); they can be repetitive and foul smelling, although pleasant-smelling auras have also been reported (Efron 1956). Insight tends to be rapid because the odors that are experienced seem to stem from the external environment and are sufficiently realistic – especially if unpleasant – to prompt people to actively search for their cause (Efron 1956).

12.3.3.3 Migraine

The literature on OHs – auras – in the context of migraine is less well developed and it is not possible to estimate any incidence rates. Based upon case reports, auras in migraine seem to have the signal quality that characterizes OHs in TLE, occurring mainly as part of the migraine prodrome (Crosley and Dhamoon 1983). In the nine cases described in the literature, most were unpleasant and environmentally localized (Diamond et al. 1985). Time course varied between 5 min and 2 h, but whether this represents a distinct feature or a sampling bias (i.e., a long-lasting OH is likely to be both more notable and to prompt verification) is not currently known (Diamond et al. 1985). In several of the reported cases, patients had actively attempted to identify the odor, leading them to recognize the experience as hallucinatory (Crosley and Dhamoon 1983).

12.3.3.4 Brain Tumors and Injuries

One of the first papers to link the characteristic clinical features of TLE with OHs (Jackson and Stewart 1899) concluded that the epilepsy, the other symptoms (diplopia, facial weakness, hemiplegia), and the OHs probably resulted from a tumor in the temporal lobe. Tumors can present with symptoms that may initially resemble TLE, and in Chen et al.'s (2003) detailed case series of 217 patients, of whom 12 had olfactory auras, 3 of these were revealed to have brain tumors (astrocytoma and glioblastoma; the rate of brain tumors without olfactory auras was not reported). This type of observation has led some authors to conclude that olfactory auras signal tumors (Acharya et al. 1998). Not only can a variety of tumors (e.g., gliomas, meningiomas; see Greenberg 1995) in the temporal lobe produce seizures and OHs but so can tumors at more distant sites that indirectly impact on olfactory centers. Faris and Terrence (1989) describe a case with extensive OHs resulting from a cyst in the third ventricle, which they suggest exerted a mass effect on the medial dorsal nucleus of the thalamus (MDNT) – the thalamo-cortical connection of the olfactory system. While tumors and other masses adjacent to olfactory structures may be associated with the presence of OHs, direct injury to similar regions of the brain via aneurysm, stroke, or hematoma can also result in OHs (Toone 1978). The relatively few reports make any general remarks about the phenomenology uninformative, especially as the time courses for the OHs identified in these reports varied from minutes to days.

12.3.3.5 Miscellanea

OHs have also been reported following cancer chemotherapy (Nesse et al. 1983), in chronic cocaine users (Brasic 1998), and in acute alcohol withdrawal (Bromberg and Schilder 1934). Several reports have identified OHs as occurring when a person was reexposed to cues relating to an earlier traumatic incident – such as smelling petrol while traveling in a car (following an earlier car accident) and smoke (following an earlier experience of fire; Burstein 1987). OHs have also been reported in Parkinson's disease (Sandyk 1981), depression (Brasic 1998), Alzheimer's disease (Greenberg 1995), and in Charles Bonnet syndrome (Alroe and McIntyre 1983), which is normally characterized by visual hallucinations (see Chap. 6).

12.4 Cause

It seems likely that several different causes contribute to the occurrence of OHs. This is suggested by the diverse conditions in which OHs are found (Greenberg 1995) and also by emerging evidence that there may be variations in cause within a particular disease state, notably in psychotic disorders (Stevenson et al. 2011). Moreover, different disease states may share common causes. For these reasons, the following section is organized around putative causes, not conditions, and for each class of cause its potential contribution to different conditions is outlined. Three primary causes are presented, peripheral (receptors) and central (brain), with a predominantly physiological focus and psychological explanations. These are not discrete and the overlaps are highlighted. Finally, it should be borne in mind that it is only recently that efforts have been made to understand the cause of OHs, and so what follows should be considered a preliminary survey.

12.4.1 Peripheral Contributions

There are two basic types of peripheral cause. The first concerns some form of olfactory receptor abnormality, resulting from an infectious agent, mechanical or chemical damage, or genetic disposition, which affects the ability to sense volatile chemicals (Smith and Duncan 1992). Such damage could produce three forms of abnormality that might lead a person to experience an OH or regard an experience as an OH – a distinction that will become apparent below. If the damage is extensive, such as sheering of the olfactory nerve (with the cribriform plate acting as a "guillotine"), the ability to detect an odorant may be impaired or even lost (Smith and Duncan 1992). This may result in release hallucinations whereby reduced peripheral input leads to cortical hyperexcitability, producing activations of olfactory sensory memories – and thus OHs (Donnelly et al. 1989). However, if the damage is less severe, or if there has been damage followed by abnormal neuronal

regrowth, this may lead to misperceptions – parosmia – which are typically unpleasant (Leopold 2002). In this case, the pattern of neural activity generated by the receptors for a particular odorant becomes deviant, and so the resulting percept does not match external cues (e.g., lemon detergent may be perceived as smelling of feces). The unusual and alarming nature of the misperception (or parosmia) may then lead a person to falsely conclude that they have experienced a hallucination (Greenberg 1995).

A characteristic feature of olfaction is rapid adaptation, so that the system is optimized to detect new environmental odorants (Wilson and Stevenson 2006). Adaptation has both a peripheral and a central component, and either or both of these can be compromised. Adaptation failures might lead to misperceptions, if, for example, spontaneous recovery occurred to an odor to which a person had adapted. If this occurred, it would *seem* as if an odor had spontaneously appeared in the environment, and again, this might be regarded, incorrectly, as a hallucination.

A case for such peripheral contributions can be made in psychotic disorders, brain injury, phantosmia, and TLE. For psychotic disorders, there is a large literature demonstrating abnormalities in olfaction, and these abnormalities are independent of antipsychotic medication (Moberg et al. 1999). People diagnosed with schizophrenia are more likely to have elevated detection thresholds, impaired odor identification ability, restricted affective response to odors, as well as poorer discriminative and odor memory capacity (Moberg et al. 1999). At least some of these impairments can be observed in healthy first-degree relatives of patients, and one report has obtained evidence of small cranio-facial abnormalities that may contribute to olfactory impairments (Moberg et al. 1999). In particular, the presence of elevated detection thresholds suggests some peripheral abnormality, although these are probably of insufficient magnitude to produce release hallucinations. Only three studies have examined whether people diagnosed with schizophrenia who experience OHs have peripheral deficits. Kerekovic (1972) conducted a detailed otorhinological examination of 39 patients diagnosed with schizophrenia and experiencing OHs, comparing them to 155 who did not report OHs. The OH group did not differ in nasal pathology, the presence of anosmia, hyposmia, or nasal allergies, from the remainder, suggesting that a peripheral cause of their OHs was unlikely. A similar conclusion was reached in two further studies in individuals diagnosed with schizophrenia by Stedman and Clair (1998) and Kopala et al. (1994), who found no difference in odor identification ability between those with or without OHs. Impaired ability to detect odors is known to impact on identification ability, and so this test is sensitive to peripheral damage.

While these findings point toward a more central cause for OHs in individuals diagnosed with schizophrenia, it would be premature to abandon peripheral accounts just yet. First, it may be that only a subgroup of OHs in those individuals result from a peripheral cause. This possibility was suggested in a recent study, which used an exploratory cluster analysis of participants' hallucinatory phenomenology (Stevenson et al. 2011). This analysis revealed that a subset of participants scored higher on a "sensory dysfunction" score (i.e., presence of sinusitis, prior head injury, smoking history, smoky OHs, length of OHs), all of which are associates of

parosmia (Leopold 2002). Second, a further study (Stevenson and Langdon in press) suggests that there may be impairments in adaptation, which may well have a peripheral basis.

Peripheral damage to the olfactory epithelium may also be a contributory factor in TLE, brain injury, and phantosmia. For TLE, several studies have found that preoperative otorhinological workouts show significant differences in olfactory thresholds (both increased and decreased sensitivity), indicative of peripheral abnormality (West and Doty 1995). For brain injury, as noted above, especially following shearing injury, not only will anosmia occur, but during recovery there may be significant distortions of smell, which are frequently unpleasant (parosmia), and which may be misinterpreted as OHs (Greenberg 1995). For phantosmia, the evidence for peripheral involvement is more direct (Donnelly et al. 1989), and it has been suggested that it results from a peripheral deafferentation syndrome following trauma of some kind (Frasnelli et al. 2004). Nonetheless, some patients with phantosmia do not appear to have abnormal detection thresholds, and at least one study has suggested that there may be abnormalities in levels of the neurotransmitter gamma-aminobutyric acid (GABA) at several central olfactory sites, including the amygdala (Levy and Henkin 2004). This highlights the problem in clearly disambiguating peripheral from central causes because the olfactory system contains extensive feedforward and feedbackward circuits (Wilson and Stevenson 2006). Abnormalities in one will inevitably lead to abnormalities in the other, making determination of the initial locus difficult.

There may be an additional peripheral cause, although its inclusion in this section could be disputed. As noted earlier, the presence of tactile and olfactory hallucinations are associated in individuals diagnosed with schizophrenia (Greenberg 1995). In our recent study of OHs, a cluster analysis also revealed a group characterized by highly frequent tactile hallucinations (Stevenson et al. 2011). Nasal somatosensation is important in olfaction, both for magnitude constancy (i.e., bigger sniffs deliver more odorant but are not accompanied by equally large increments in perceptual magnitude) and for localization (i.e., is the odorant in the mouth or at the nose; Wilson and Stevenson 2006). The act of sniffing invokes neural activity in all parts of the olfactory system even if odorless air is used (Sobel et al. 1998). It may be that a tactile hallucination of nasal airflow may activate olfactory pathways sufficiently to generate an OH in some people diagnosed with schizophrenia, which might constitute a form of synesthesia.

12.4.2 Central Contributions

While cortical release represents one account of hallucinations, another is cortical irritation. The essence of this latter theory is that some form of irritation results in excess neural activity, which results in hallucinatory experience. This theory owes much to the brain stimulation experiments of Wilder Penfield (1891–1976), but in fact these and more recent studies find little evidence that

stimulation of olfactory brain regions can generate any olfactory experience (Penfield and Perot 1963). Nonetheless, olfactory experiences were noted by one patient of Gloor's (1990) with amygdala stimulation and in four out of five non-epileptic participants receiving stimulation of the thalamus (Nashold and Wilson 1969). So while induced electrical activity can generate illusory olfactory percepts, it does not appear to be common.

The amygdala has been one site that has attracted attention as a potential neural locus responsible for the mediation of OHs. The amygdala is involved in processing affective reactions to odors (Royet et al. 2000). Amygdala abnormalities are also known to occur in association with psychotic disorders (Shenton et al. 2001) and TLE (West and Doty 1995), and these abnormalities may in turn be associated with the generation of OHs in the following way. Rather than experiencing an odor memory per se, cortical irritation (generated by diseased tissue) may lead to amygdala activity and hence negative affect, which is then misattributed to the olfactory system. It is possible to generate variants of this type of model. For example, if particular parts of the amygdala were selectively associated with olfaction, abnormal activity at that location could be automatically rendered "olfactory" without any need for misattribution. Whatever, a general prediction would be of greater amygdala dysfunction in olfactory hallucinators with TLE or psychotic disorder. So far, the only evidence pertinent to this hypothesis – one advanced by a number of authors (e.g., Chen et al. 2003; Acharya et al. 1998) – comes from a study comparing the neuropsychological profile of people diagnosed with schizophrenia who experience OHs with those who experience auditory verbal hallucinations (but no OHs) and normal matched controls (Arguedes et al. submitted). We found a small impairment in facial recognition of negative emotions, consistent with amygdala dysfunction, in just the patients who had experienced OHs. However, the most notable impairment was in tests sensitive to orbitofrontal cortex processing. While this structure functions as secondary olfactory cortex, it has not previously been implicated as a putative neural correlate of OHs. Interestingly, it too has a major role in olfactory hedonics (Wilson and Stevenson 2006).

12.4.3 Psychological Contributions

The presence of OHs in otherwise healthy individuals would suggest that psychological accounts are important to consider as well. In this regard, olfactory stimuli often present a special problem relative to those detected by the other senses in that olfactory experiences can be difficult to independently verify (e.g., if you smell pizza, is it *really* there, especially if there are no other cues to its presence?). A further problem concerns misidentification. Human ability to name odors, again in the absence of other contextual cues, is demonstrably poor, and it may be that misidentified innocuous household odors lead to an erroneous report of a hallucination (Stevenson and Case 2005). This could apply with equal force to any of the other conditions discussed in this chapter.

Explanations of visual and auditory hallucinations, especially in psychotic disorders, have also had recourse to psychological accounts (Slade 1994). One possibility concerns the misattribution of mental imagery or involuntary memories to the external milieu – a source-monitoring failure (Bentall et al. 1991). The applicability of this type of account to olfaction is potentially problematic because there is active debate as to whether we can experience olfactory sensation in the absence of any appropriate stimulation (Stevenson and Case 2005). This has led some observers, including ourselves, to question the relevance of this type of account to OHs. However, recent evidence suggests that this conclusion may be premature. Using a novel odor-source-monitoring task, in which participants either imagined or smelled several odors, revealed that participants diagnosed with schizophrenia and experiencing OHs were far less efficient at distinguishing real from imagined odors on a later source-discrimination task than either participants diagnosed with schizophrenia and experiencing auditory verbal hallucinations or healthy controls (Arguedes et al. submitted). These results, albeit on a small sample, suggest that the ability to track "real" and "imagined" stimuli may be compromised in people diagnosed with schizophrenia who experience OHs. Moreover, it raises the interesting possibility that olfactory imagery in this group might differ in some qualitative way relative to normal participants, namely that people who experience OHs may under certain conditions be able to experience odor images.

12.5 Discussion and Conclusions

Hallucinations in the chemical senses are unusual. While OHs have received rather limited attention, even less is known about gustatory and flavor hallucinations. OHs can be observed in healthy normal people, possibly due to the difficulty in verifying the source of an odorant, and they can occur as an independent disease – phantosmia – which may stem initially from damage to the periphery of the olfactory system. OHs can also occur as secondary symptom in several conditions, notably in psychotic disorders, TLE, and migraine, as well as with brain tumors and injuries. These conditions all affect some part of the olfactory system – either centrally and/or peripherally. OHs also occur, albeit more rarely, in post-traumatic stress disorder (PTSD), drug abuse, depression, Parkinson's disease, and Alzheimer's disease.

That the causes of OHs in particular have not been well investigated is to be lamented for two reasons. First, its study may shed light on the genesis of hallucinations in other modalities, especially if conventional theories turn out to be inapplicable to olfaction. Indeed, even if conventional theories are correct – as some recent data on source monitoring may suggest – this provides a new avenue of theory verification, as it may for others. The second reason for lamenting the lack of study of OHs is because of what it may tell us about routine aspects of olfactory perception. Olfaction is emerging as a particularly interesting system to study in regard to consciousness, as its divergent neural organization and unusual psychological properties challenge the generality of a number of contemporary theories of consciousness

(Stevenson 2009b). However, relative to the visual and auditory systems, we know little about olfaction. Many of its basic cognitive capacities (e.g., for imagery and the nature of short-term memory) are unresolved; the neural basis for these and other processes, especially attention, are not understood; and even apparently basic questions such as the "stimulus problem" (i.e., which features of the stimulus are associated with particular types of sensation) remains unsolved. Studying OHs can provide a new approach to addressing many of these questions.

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Chapter 13
Hallucinations of Bodily Sensation

Jan Dirk Blom and Iris E.C. Sommer

13.1 Introduction

A young man complains of a scraping sensation inside the head, as if a plant with pointed leaves were going up and down against the inner surface of his skull. Another person complains of needle pricks in the back. Because he repeatedly feels them while sitting alone in the waiting room, he figures that there must be "some sort of James Bond elevator" rising and falling behind him, carrying a person who sticks the needle in before he silently disappears. A third man complains of a pressure in the corners of the mouth, and the sensation of his toes turning into paws. He has searched the internet for possible explanations, and the one that seems most plausible to him is that he is turning into a werewolf. A patient in her 30s keeps visiting doctors because she is convinced that the left side of her body is much larger than the other side. Not only her extremities, but even the left side of her brain appears to have grown, so that they no longer match the other half. Another young woman feels snakes moving inside her belly, and yet another one cannot feel her body at all. In bed, in the dark, she is unable to tell whether she is lying on her back or otherwise, and needs tactile information to verify her position. An elderly woman suffers from continuous orgasmic sensations which seriously incapacitate her daily functioning. Among a group of 176 medical staff members of a hospital in Springfield, MA, 75% experienced vibrations of their pager or cellular phone while

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the devices are not vibrating (Rothberg et al. 2010). What do experiences such as these have in common? As varied as they may be, they all represent some aberration of corporeal sensation. In this chapter, these phenomena are subsumed under the heading of "bodily hallucinations," an umbrella term used to designate a group of widely divergent corporeal percepts, phenomenologically rich in nature, yet poorly described and often equally poorly understood.

13.2 The Psychopathology of Bodily Sensation

Bodily hallucinations are also known as hallucinations of bodily sensation and body sensation hallucinations. They are hallucinatory percepts which have bearing on the body itself, as opposed to visual, auditory, olfactory, and gustatory hallucinations, which all constitute percepts projected into the extracorporeal world. Although the latter are sometimes designated as "hallucinations of the distance senses" (Berrios 1982), bodily hallucinations defy characterization as mere hallucinations "of the proximity senses" or "of intracorporeal sensation." They are also more variegated than hallucinations of the "distance senses," if only because the latter are all unimodal in nature. Table 13.1 provides a classification of the various types of bodily hallucination and the sensory modalities involved. The exact delineation of these phenomena may be somewhat arbitrary, and different classifications may well yield different categories (for a well-considered alternative, see Gibson 1966), but what this overview illustrates is that they are definitely multimodal in nature, and that they differ in many ways from hallucinations of the so-called distance senses.

Before we proceed to discuss these types of hallucination, a few introductory remarks are in place. First of all that, historically speaking, bodily sensation has always been subordinated to the other senses, with touch only reluctantly being designated as a "fifth sense" by Aristotle (Aristotle 1968), and pain being classified for centuries as a "bodily passion" rather than a percept (Starobinski 1990). The exact source of this conceptual uneasiness is unknown, but it would seem to be connected with varying philosophical and biomedical insights into the nature of the senses – referring to the sense organs themselves, as well as to the mental constructs based on perceptual information – and associated concepts of "reality" (Rodaway 1994). It was only near the end of the eighteenth century that bodily sensation became an object of study in its own right, with notions such as coenesthesis (the sensation of physical existence) and *Gemeingefühl* ("common sensation") reigning supreme (Jütte 2005). But this Golden Age of bodily sensation lasted no longer than a century. Late nineteenth- and early twentieth-century discoveries of modality-specific neural substrates such as the pain spots (Von Frey 1894) and nociception (Sherrington 1906) gave the deathblow to the coordinating concepts of olden days (Boring 1942). Ever since, the focus of biomedical research has been primarily on constituent parts of bodily sensation rather than on bodily sensation as a whole.

Secondly, it should be noted that some types of hallucination listed in Table 13.1 would seem to pose irreconcilable conceptual and methodological problems, in the

Table 13.1 Classification of bodily hallucinations and concomitant sensory modalities

Sensory modality	Type of hallucination
1. Exteroceptive modality	Tactile (haptic) hallucination
2. Interoceptive modality	Somatic hallucination, visceral hallucination
3. Proprioceptive modality	Proprioceptive hallucination
4. Kinesthetic modality	Kinesthetic hallucination
5. Vestibular modality	Vestibular hallucination
6. Coenesthetic modality	Coenesthetic hallucination
7. Pain modality	Hallucinated pain, central pain
8. Sexual modality	Sexual hallucination
9. Temperature modality	Thermal (thermic) hallucination

sense that they appear to stretch the definition of the term "hallucination" beyond its rightful limits. Pain, vertigo, and sexual arousal are cases in point of subjective sensations that can only counterintuitively be pictured as hallucinations. Below we will explain why the concept of hallucinated pain arose in the first place, but the very existence of concepts such as these begs the question of whether "imagined" or "unreal" subjective experiences can ever be said to exist. As observed by the American philosopher Saul Kripke, "For a sensation to be felt as pain is for it to be pain" (Kripke 1980). This simple statement pretty much sums up the central problem of the bodily hallucination concept and explains many of the difficulties we meet in clinical practice, notably in trying to differentiate between bodily hallucinations and bodily percepts due to unexplained somatic conditions.

That being said, we will now turn to the major classes of bodily hallucination, outline the phenomenological characteristics of their various members, and summarize the findings regarding their neurobiological correlates.

13.3 Tactile Hallucinations

Tactile hallucinations, also known as tactile phantasmata, haptic hallucinations, superficial hallucinations, touch hallucinations, and hallucinations of touch (Blom 2010; Sims 2003), are corporeal percepts seemingly evoked by a stimulus from outside the body. Examples are the needle pricks experienced by the young man described above, and the phantom vibrations experienced by medical staff members, a condition recently introduced into the literature as "phantom vibration syndrome" (Rothberg et al. 2010). The group of tactile hallucinations comprises many other variants, an overview of which is given in Table 13.2.

Among them are formicative hallucinations, characterized by the sensation of ants or other bugs crawling upon or beneath the skin (Bers and Conrad 1954). When attributed to the use of cocaine, these hallucinations are referred to as Magnan's sign, Magnan-Saury's sign, or "cocaine bugs," and in the context of amphetamine use as "crank bugs" (Siegel 1978). Hygric hallucinations, mimicking the sensation

Table 13.2 Classification of tactile hallucinations (Adapted from Blom 2010)

Type of tactile hallucination	Characterization
Allachesthesia (allesthesia, atopognosis)	A horizontal or diagonal displacement of localization for touch, confined to the ipsilateral side of the body
Allochiria	A displacement of localization for touch to the contralateral side of the body
Auditory-tactile synesthesia	A tactile hallucination triggered by a regular auditory percept
Extracampine hallucination	A hallucination experienced outside the regular field of perception (in the case of tactile hallucinations: e.g., in the hair or the brain)
Formicative hallucination (formication, dermatozoic hallucination, insect hallucination)	The hallucinated sensation of ants or other bugs crawling upon or beneath the skin
Hygric hallucination	A tactile hallucination mimicking the sensation of wetness and fluids upon the skin
Mirror-touch synesthesia	A tactile hallucination triggered by observing touch to another person
Phantom alloesthesia	A tactile hallucination experienced beneath the stump of an amputated limb, following touch to the contralateral, remaining limb
Phantom vibration syndrome	A tactile hallucination mimicking the vibrations of an electronic device such as a pager or a cellular phone
Stereognosic hallucination (stereognostic hallucination)	A tactile hallucination characterized by the sensation of touching one or more solid objects
Spontaneous stereognosic sensation (spontaneous stereognostic sensation)	A stereognosic hallucination mimicking the sensation of a solid object held in the palm of one's hand
Synchiria (diplohaptia)	A bilateral tactile sensation produced by unilateral tactile stimulation
Tactile polyesthesia	A tactile phenomenon in which a single tactile stimulus is at first perceived and localized properly, and then perceived again in one or more different parts of the body
Visual-tactile synesthesia	A tactile hallucination which is triggered by a regular visual percept

of wetness and fluids upon the skin (Jaspers 1997), are considered quite rare. The same holds true for stereognosic (or stereognostic) hallucinations, characterized by the sensation of one or more solid objects touching the skin, and a variant called spontaneous stereognosic sensation, which mimics the sensation of a solid object held in the palm of one's hand (Critchley 1953).

Allachesthesia and allochiria are hallucinations characterized by a "confusion of sides" rather than a spontaneous tactile sensation (Halligan et al. 1992). In allachesthesia, stimuli are experienced upon actual touch, affecting the ipsilateral side of the body, although in a different place, whereas in allochiria they are experienced at the contralateral side (Meador et al. 1991). Phenomenologically, both types of percept are related to synchiria – in which unilateral tactile stimulation produces a bilateral

tactile percept – and tactile polyesthesia, in which a single tactile stimulus is at first perceived and localized properly, and then perceived again in one or more different parts of the body (Critchley 1953). Perhaps these phenomena are also related to extracampine hallucinations (i.e., tactile hallucinations experienced outside the regular field of tactile perception; see Bleuler 1903; Chan and Rossor 2003) and tactile hallucinations triggered by a regular percept in any of the other sensory modalities, such as a sound (auditory-tactile synesthesia) or a specific color (visual-tactile synesthesia) (Ward 2007, see also Chap. 7). Yet another variant of this class of phenomena is mirror-touch synesthesia, in which a tactile hallucination is triggered by observing touch to another person (Banissy et al. 2009).

The neurobiological correlates of these phenomena have not been fully elucidated, but the cross-activation hypothesis is traditionally considered an attractive explanation (Parish 1897; Harrison 2001). It suggests that perceptual information may feed (or "cross over") from one sensory modality into another or, when the information remains within the tactile modality, from one representational center into another. Competing models attribute the mediation of such secondary hallucinatory phenomena to (1) disinhibition of adjacent brain areas, (2) an increase in feedback connections between successive stages of the sensory hierarchy, and (3) excess activity between those successive stages, for example, as a result of a disinhibition of feedback connections (Ramachandran and Hubbard 2001).

13.4 Somatic Hallucinations

Somatic (i.e., somesthetic, visceral) hallucinations are experienced within the body rather than at its surface. The woman described above, with the sensation of snakes moving about in her belly, as well as the young man with the scraping sensation inside the skull, provide apt examples of this class of phenomena. Although it is very likely that the phenomena at hand were hallucinations proper, one can never rule out with certainty whether they may rather be sense perceptions caused by some unknown somatic condition. The same holds true for other types of somatic hallucination, an overview of which is given in Table 13.3. This basic uncertainty is incidental to this group of phenomena, and practically insoluble given the state of the art of present-day medicine, but in clinical practice we use the rule of thumb that we are dealing with a somatic hallucination when the percept at hand is inexplicable in physiological terms, especially so when it is provided with a delusional explanation by the patient (Berrios 1982).

Somatic hallucinations are notoriously hard to classify, but traditionally the following phenomena are distinguished. Audioalgesic synesthesias are painful sensations triggered by a regular auditory percept (Jacome and Gumnit 1979). Not unlike the types of synesthesia discussed above, they tend to be attributed to intermodal cross-activation. Hallucinated headache is a painful sensation experienced within the head, occurring in the absence of any demonstrable organic cause. It may be considered similar to tension headache (i.e., psychogenic headache), but there is a

Table 13.3 Classification of somatic hallucinations (Adapted from Blom 2010)

Type of somatic hallucination	Characterization
Audioalgesic synesthesia	A painful bodily sensation triggered by a regular auditory percept
Hallucinated headache	A somatic hallucination characterized by pain in the head, attributed to psychic "emptiness"
Hallucinated pain	A painful somatic hallucination attributed to psychic "emptiness"
Painful somatosensory hallucination	A painful somatic hallucination
Paresthesia	A sensation of "pins and needles," usually located in or beneath the skin
Somatosensory aura	A somatic hallucination experienced within a clearly defined region of the body, attributed to epilepsy

subtle conceptual difference here that is worth noting. The concept of hallucinated headache evolved out of the psychoanalytic dictum that any type of hallucination can be caused by hunger – either actual hunger or affective hunger (Forrer 1962). Rather than attributing hallucinated headache to muscular or peripheral nervous stimulation, Forrer conceptualized it as a means to fill a subjectively experienced "void" or "emptiness." Elaborating on that theme, he expanded the hallucinated headache concept to arrive at hallucinated pain (Forrer 1968). For this type of pain, he designed a diagnostic triad, comprising (1) description by the patient in vague, uncertain, inappropriate, or bizarre terms, often violating neuroanatomical boundaries; (2) contingent circumstances such as actual or psychological emptiness, hunger, or thirst; and (3) improvement or disappearance of the pain with oral activity such as eating or drinking. A fundamental objection against Forrer's concept of hallucinated pain is the above-mentioned argument of Kripke's that "for a sensation to be felt as pain is for it to be pain." However, the concept finds some support from the experience of dentists and surgeons that physical pain is not seldom indicated by patients moments before a tooth or other body part is actually being touched, and of hypnotists who find that pain can be evoked as well as alleviated through suggestion. Although clinical experiences such as these may not suffice to legitimize the concept of hallucinated pain, they do confirm that the dynamics of painful sensations involve more than tissue damage and nociception alone. Stripped from its psychoanalytic overtones, the concept is known today as "painful somatosensory hallucination," and operationalized in terms of a spontaneously occurring pain without adequate external stimuli (Bär et al. 2002). The neural correlates of that type of pain are as yet unclear, but an fMRI experiment by Bär et al. (2002) suggests that – in their patient, at least – a parietal area of the posterior medial wall may be involved in its mediation. All in all, it has evolved from a psychoanalytic concept to a neuroscientific one that comes close to the concepts of central pain (which is associated with damage to specific areas of the brain, brainstem, or spinal cord; see Canavero and Bonicalzi (2007) as well as Chap. 14) and phantom pain (i.e., pain experienced in an amputated, aplasic, or anesthetic limb; see Brugger et al. 2000, as well as Chap. 16, this volume).

Somatic hallucinations can also occur in the context of paroxysmal neurological disorders such as epilepsy or migraine. In such cases, they are called somatosensory aurae. Theoretically, an aura may mimic any type of bodily sensation, but in clinical practice, it tends to present chiefly in the form of paresthesias (Lüders et al. 1998). These tingling somatic sensations in or beneath the skin ("pins and needles") also occur in the context of peripheral nerve compression and a variety of other conditions, but among the somatosensory aurae they are reportedly the most prevalent. Other well-known manifestations of somatosensory aurae are numbness, pain, rising epigastric sensations, thermal hallucinations, splitting of the body image (i.e., the subjective sensation of one's body being split in two; see Podoll and Robinson 2002), and other body schema illusions.

13.5 Sexual Hallucinations

The term sexual hallucination refers to a variety of hallucinated percepts that are sexually charged, such as visual hallucinations with a sexually explicit or pornographic quality, auditory hallucinations delivering a message with a sexual connotation, and bodily hallucinations experienced in an erogenic zone. It is the latter type of hallucination that concerns us here. When experienced in the penis or vulva, such hallucinations are referred to as genital hallucinations. It should be noted, however, that hallucinations experienced in the mammae, buttock, anus, mouth, and in fact any other erogenic zone can also qualify as sexual hallucinations, depending on their ability to arouse sexual feelings. When occurring during or after anesthesia, the term nitrous oxide hallucination applies (Bennett 1980; Balasubramaniam and Park 2003). Persistent sexual arousal syndrome (PSAS) is a condition occurring mostly in women between ages 40 and 65, characterized by a persistent feeling of genital arousal – or orgasmic sensation – that is incongruous with the patient's affect (Leiblum and Nathan 2001). An example is the description above of the elderly woman whose continuous orgasmic sensations had nothing to do with hyperarousal or hypersexuality, and were experienced by her as ego-dystonic. The pathophysiology of PSAS is largely unknown, although a few case reports exist about associations with the use of trazodone and other drugs, and with pelvic arteriovenous malformations.

13.6 The Coenesthesiopathies

The coenesthesiopathies comprise a group of somatic hallucinations that alter one's sense of physical existence. The young man described above whose subjective physical changes made him think he was turning into a werewolf, and the woman who was unable to feel her body at all, suffered from coenesthesiopathy (for a detailed account, see Blom et al. 2010). More specifically, the man was diagnosed with clinical lycanthropy, and the woman with acenesthesia (see below).

Table 13.4 Classification of coenesthesiopathies (Adapted from Blom et al. 2010)

Type of coenesthesiopathy	Characterization
Coenesthesiopathy (cenesthopathy)	A pathological alteration in the sense of bodily existence, caused by aberrant bodily sensations
Acoenesthesiopathy (acenesthesia, total asomatognosia)	A total absence of the sense of bodily existence
Hypercoenesthesiopathy	A hypertrophic alteration in the sense of bodily existence, caused by aberrant bodily sensations
Hypocoenesthesiopathy	A hypotrophic alteration in the sense of bodily existence, caused by aberrant bodily sensations
Paracoenesthesiopathy	A qualitative alteration in the sense of bodily existence, caused by aberrant bodily sensations
Clinical lycanthropy	The delusional conviction of having changed into a wolf or having the potential of becoming a wolf

The concept of coenesthesiopathy proceeds from the late eighteenth-century notion of coenesthesis (coenesthesia, cenesthesis, or in German, *Gemeingefühl*), which refers to the "common sensation" or "common general sensibility" arising from the sum of all bodily sense impressions. As explained by Tanzi (1909), "The united and incessant exercise of the sensory functions is the perennial source, not only of all special information that is supplied to us regarding the external world and our body, but also of a general and indistinct, but often very active, consciousness that enables us from moment to moment to recognize the functional intactness of the body in all its parts, including those which, owing to being isolated and in a normal condition, never make themselves felt." Thus, coenesthesis stands for a strictly intimate, personal feeling of physical existence (Schiller 1984), characterized in general terms as "the sense of feeling well." The notion that this "sense of feeling well" can be compromised by all sorts of bodily discomfort was recognized right away, but interestingly the concomitant concept of coenesthesiopathy was introduced only a century later when the general scientific interest in coenesthesis was already on the wane (Deny and Camus 1905a, b; Dupré and Camus 1907). Table 13.4 provides an overview of this group of disorders, which were found to be so prevalent in psychosis (i.e., 18% in a group of 223 individuals with a clinical diagnosis of schizophrenia) that they led Huber (1957, 1992) to conceptualize a special subgroup of schizophrenia, featuring in the International Classification of Diseases as cenesthopathic schizophrenia (WHO 1992; Jenkins and Röhricht 2007).

If we follow the classification devised by Deny and Camus, the woman who was unable to feel her body should be diagnosed with hypocoenesthesiopathy (i.e., a strongly diminished sense of bodily existence) or even acoenesthesiopathy (a total absence of the sense of bodily existence, see Meador et al. 2000). The man who thought he was turning into a werewolf, on the other hand, experienced a hypertrophic alteration in the sense of bodily existence, diagnosable as a hypercoenesthesiopathy

Fig. 13.1 Lycanthropy, artist's impression (Copyright 2011 by Marten Blom)

or paracoenesthesiopathy. And yet, because of the werewolf theme, he also fits the criteria for clinical lycanthropy, a rare delusional conviction that should be distinguished from lycanthropy (see Fig. 13.1) as described in mythological accounts referring to the actual transformation of humans into wolves and back again (Moselhy 1999; Garlipp et al. 2004).

Today the coenesthesiopathies would seem to be underreported, underdiagnosed, and undertreated (Blom et al. 2010). And yet one should be cautious to establish those diagnoses too soon. As demonstrated by the following case vignette, the differential diagnosis includes a number of somatic disorders, some of which may require urgent treatment.

> A man diagnosed with chronic schizophrenia had repeatedly complained that the size of his feet had increased to the extent that the wearing of shoes had become a painful affair. He also complained that his rings had become too narrow for his fingers, and that his hat had become too small for his head. He interpreted these signs as messages from God that he was not allowed to wear any shoes, jewelry, or hats. While participating in an MRI study for entirely different reasons, it turned out that he suffered from a large pituitary tumor. That tumor had produced growth hormone responsible for an actual increase of the size of the body parts he had mentioned.

13.7 Discussion

As the neuronal circuits within the parietal lobe and thalamus play an important role in the mediation of bodily percepts and the representation of the body scheme, it would seem there – and in the interconnecting white-matter tracts – that we should localize the neurobiological correlates of hallucinations of bodily sensation. Imaging studies indicate that this is at least partly correct. Arzy et al. (2006) found damage to the right premotor cortex in a patient with acoenesthesiopathy, and Bär et al. (2002) found transient activation of the precuneus and supplementary motor cortex in a patient with painful somatosensory hallucinations. Functional imaging studies also indicate that bodily hallucinations and artificially induced bodily sensations have shared correlates in primary and secondary somatosensory cortical areas (Bär et al. 2002; Shergill et al. 2001). This may well be the reason why the two types of percept can be experienced as equally "real" (Sommer et al. 2005). Another, and only recently "rediscovered" structure that would seem to play a major role in the mediation of bodily sensations and corporeal awareness is the insula, also referred to as the "fifth lobe of the brain" (Brooks et al. 2005; Craig 2009). Featuring a somatotopic organization, this structure may well hold the key to our future understanding of the pathophysiology of bodily hallucinations.

All things considered, however, we must conclude that our understanding of bodily hallucinations is still very limited. Phenomenologically, these hallucinated percepts would seem to lie on a continuum with hyperschematia or left size distortion (i.e., the conviction that the left side of the body is larger than the right one, as described by the woman above), body schema illusions (Kelly 1992), body dysmorphic disorder, phantom sensations, macrostereognosia (i.e., the sensation that an object held in the palm of one's hand, for example, is significantly more bulky and massive than it actually is; see Halpern 1945), macro- and microsomatognosia (i.e., the sensation that the body, or a part thereof, is significantly larger or smaller than it actually is; see Podoll and Robinson 2000), the Isakower phenomenon (a sleep-related group of phenomena that includes the sensation of a shrinking or swelling of the hands, the sensation of having something dry, crumpled or sandy on the skin or in the mouth, and the sensation of floating; see Isakower 1938 and Dann 1992), and numerous other symptoms and syndromes described in the literature, as well as bodily percepts due to unknown somatic conditions. It may be tempting to attribute our lack of understanding of these phenomena to the limited availability – as well as the modest size – of neurobiological studies in this area, but an equally grave problem would seem to be at the level of conceptualization. As noted above, the conceptual distinction between sense perceptions and hallucinated percepts allows for a practicable operationalization in clinical and neuroscientific terms as long as the "distance senses" are involved but fails to do so in the case of many types of bodily sensation. The notion that any type of percept can be either "real" or "imagined" may well be true, but it quickly loses its meaning when our judgment must be made without the possibility of the external verification of sensory input signals.

13.8 Conclusion

The umbrella term "bodily hallucination" refers to a group of widely divergent and only rudimentarily understood corporeal sensations. In clinical practice it may be helpful to let the diagnosis of bodily hallucination depend on the co-occurrence of a delusional explanation by the patient, but even this procedure is not airtight. Future studies seeking to enhance our understanding of these phenomena will have to address – as always, in biomedicine – neurobiological as well as conceptual issues.

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Chapter 14
Hallucinatory Pain: Central Pain

Sergio Canavero

14.1 Introduction and Historical Note

Pain from physical trauma is a common experience. Pricking a finger, for example, engenders acute, temporary pain, classified by physiologists as nociceptive pain since specialized receptors (i.e., nociceptors) are involved in their mediation. The mere possibility that pain may also arise "spontaneously," that is to say in the absence of a direct noxious stimulus, has been considered an impossibility until the latter half of the nineteenth century. In fact such "spontaneous" pains are very much akin to visual and auditory hallucinations, as they stem from a focal disturbance of the brain.

In 1521 the French surgeon Ambroise Paré (c. 1510–1590) described with great clarity phantom limbs (see also Chap. 16), and in 1866 the US neurologist Silas Weir Mitchell (1829–1914) published his first account of phantom limbs in the *Atlantic Monthly* as an anonymously written short story, *The Case Of George Dellow*, wherein the protagonist has both legs amputated during the American Civil War and upon awakening is suddenly aware of a "sharp cramp" in the left leg, which, however, is missing. In 1888 "Frau R.," having agonized with "terrible pains" for 2 years, committed suicide; not even opium could relieve her pains, which followed cerebral infarction. By studying this case in 1891, Ludwig Edinger (1855–1918), working in Frankfurt am Main, published his seminal paper in which he hypothesized the existence of "centrally arising pains" (Edinger 1891). The concept that pain could be released independently of peripheral nociceptive stimulation was born.

Actually, patients suffering from central pain (CP) had already been described by other authors, both in western and eastern sources, at least since the early 1800s; nonetheless, nobody actually intuited that brain damage alone could trigger spontaneous, unrelenting pain. In 1938 George Riddoch (1888–1947) published his three-part

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review of CP in *The Lancet*, thereby establishing it as a definite nosological entity (Riddoch 1938). By that time, it was clear that CP could be caused by brain damage at various levels (cortex, subcortex, thalamus, brainstem), but also by spinal cord injury (so-called paraplegia pain), as amply noted during World War I.

In 1906 Jules Dejerine (1849–1917) and Gustave Roussy (1874–1948) described the so-called thalamic syndrome, in which pain was experienced among other symptoms and signs due to thalamic stroke (Dejerine and Roussy 1906). A few years later, a scholarly paper by Henry Head (1861–1940) and Gordon Holmes (1876–1965) defined the sensory deficits that characterize CP (Head and Holmes 1911). Unfortunately, an exclusive focus on the thalamus sidelined the cortex and other brain areas, and for the best part of the twentieth century, CP was attributed mainly to thalamic stroke. Only with the advent of computerized tomography (CT) in 1973 and magnetic resonance imaging (MRI) in 1981 it became clear that pure thalamic lesions are not the primary triggers for CP (Canavero and Bonicalzi 2011). Finally, a series of epidemiological studies found CP to be a major, under-recognized nosological entity.

14.2 Definition and Epidemiology

CP is an all-encompassing term which refers to pain, dysesthesias, paresthesias, and – as recently realized – pruritus (Canavero et al. 1997; for an explanation of all these terms see Table 14.1) initiated by a central nervous system (CNS) lesion impinging on or interfering with the spinothalamic tract en route to the parietal somatosensory areas, i.e., the path responsible for the conduction of nociceptive and thermal stimuli. The anatomical basis of CP was highlighted in a major work by Cassinari and Pagni (1969) and was later confirmed by electrophysiological studies employing laser-evoked potentials, which specifically explored the pain- and temperature-conducting pathways in the CNS (Canavero and Bonicalzi 2011).

Before the term "central pain" gained general acceptance, various other terms were proposed, including thalamic pain, pseudothalamic pain, and insular pain. CP after spinal injury was priorly referred to as paraplegia pain or remote pain (as opposed to end-zone pain), among many other terms. All those terms have now been discarded in favor of *central pain of brain or brainstem origin* (as seen in medullary stroke, i.e., Wallenberg's syndrome) and *central pain of cord origin* (Canavero and Bonicalzi 2011).

Long considered to be a neurological rarity, we now know that no less than 9–10% of all CNS strokes (both ischemic and hemorrhagic, see Andersen et al. 1995 and Bowsher 2001); no less than 20–25% of all spinal cord injuries (SCI), including syringomyelia (Siddall et al. 1999); almost 20% of all cases of multiple sclerosis (MS) (Solaro et al. 2004); perhaps 2% of all cancer cases (Gonzales et al. 2003); and an undefined number of other neurological conditions coincide with CP, thus running in the millions worldwide (see further series in Canavero and Bonicalzi 2011). In the USA alone, no less than 600,000 patients suffer from CP, which is ten times more than previously estimated. Males are generally overrepresented, in older age in cases

Table 14.1 Types of central pain

Type of pain	Characterization
Allodynia	Pain due to a stimulus which does not normally evoke pain
Central pain	A group of spontaneous and/or evoked anomalous bodily sensations, painful or nonpainful in nature, which are projected into a body part congruent with a clearly imaged lesion of the central nervous system
Dysesthesia	An unpleasant and abnormal bodily sensation, whether spontaneous or evoked
Evoked pain	An umbrella term for allodynia, hyperalgesia, and hyperpathia
Hyperalgesia	An increased response to a tactile stimulus which normally is painful
Hyperpathia	An abnormally painful reaction to a tactile stimulus which lasts beyond the stimulus duration
Paresthesia	An abnormal bodily sensation of "pins and needles," whether spontaneous or evoked

of stroke, in younger age after SCI, the only exception being MS, which predominantly affects females. An often unrecognized cause of CP is iatrogenic lesions: CP can be a complication of neurosurgical procedures both on the spine and the brain, ranging from disc ablation at dorsal levels to tumor excision in the parietal lobe, brainstem, or cord. Unfortunately, the lack of awareness of this possibility tends to delay effective treatment. On the other hand, the possibility that neurosurgical pain-relieving procedures (e.g., thalamotomies, mesencephalotomies, cordotomies, and so on) inadvertently entail a new type of pain, i.e., CP, is a well-recognized paradox (Cassinari and Pagni 1969).

Roughly 1% of all epileptic patients suffer painful fits at least once in their lives: we consider this a central-pain-allied condition (CPAC) since there is no actual damage to the parietal projection of the spinothalamic tract. Nonetheless, the end cells of that pathway are likely to be involved (Canavero and Bonicalzi 2011). For a long time, dysesthetic pain as reported by some patients with Parkinson's disease was considered a form of CP, but this has been refuted (Canavero 2009a, b).

14.3 Clinical Features and Diagnostic Evaluation

CP has three components (Tasker 2001): (1) a continuous, spontaneous pain (which may be described as aching, burning, pricking, lacerating, or cramping); dysesthesias; paresthesias; pruritus; or combinations thereof; more than one kind of pain is experienced in more than 90% of the patients, while in cord CP and MS-associated CP, dysesthesias are often reported (Beric 1999); (2) a spontaneous, intermittent, generally lancinating pain, which is experienced by about 10–20% of the cases; and (3) evoked pain, experienced by about two thirds of the patients (rarely constituting the sole presenting symptom). In the latter cases, a nonpainful or only mildly painful stimulus is felt as painful or burning (i.e., allodynia) or very painful (hyperalgesia, or hyperpathia if it lasts beyond the moments of stimulation; see also Table 14.1). Evoked pain, just as in peripheral neuropathic pain, can be elicited by mechanical (static or dynamic) or thermal (cold more than heat) stimuli. In cases described as

hyperpathic, the pain is usually unbearable and evokes violent emotional and defensive reactions; characterized by late onset and poor localization, it generally irradiates from the stimulated point to the entire half of the body and persists for an unusually long time after the stimulation has ceased. Evoked pain and intermittent shooting pains can hinder the patient's daily activities because innocuous maneuvers can trigger fits of intolerable pain. Patients may have to wear a glove when the hand is affected. All those anomalous sensations are referred inside a larger area of sensory loss or hypesthesia on the side of the body contralateral to the cerebral or spinal damage. Pain may be felt superficially, deep, or both. Symptoms may be focal (hand/arm, hemichest, foot and/or leg) or affect half of the body – as generally seen after thalamic and cortical lesions – or one side of the face, ipsilaterally, and the rest of the hemisoma, contralaterally (Wallenberg's syndrome) following brainstem injury. CP after SCI (both complete and incomplete) may affect the entire body region below the level of injury, but usually it is more intense in the sacral dermatomes, buttocks, genitalia, and feet. Signs of dystrophy in affected areas may be observed in some CP patients (Canavero and Bonicalzi 2011). The intensity of the pain varies from a mild, unpleasant tingling to one of the most agonizing torments known to humans.

CP greatly impairs one's quality of life, interfering with sleep patterns and driving people to suicide. Its highly unpleasant quality tends to disable patients even when the intensity is low (Canavero and Bonicalzi 2011; Tasker 2001).

The diagnosis of CP is rather straightforward when a patient complains of pain or other abnormal sensations following CNS injury. The neurological examination usually reveals areas of hypoanesthesia to thermal stimuli and pinches. Those areas must be assessed clinically with cold (e.g., an ice cube) and warm stimuli as well as with pinpricks. Frequently, evoked pain will be elicited. In the clinical setting, pain scales may be employed, although they are more useful in research settings.

Due to its clinical features, which can be misinterpreted as peripheral neuropathic pains (e.g., diabetic neuropathy), all patients must be assessed neuroradiologically and neurophysiologically to exclude any sensory neuropathies. MRI is the instrument of choice in the assessment of CP; a lesion (whether it be an ischemic or hemorrhagic lesion, a tumor, a demyelinating plaque, etc.) is usually seen along the spinothalamic pathway. In doubtful cases, laser-evoked potentials (LEPs) may confirm damage to the (sensory) C/A delta fibers. Shoulder-hand pain, which frequently accompanies stroke, is generally considered nociceptive, but a neuropathic component cannot be excluded (Canavero and Bonicalzi 2011). Pain caused by muscle cramping or dystonia due to an abnormal tone, posture, or muscle excitability is often seen after CNS damage and must be differentiated from CP.

14.4 Natural History

CP generally starts days, weeks, or months after a CNS insult but may present suddenly or take one or more years to develop; when the delay is in the year range after SCI, a syrinx may be found on MRI (Beric 1999). Once set in, CP remains with the

patient for a lifetime in the vast majority of the cases. It may fluctuate during the day, depending on such factors as stress, weather changes, and effort. Rest and distraction may lessen CP. Unlike brain CP, which usually does not change significantly over time, except in degree, cord CP may change remarkably over the years: it may increase in severity for several years and even change in distribution and quality, sometimes dramatically (Canavero and Bonicalzi 2011; Beric 1999).

Careful studies reveal that CP may completely and suddenly regress after removal of the inciting lesion in some patients (Canavero and Bonicalzi 2001; Kim et al. 2006; Schott 2001). Likewise, a further stroke along the parietothalamic axis may abolish the pain (Canavero and Bonicalzi 2011; Canavero 1994). These observations have pathophysiological consequences that will be discussed below.

14.5 The Genesis of Central Pain

Scores of different theories have been proposed to explain CP. For a long time, the thalamus has played a starring role in them. Animal studies over the last 20 years have not added any insights to the field for the simple reason that the brain structure and neurochemistry of animals differ significantly from those in humans (Canavero and Bonicalzi 2011). In the end, a theory in biomedicine is considered a good one if it leads to therapeutic advances. In that sense, most theories have failed.

The highly popular view that central and peripheral neuropathic pain can both be understood within the framework of so-called deafferentation pain (Tasker 2001) has never made it into international classifications, and although sharing similar pain descriptors, differences between the two types of neuropathic pain are so numerous that a common genesis is out of the question. For instance, while brachial plexus avulsion pain responds well to standard dorsal root entry zone (DREZ) lesions, since the pain generator is a hyperactive focus in the spinal dorsal horns, CP of cord origin does not; likewise, thalamic stimulation and thalamic surgical lesions are far more effective for peripheral neuropathic pain than for CP (Canavero and Bonicalzi 2011). Subhypnotic propofol, an intravenous anesthetic with gamma-aminobutyric-acidergic (GABA-ergic) properties, can relieve CP but only rarely peripheral neuropathic pain (Canavero et al. 1995).

It has become clear that CP must be understood within a framework that includes both the thalamus and the sensory (somatosensory area I/motor area I) cortex (Canavero 1994; Canavero et al. 1995). In particular, it is a derangement of the oscillatory pattern (and hence of the content of the information transmitted) inside the sensory corticothalamocortical loop that best explains the pathophysiology of CP (dynamic reverberation theory of central pain, Canavero 1994). That derangement is possible because of the establishment of an "attractor state" (see Chap. 4, this volume; Canavero and Bonicalzi 2011, Chap. 26) in the cortical energy landscape, exploiting the highly recurrent nature of cortical microcircuitry. Layers V and VI of primary somatosensory cortex (SI) responsible for the massive output to the thalamus cannot "escape," unless supraphysiologic inhibition is applied pharmacologically or by way of electrical stimulation.

In-depth recordings in patients' brains point to various anomalies in the brainstem, thalamus, and cortex (Canavero and Bonicalzi 2011; Tasker 2001). In particular, hyperactivity of the bursting type within the thalamus, both in sensory and aspecific (central lateral) nuclei, has been considered indicative of a local dysrhythmia (Sarnthein et al. 2006; Lenz and Dougherty 1997). This has been refuted, however, as bursting is a modality of transmission of the normal brain (Radhakrishnan et al. 1999; see Canavero and Bonicalzi 2011 for further contrary evidence). Thalamic dysrhythmia as a mechanism for central pain is also unlikely because of two simple observations: (1) central-lateral (CL) thalamotomies are poorly effective for CP, and (2) the descending corticothalamic arm is facilitatory, not inhibitory (Canavero and Bonicalzi 2011). On the other hand, a disturbance in neural patterns of activity applies to CP as well as to many other neurologic disorders (Montgomery 2010).

Another popular theory emphasizes neuroplastic changes in the CNS following "deafferentation" (Canavero and Bonicalzi 2011; Tasker 2001). "Entrenched" neuroplasticity, spanning from the changes in brain maps to the sensitization of central structures, has been put forth to explain chronicity – and so purported neurodegenerative changes as evidenced by MR spectroscopy studies – but a sudden resolution of CP after the extirpation of inciting lesions (Pagni and Canavero 1995) or a further stroke (Canavero 1994) clearly suggests that plasticity (or neurodegeneration) cannot underlie constant pain, as both would then be reversible under such circumstances (Schott 2001). Moreover, careful studies by Tasker's group reveal major differences between what occurs in the human patient and the experimental animal in terms of plastic changes (Kiss et al. 1994).

Importantly, CP can be canceled by lesions interrupting the thalamocortical loop in the subparietal corona radiata and internal capsule. Careful analysis of such cases reveals that it is the much larger descending arm of the thalamocortical loop that is key to maintaining CP over time (Canavero and Bonicalzi 2011; Canavero 1994). A role in feeding the loop comes from hyperactive reticular cells along the spinotruncothalamic axis, whose destruction may help allay CP (Bowsher 2001; Finnerup et al. 2003). This has been highlighted by studies dealing with mesencephalic reticulotomy (Amano et al. 1992) and extended DREZ-tomies (Falci et al. 2002). The difference between subparietal lesions and the latter ones lies in the rate of disappearance of CP, i.e., suddenly versus gradually.

The possibility of hyperexcitation of the spinothalamic pathway by the reticulothalamic system, which is in turn modulated by the medial lemniscus, is supported by clinical data (Kim 2007). Neuroimaging studies using techniques such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have provided valuable data in this area of research. Unfortunately, however, most of those studies focused on evoked pains, which, as stated, are not key to CP. Studies investigating the spontaneous component with drug dissection, although few, have confirmed the role of the sensory cortex as well as the thalamus (Pagni and Canavero 1995; Canavero et al. 1993; Hirato et al. 1993; Canavero et al. 1996; see also Figs. 14.1, 14.2, 14.3, 14.4, and 14.5), while evoked pains elicit different – and wider – patterns of neural activity, particularly in prefrontal areas (Ducreux et al. 2006).

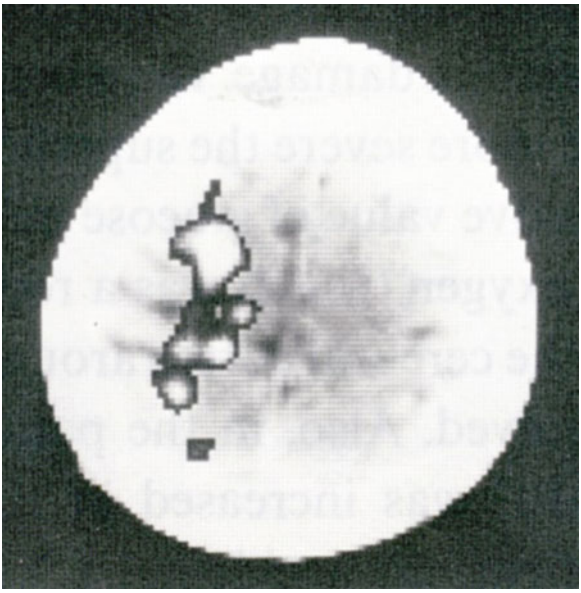

Fig. 14.1 Superposition of computerized tomography (*CT*)/positron emission tomography (*PET*) images in a case of brain central pain. Note that the regional oxygen extraction ratio is increased in the cerebral cortex around the central sulcus (sensory cortex I/motor cortex I) (From Hirato et al. (1993). Reproduced with permission)

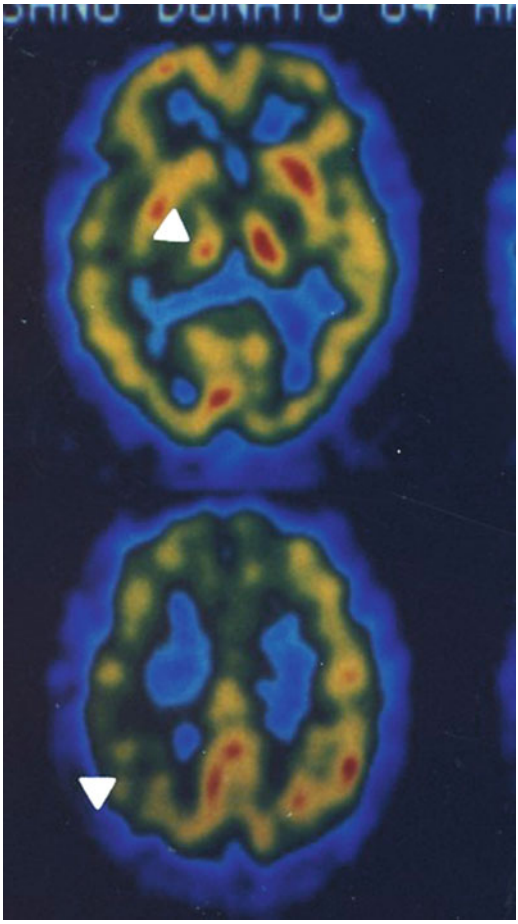

Fig. 14.2 Regional cerebral blood flow (*rCBF*) decreases at primary somatosensory cortex (*SI*) and thalamic levels in a case of cord central pain (From Canavero and Bonicalzi 2011)

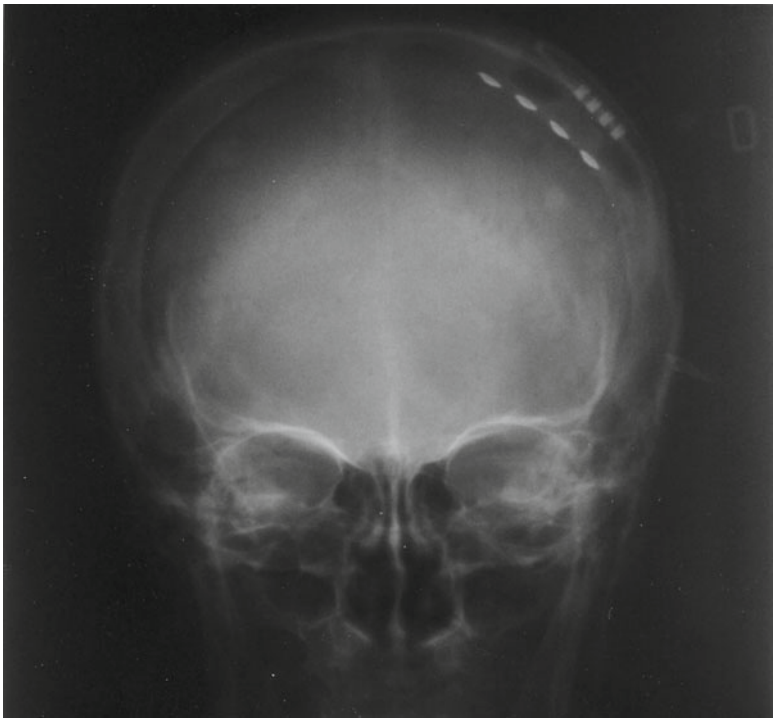

Fig. 14.3 Skull X-rays of an extradural cortical stimulating (*ECS*) paddle in place

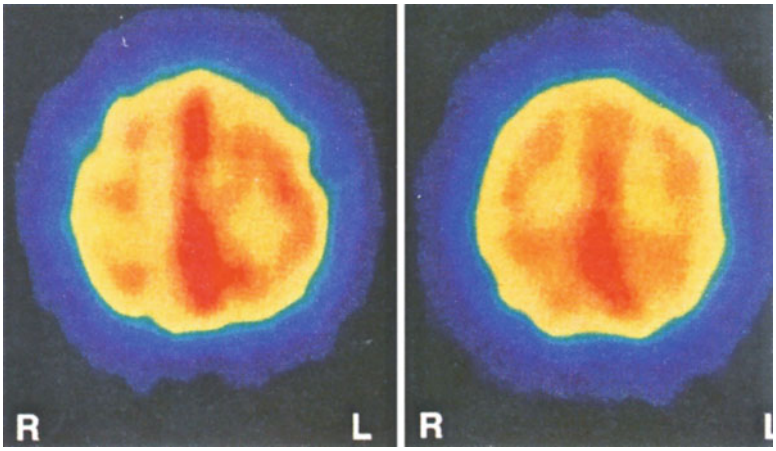

Fig. 14.4 Regional cerebral blood flow (*rCBF*) renormalization at the primary somatosensory cortex (*SI*) level following extradural cortical stimulation (*ECS*) (From Canavero and Bonicalzi 1995)

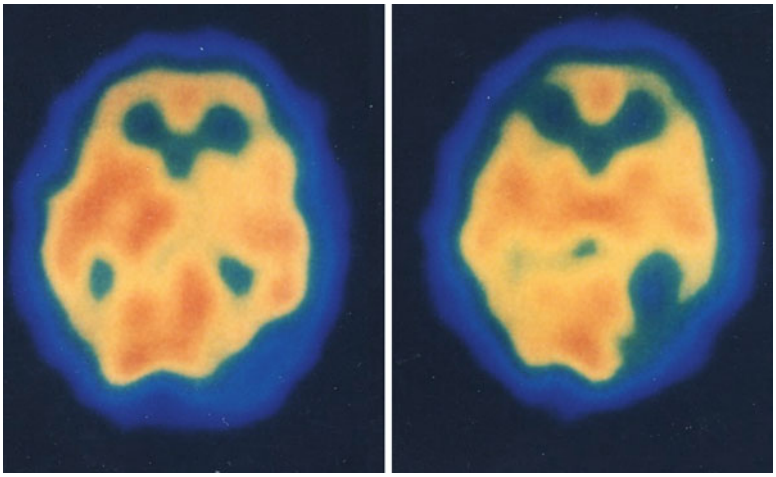

Fig. 14.5 Renormalization of thalamic hypoperfusion following a bolus of propofol at subhypnotic doses in a case of brain central pain (From Canavero et al. 1995)

A recent study espoused the view that "the evidence of blood flow, stimulation, and lesion studies forcefully make the case that (thalamic primary sensory nucleus) Vc and sensorimotor cortex are involved in [central post-stroke pain]" (Kim et al. 2007).

Data from Tasker's group also support the view that the generator of ongoing CP can be shifted to the healthy hemisphere (Parrent et al. 1992), thus explaining cases of CP after massive destruction of one thalamus or sensory cortex. Clinical observations likewise support the possibility of a unilateral CNS lesion triggering bilateral CP (Canavero 1996; Kim 1998, 1999).

It has been proposed that a certain number of people may be genetically predisposed to develop CP. In fact a lesion anywhere along the spinothalamocortical pathway only triggers CP in a minority of patients, while sparing most others (Tasker 2001). Thus spinothalamocortical damage is necessary, but not sufficient, for CP to arise (Canavero and Bonicalzi 2011; Finnerup et al. 2003; Ducreux et al. 2006). In particular, there is a suggestion that sparing of the lemniscal system, along with damage to the spinothalamic system, may trigger dysesthetic pain (Beric 1999). Neuropharmacological data with GABA agonists point to a specific derangement of GABA transmission at the basis of CP (Canavero and Bonicalzi 1998). It is surmised that CNS damage in these cases triggers an acute GABA loss, which then unbalances the oscillatory pattern along the thalamocortical loop responsible for conscious sensory processing, starting in the somatosensory cortex (Canavero and Bonicalzi 2011).

In this context, anomalies seen in the cingular and temporal areas are unspecific findings present in most chronic pain patients without them constituting the primary cause of CP. According to Craig (1998), CP is subtended by a hyperactive spinothalamocingular pathway after selective damage to a specific spinothalamoinsular

pathway, i.e., the posterior part of the ventral medial nucleus (VMpo). However, this thermosensory disinhibition hypothesis has been disproven on clinical and neurophysiological grounds (see Canavero and Bonicalzi 2011 for discussion and references), and its anatomic foundations have been refuted (Jones 2007). The insula, unlike what some authors currently think, is not paramount to the genesis of central pain: primary somatosensory cortex (SI) is central to pain awareness even in acute pain (Nir et al. 2008), and it is the only area which topographically feeds back to the sensory thalamus along the path that cancels central pain.

On the other hand, the different components of evoked pain are most likely due to different pathophysiological mechanisms, i.e., thermal versus mechanical allodynia (Canavero and Bonicalzi 2011; Ducreux et al. 2006; Greenspan et al. 2004). Thus central sensitization along spared – thermally or mechanically coded – pathways may well play a major role in the genesis of those types of pain (Canavero and Bonicalzi 2011; Tasker 2001; Greenspan et al. 2004).

The sympathetic nervous system plays no role whatsoever in the genesis or sustenance of CP (Canavero and Bonicalzi 2011; Rondinelli et al. 2008; Bonicalzi and Canavero 2000) for the simple reason that sympathetic-nociceptor interactions do not exist (Campero et al. 2010).

14.6 Therapy

CP is best understood as a "cancer of the spirit" which nibbles away each day at the patient's quality of life until severe disruption in daily living inexorably sets in. Therefore, it is of the utmost importance that valuable time not be lost trying a smorgasbord of – often useless – drugs. If a trial of oral pharmacotherapy produces no benefit within 6 months, neuromodulation must be the next therapeutic step without any further delay.

14.6.1 Drug Therapy

Various effective agents have been identified for the purpose of reducing CP, but only few are suitable for oral use. Lamotrigine and amitriptyline are the only oral drugs that have a proven benefit for brain CP, whereas they appear to be less effective for CP of cord origin. Although not submitted to any formal studies, mexiletine appears to be a valuable drug, whereas gabapentin and pregabalin are effective in only few patients (Canavero and Bonicalzi 2011). Many other drugs, including opioids, have been tried, with most patients failing to benefit or only mildly so (Canavero and Bonicalzi 2003). Cannabinoids have not advanced therapy to any meaningful extent, and a major drawback is that they can trigger psychosis. It should be noted anyway that all these drugs have side effects that limit their use, above all in special patient populations such as the elderly and those with spinal injuries (who are vulnerable to

the anticholinergic effects of amitriptyline), while some of them can lead to rare but major toxicities (e.g., Stevens-Johnson syndrome during lamotrigine consumption). Topiramate, levetiracetam, reboxetine, valproate, duloxetine, and the selective serotonin reuptake inhibitors (SSRIs) – among others – are generally ineffective (Canavero and Bonicalzi 2011), whereas oral NMDA (N-methyl-D-aspartate) blockers such as dextromethorphan are modestly effective yet poorly tolerated.

14.6.2 Electrical Neuromodulation

As far as medication-resistant brain CP is concerned, the technique of choice is extradural cortical stimulation (ECS) of the primary motor or sensory cortex contralateral to the pain (Canavero 2009b). This is a minimally invasive neurosurgical technique in which a stimulating paddle is inserted through two burr holes or a small craniotomy and placed on the dura overlying the appropriate area to cover the painful region. More than half of the patients experience a pain reduction greater than 40% after 4 years of treatment (Canavero 2009b). No mortality or permanent morbidity (including the kindling of an epileptic syndrome) has been reported in hundreds of reported cases since the technique's introduction in 1989 (Canavero 2009b). Both spontaneous and evoked components are altered favorably. Patients may be selected for ECS on the basis of pharmacological dissection with GABA agonists (propofol, barbiturates) and trials of transcranial magnetic stimulation (TMS) (see also Chap. 25) or transcranial direct current stimulation (tDCS), in which stimuli are applied noninvasively (Canavero 2009b). The latter techniques per se may give relief to some patients, but the therapeutic benefits tend to be short-lived, even when repeated cyclically. Neuroimaging studies and neuroengineering modeling clearly show that cortical stimulation (CS) can affect the underlying sensory cortex and the corticothalamic loop; the contention that CS works by altering the affective component of pain is not supported (Canavero 2009b). Deep brain stimulation (DBS), in which one or two electrodes are inserted into the sensory thalamus or mesencephalon (periaqueductal-gray-matter (PAG) and periventricular-gray-matter (PVG) areas), is not effective in the great majority of the patients. Surgical complications include intracranial hemorrhage (up to 10%), stroke (up to 2%), and death (up to 4.4%). DBS has a long history, having been introduced for the treatment of CP during the 1960s. Experience over the years has not borne out the initial results (Hamani et al. 2006; Rasche et al. 2006). Spinal cord stimulation (SCS), in which a paddle is extradurally directed at cord segments, plays a limited role in no more than a few patients suffering from brain CP. For CP of cord origin with at least partially preserved lemniscal sensibility, SCS is the primary technique although its effects often abate within 1 year (Canavero and Bonicalzi 2011). In treatment-resistant cases and cases with complete loss of sensibility, and in which SCS is totally ineffective, the choice is between ECS and DBS. Unfortunately, not enough patients have accrued over time to evaluate the effects of ECS, while DBS is often ineffective. Transcutaneous electrical nerve stimulation (TENS), although the least invasive of

all the electrical neuromodulatory procedures, is of scarce benefit in the vast majority of patients. Moreover, it must be applied several times a day, thus hindering activities of daily living. If elected, it is best added on to an oral drug therapy (Canavero and Bonicalzi 2011). Some patients have been submitted to electroconvulsive therapy (ECT; see also Chap. 24), however, with mixed results. As a consequence, this is considered a technique of last resort reserved for highly refractory cases (Canavero and Bonicalzi 2011).

14.6.3 Chemical Neuromodulation

Various drugs can be infused into the subarachnoid space in order to control CP. However, no evidence-based recommendations are possible; only anecdotal evidence exists, and the few controlled studies lack the necessary power and follow-up data. A GABA-ergic agent like baclofen or midazolam can be infused with the aid of an implanted pump, best in combination with clonidine, an adrenergic agent (Canavero and Bonicalzi 2011). Opioids are only rarely effective and, in the long term, have major endocrinologic and immunologic toxicity. Ziconotide, a recently approved drug, appears insignificantly effective on CP and must be considered unsafe.

14.6.4 Neuroablation

Ever since the introduction of stereotactic surgery at the end of the 1940s, neurosurgical ablative techniques such as thalamotomies and mesencephalotomies have been offered to distraught patients, but results have not held up over time in most studies, in particular as regards the spontaneous components of CP (Canavero and Bonicalzi 2011; Tasker 2001). Furthermore, mortality and permanent morbidity often offset an initially positive result. Cingulotomy has proven of no benefit to the sensory components of CP. Surgery on the cord, including cordectomies and DREZ coagulations, may relieve evoked and paroxysmal components in some patients in the long run, but with unacceptable morbidity (Canavero and Bonicalzi 2011; Tasker 2001). The only ablative technique that makes sense in the light of the discussed pathophysiology is a small stereotactic lesion deep in the corona radiata/internal capsule in order to interrupt the descending arm of the corticothalamic loop: this has been confirmed in a patient with central post-stroke pain (CPSP), who was totally and immediately relieved by subparietal leucotomy/capsulotomy (Koszewski et al. 2003; see also Figs. 14.6 and 14.7). Such a selective lesion can also be produced by stereotactic radioneurosurgery or high-intensity focused ultrasound (HIFU) and DTI imaging of the descending arm in the individual patient.

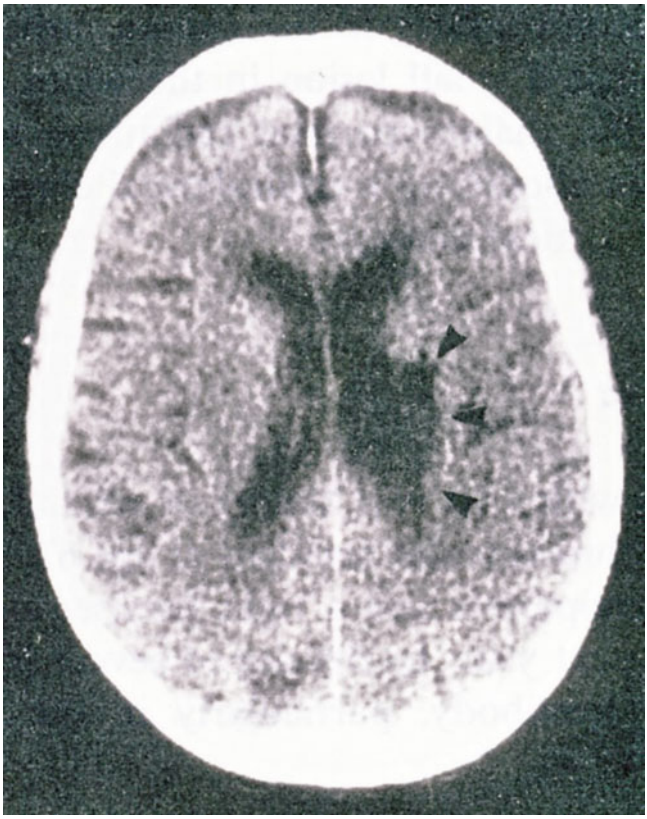

Fig. 14.6 Stroke in the subparietal corona radiata abolishing brain central pain (From Canavero and Bonicalzi 2011)

14.7 Conclusion

Central pain can easily be described as "hallucinatory pain," being couched as a disturbance of sensory information transfer along an uninhibited reverberating corticothalamocortical sensory channel. This generator alters the widely distributed small-world architecture of the brain (see Chap. 4, this volume, and Canavero and Bonicalzi 2011, Chap. 26), which can be neuroimaged, for instance, as an alteration of brain rhythms in multiple brain areas. These by themselves are not responsible for the sustenance of the pain but may contribute to the different qualities thereof. Incidentally, phantom pain can be abolished by a lesion along the same axis (Canavero 1994), disclosing a common mechanism underlying such hallucinatory pains.

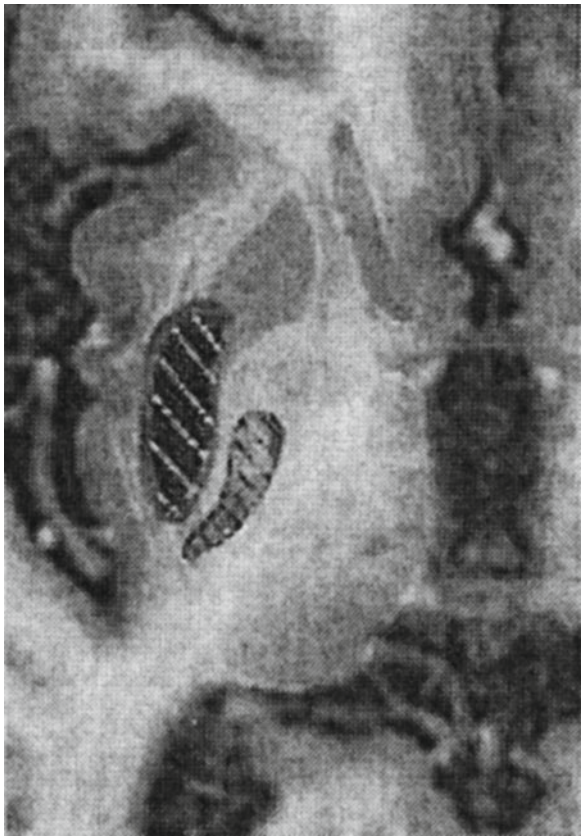

Fig. 14.7 Surgical stereotactic lesion interrupting the descending arm of the corticothalamocortical reverberatory loop abolishing brain central pain (From Canavero and Bonicalzi 2011)

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Chapter 15
Autoscopic Phenomena: Clinical and Experimental Perspectives

Anna Sforza and Olaf Blanke

15.1 Introduction

Autoscopic phenomena (from the Greek *autos* (self) and *skopeo* (looking at)) encompass a wide range of experiences involving the visual illusory reduplication of one's own body in extrapersonal space. They have been described in psychiatric disorders such as dissociation, schizophrenia, depression, and anxiety, as well as in various neurological disorders. Those neurological disorders include generalized diseases such as cerebral infection, meningitis, encephalitis, intoxications and generalized epilepsy, as well as focal diseases such as focal epilepsy (Devinsky et al. 1989), traumatic brain damage (Todd and Dewhurst 1955), migraine (Lippman 1952), vascular brain damage (Kölmel 1985), and neoplasia (Todd and Dewhurst 1955). Autoscopic phenomena have also been described in the healthy population, and they have widely inspired the literature (i.e., Fjodor Dostoevsky (1821–1881), Vladimir Nabokov (1899–1977), E.T.A. Hoffmann (1776–1822), Edgar Allan Poe (1809–1849), and Guy de Maupassant (1850–1893)) and the visual arts (for an overview see Blanke 2005).

15.1.1 Classification and Phenomenology

The scientific systematization of autoscopic phenomena (AP) began later than that of visual and non-visual illusions related to single body parts such as disconnection, dislocation, illusory movement, and the illusory reduplication of body parts (Brugger et al. 1997; Hécaen and de Ajuriaguerra 1952; Ramachandran and Hirstein 1998;

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Heydrich et al. 2010). The initial classification proposed by Devinsky et al. (1989) was extended by Brugger et al. (1997, 2002; see also Chap. 16), and subsequently by Blanke et al. (2004, 2008). It distinguishes three main forms of AP: out-of-body experiences (OBEs), heautoscopy (HAS), and autoscopic hallucinations (AHs), which differ with respect to phenomenological characteristics such as (1) self-location (i.e., the apparent location of the self within or outside one's body) and (2) the experienced visuo-spatial perspective. Autoscopy (i.e., the seeing of one's own body) is generally common to all three forms of AP.

15.1.1.1 OBEs: Out-of-Body Experiences

During an OBE, the experient has the subjective feeling of being awake, and typically experiences the "self," or center of awareness, as being located outside the physical body, at a somewhat elevated level. It is from this elevated extrapersonal location that the body and the world are experienced (Blackmore 1982; Devinsky et al. 1989; Brugger 2002; Blanke et al. 2004). Most OBE experients see their own body as lying on the ground or in bed, and the experience tends to be described as vivid and realistic. Thus an OBE is characterized by an abnormal, extracorporeal self-location (disembodiment), a distanced and elevated first-person perspective, and the seeing of one's own body (i.e., autoscopy) from the vantage point of this elevated perspective (see Fig. 15.1 for a graphic depiction of these OBE features).

15.1.1.2 AHs: Autoscopic Hallucinations

During an AH, people are seeing a double (doppelgänger) of themselves in extrapersonal space. Compared to OBEs, AHs are seen from the habitual first-person perspective, while the "self," or center of awareness, remains inside the physical body (normal self-location). Experientially, AHs are set apart from the other AP in the sense that the subject tends to realize the hallucinatory nature of the experience. AHs are usually very brief, and they are often accompanied by other visual hallucinations or illusions, as well as by visual field deficits (Blanke and Mohr 2005). Often only one's own face or the upper part of the trunk is perceived (Blanke and Mohr 2005; Zamboni et al. 2005, see also Fig. 15.1). Recently, however, Bolognini et al. (2011) described an atypical case of AH in which the patient reported seeing a profile view of the autoscopic body. What made this case even more interesting was the autoscopic body's tendency to react to motor activity. As long as the patient was standing still, the hallucination was limited to the head and upper trunk. Passive displacement of the patient's arms and active walking, however, were followed by an "extension" of the autoscopic body with arms and legs. As we shall explain in Sect. 15.1.2, these findings suggest that not only sensory mechanisms but also sensorimotor and proprioceptive mechanisms would seem to play a role in the mediation of AHs.

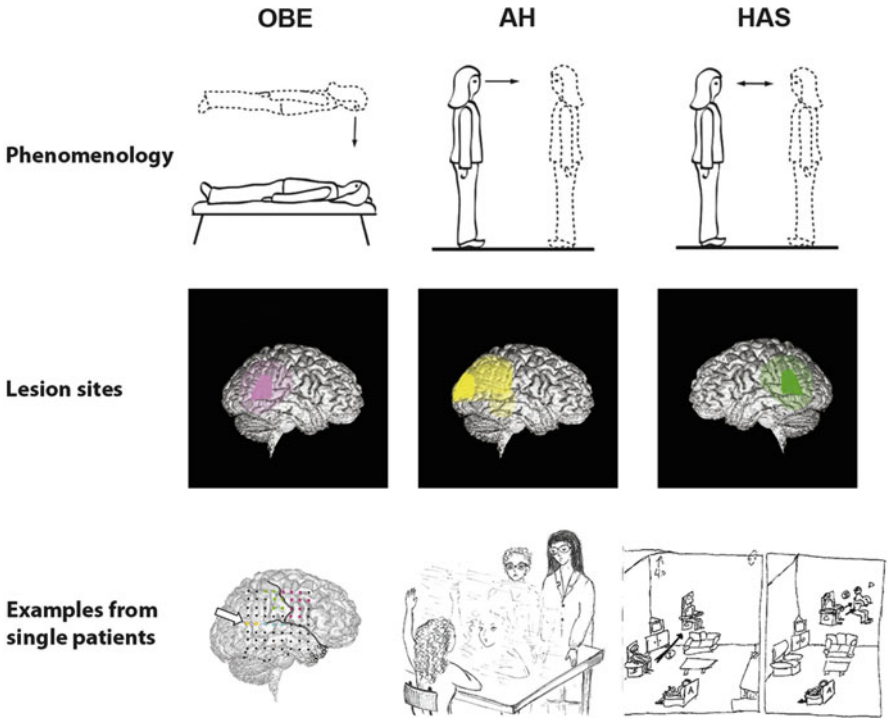

Fig. 15.1 Summary of the phenomenological and neural aspects of autoscopic phenomena: *Phenomenology.* In out-of-body experiences (*OBEs*), self-localization and the first-person perspective are at the position of the illusory body, that is, a position that is somewhat elevated with respect to the physical body; during an autoscopic hallucination (*AH*), the person sees an illusory copy of his own body from the vantage point of the habitual first-person perspective, thus maintaining a normal self-localization; heautoscopy (*HAS*) is an intermediate form in which self-localization and the first-person perspective are either at the position of the physical body, at the position of the illusory body, or at both positions simultaneously or alternatingly (Lopez et al. 2008). *Lesion overlap of brain damage.* Patients with OBEs show damage in the right temporo-parietal cortex; patients with AHs in the right parieto-occipital or right temporo-occipital cortex; patients with HAS in the left temporo-parietal cortex (Blanke and Metzinger 2009). *Examples from single-case studies.* Stimulation of the electrode sites indicated by the arrow (on the right angular gyrus) induced OBEs in an epileptic patient with implanted subdural electrodes (Blanke et al. 2002); graphical representation of an AH by Zamboni et al. (2005), based on their patient's description: visual features and movements appear in a mirror fashion; only the upper trunk and the face were seen; graphical illustration of experienced HAS (as drawn by the patient himself): during an initial episode he experienced being elevated with his living room chair into the air. In an immediately following moment, he experienced a "second" body, which continued to be elevated, but left the patient's body from the elevated position in the chair (Blanke et al. 2004)

15.1.1.3 HAS: Heautoscopy

A third form of AP is HAS, which can be conceptualized as lying on a continuum between AHs and OBEs. The person experiencing HAS is also seeing a double of himself/herself in extrapersonal space. However, it is difficult for him/her to decide

whether the self is located within the physical or the autoscopic body (Blanke et al. 2004, see also Fig. 15.1). In addition, the subject often reports seeing the physical and autoscopic bodies alternatingly or even simultaneously from different first-person perspectives (physical body, double's body). Moreover, the double may or may not mirror the subject's exact physical characteristics. And yet, it tends to be recognized as "being one self." This feeling of self-identification is usually accompanied by marked alterations in bodily awareness, such as an unusual lightness of the body, vestibular illusions, or feelings of detachment. Frequently, heautoscopic echopraxia, that is, the imitation of bodily movements by the double, helps to create the illusion that it is the doppelgänger that "contains the real mind" (Lukianowicz 1958; Brugger et al. 1994).

15.1.1.4 Other Forms of AP

In addition, three other phenomena tend to be classified as AP: internal heautoscopy, negative heautoscopy (Hécaen and de Ajuriaguerra 1952; Lhermitte 1939; Sollier 1903), and the feeling of a presence (Grüsser and Landis 1991; Brugger et al. 1996; also called "sensed presence," see Chap. 17). During internal heautoscopy, subjects perceive one or several of their inner organs. During negative heautoscopy, they fail to see their reflection in a mirror or any other reflecting surface. In the latter case, the confinement of the (negative) hallucination to one's own body and the frequent association with depersonalization are considered evidence of the close relationship of the phenomenon with positive autoscopic experiences. Negative heautoscopy and internal heautoscopy are considered extremely rare. Only few case reports exist, and even fewer discussing their neuropsychological characteristics or their association with focal brain damage (see also Brugger et al. 1997 and Blanke et al. 2008).

The feeling of a presence (FP), described by Jaspers 1913 as *leibhafte Bewusstheit*, is defined as the conviction that there is another person close by without the percipient being able to actually perceive that person. The phenomenon has received much attention over time, and different authors have used many different names when referring to it. Thus, FP has been called *hallucination du compagnon* (Lhermitte 1939), idea of a presence (Critchley 1955), hallucination of presence, false proximate awareness, false bodily awareness, intruder hallucination, somaesthetic phantom double, somaesthetic doppelgänger, heautoscopy without optical image, phantom impressions, *Anwesenheit*, and concrete awareness (see Blom 2010).

15.1.2 Multisensory and Anatomical Mechanisms

It has been proposed that the phenomenological differences between the three main forms of autoscopy should be attributed to systematic variations in underlying brain mechanisms. Most authors conceptualize autoscopic phenomena generically as disorders of own-body perception and/or corporeal awareness and attribute them to

multisensory and/or sensorimotor disintegration. Blanke and Mohr (2005) offer a detailed review of the literature outlining the contribution of the various sensory modalities that may be involved in mediating them. Multisensory mechanisms in the higher-level integrative brain areas of the extrastriate visual system would seem to be primarily involved in the case of AH, which could be mainly described as a visuo-tactile or "specular" hallucination or pseudohallucination. Indeed those phenomena are often lateralized and associated with the side of the hemianopia, without any concomitant vestibular hallucinations or body-schema disturbances (Blanke and Mohr 2005).

Proprioceptive and kinesthetic processing are considered particularly relevant for the mediation of HAS (especially in comparison with AHs; see Sollier 1903). In 1903, Sollier already postulated that heautoscopy is essentially a proprioceptive-kinesthetic disturbance associated with a strong psychological affinity of the physical body for the autoscopic body. The aforementioned phenomenon of echopraxia, found mainly in HAS, is often mentioned to sustain the alleged role of proprioception and kinesthesia in such disturbances. However, we propose that the three main forms of AP can be accounted for more systematically by reference to the vestibular system, which conveys sensations of the body's orientation in three-dimensional space.

Elaborating on a proposal by Grüsser and Landis (1991), Blanke et al. (2004) have suggested that systematic differences in vestibular function must underlie AHs, HAS, and OBEs. That assumption was based on clinical data pointing toward a strong association of OBEs with gravitational, otolithic, and vestibular disturbances (i.e., feelings of elevation and floatation) and the presence of a more variable type of vestibular dysfunction in patients with HAS, often characterized by rotational components, as well as the absence of any dysfunctioning of this system in AHs.

Support for this clinical hypothesis comes from a detailed analysis of the brain areas that were found to be damaged most frequently in patients with AP. Early studies stressed the involvement of posterior regions within the temporal, parietal, and occipital lobes (Brugger et al. 1997; Devinsky et al. 1989). More recently, however, Blanke et al. (2002, 2008) showed that OBEs and HAS are primarily associated with structural damage or electrophysiological hyperactivity at the temporo-parietal junction (TPJ; see also De Ridder et al. 2007 and Ionta et al. 2011), an area associated with vestibular processing, multisensory integration, and the perception of human bodies and body parts (Blanke and Arzy 2005; Lopez et al. 2008), while AHs are primarily associated with damage to the parieto-occipital cortex (Brandt et al. 2005). The latter finding would seem to be in line with the phenomenology of AHs, which are predominantly visual in nature, and do not involve any dramatic alterations in perspective and embodiment.

In summary, lesion data suggest that OBEs are associated primarily with damage to the right TPJ, HAS with damage to the left TPJ, and AHs with damage to the right parieto-occipital cortex (Blanke and Mohr 2005). Thus, AP in general would seem to derive from a double failure in multisensory integration processes: those related to proprioceptive, tactile, and visual information regarding one's own body (disintegration in personal space) and an additional vestibular dysfunction leading to a disintegration of personal (vestibular) space and extrapersonal (visual) space (especially in the case of OBEs, but also in HAS). The question to be answered in

the forthcoming sections is how these clinical and neurobiological findings can be translated to the research laboratory and the study of self-consciousness.

15.2 Experimental Approaches: Rubber-Hand Illusion, Full-Body Illusion, and Face Illusion

15.2.1 The Rubber-Hand Illusion: A Method Designed to Manipulate Self-attribution

The rubber-hand illusion (RHI) is a perceptual phenomenon in which normal individuals are made to experience an artificial limb (usually a hand) as if it were a part of their own body, due to a short period of synchronous stroking of their hand, which is hidden out of view, and a rubber hand lying next to it. The RHI was described for the first time in a seminal paper by Botvinick and Cohen (1998). It provided the first experimental means to manipulate the sense of ownership for a hand in healthy subjects. Until then, knowledge about the neural mechanisms underlying the sense of bodily ownership depended almost exclusively on clinical reports of patients with somatoparaphrenia, a condition due to temporo-parietal damage, which, in right-handed individuals, leads to the misattribution of their left hand or foot to another person (Giummarra et al. 2008).

The first explanation for the RHI was that of a three-way interaction between vision, touch, and proprioception: vision of the touch to the rubber hand dominates over touch experienced by the real hand, resulting in a mislocalization of the tactile percept toward the spatial location of the visual percept. This sense of referred touch to the rubber hand, also named "illusory touch," influences the felt position (proprioception) of one's own hand, which is perceived closer to the rubber hand. This is reflected in a measurable proprioceptive drift toward the rubber hand, which has been used as an objective, behavioral proxy of the illusion for a great part of the subsequent studies exploring hand ownership (Tsakiris and Haggard 2005, see also Fig. 15.2a).

Various authors have demonstrated that the RHI can only be elicited when synchronous (rather than alternating) brushstrokes are applied to the real and fake hands, and when the rubber hand is placed in a position congruent with the subject's own hand (Botvinick and Cohen 1998; Armel and Ramachandran 2003; Tsakiris and Haggard 2005). More recently, it was demonstrated that the illusion of ownership and proprioceptive displacement can also be evoked with the aid of a three-dimensional projection of an arm, as long as the appropriate synchronous visuo-tactile stimulation is provided in a virtual environment (Slater et al. 2008; Sanchez-Vives et al. 2010).

Subsequent studies exploring the brain activity during the experience of the RHI revealed various regions possibly related to hand perception, cross-modal integration, and conflict processing (Ehrsson et al. 2004; Tsakiris et al. 2007). Those studies

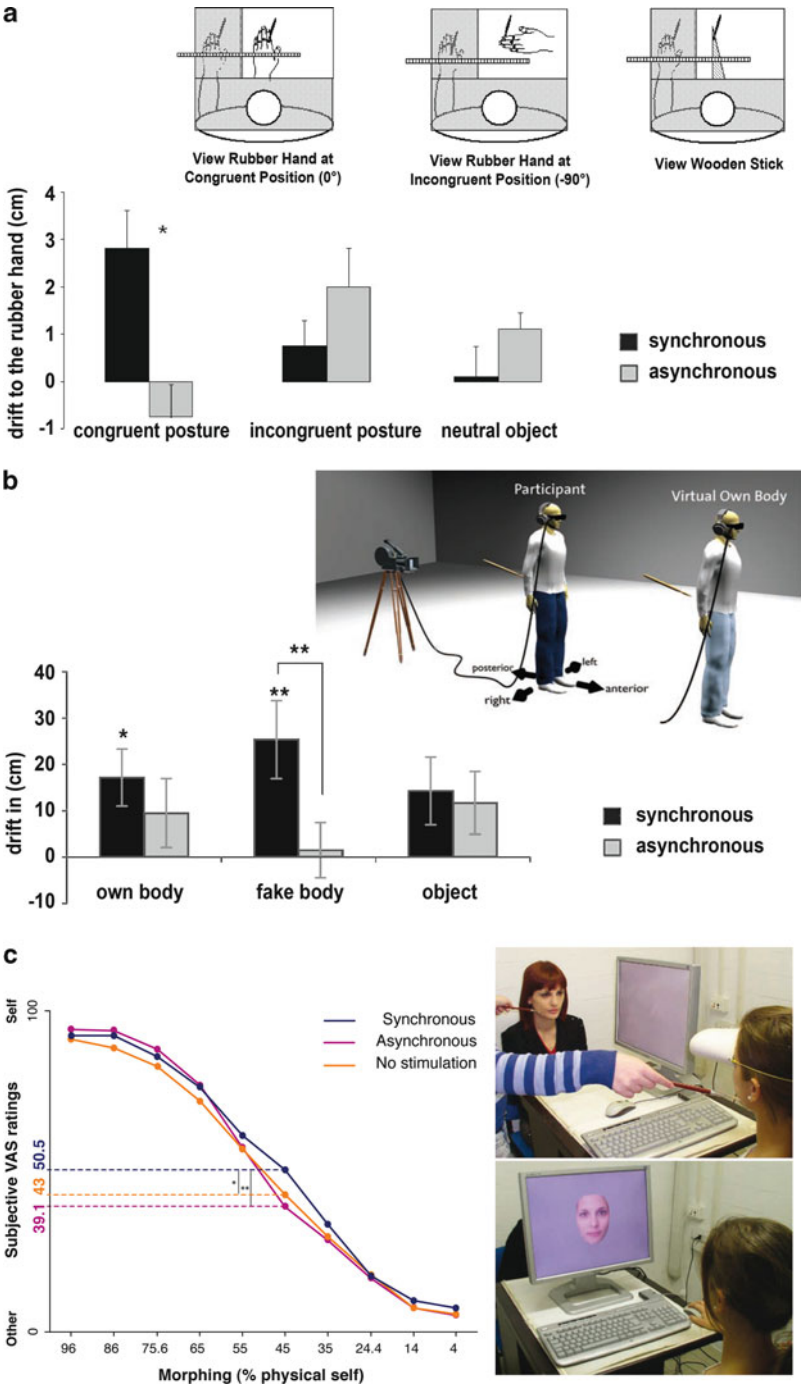

Fig. 15.2 Set-up and principal findings regarding the rubber-hand, full-body, and face-related illusions. (**a**) *Rubber-hand illusion (RHI):* stroking synchronously the subject's hand and a rubber

indicated that the feeling of body ownership is mediated by brain activity in regions involved in the integration of multisensory signals, such as bilateral premotor cortices and the cerebellum (Ehrsson et al. 2004), as well as the right posterior insula (Tsakiris et al. 2007), a region consistently implicated in self-attribution (Farrer and Frith 2002), self-processing (Vogeley et al. 2004), and the representation of an egocentric reference frame (Fink et al. 2003). The left inferior posterior parietal lobule was found to be involved in the recalibration of the perceived position of one's own limb toward the rubber hand. In fact this region is activated during the induction phase of the RHI (Ehrsson et al. 2004) and, when targeted by repetitive transcranial magnetic stimulation (rTMS, see also Chap. 25), a consistent reduction of the proprioceptive drift toward the rubber hand can be observed (Kammers et al. 2008). Interestingly, a similar effect has been described when the target region of rTMS was the right TPJ (Tsakiris et al. 2008). A role of this area in processing the sense of ownership of one's body parts is also suggested by recent evidence indicating that vestibular stimulation can increase the feeling of ownership of the fake hand in the context of the RHI (Lopez et al. 2010).

15.2.2 Full-Body Illusion: From Global Self-attribution and Self-localization to the First-Person Perspective

Even if the data from RHI studies show that important sub-global aspects of bodily experience such as self-attribution and self-localization of a fake or virtual hand can be manipulated experimentally, the fundamental sense of selfhood associated with bodily self-consciousness is still experienced as a singular feature, namely a coherent representation of the undivided, spatially situated body, rather than as multiple representations of separate body parts. This sense of self remains unaltered during the RHI (Blanke and Metzinger 2009), but is altered in OBEs and HAS. Inspired by both clinical phenomena, Lenggenhager et al. (2007) and, independently, Ehrsson (2007) induced changes in self-localization and self-identification for the entire body in healthy subjects by combining the multisensory conflict paradigm with virtual-reality technology, thus creating a full-body illusion (FBI). In the study by

Fig. 15.2 (continued) hand induced a proprioceptive drift toward the rubber hand. The effect is absent when the stroking is asynchronous, when the rubber hand is placed in an incongruent position with respect to the real hand, or when an object is placed in front of the subject which does not resemble a hand (Tsakiris and Haggard 2005). (**b**) *Full-body illusion* (*FBI*): a similar effect can be induced by stroking the subject's back synchronously with that of a virtual body displayed in a head-mounted display (*HMD*). The manipulation leads to self-identification with the virtual body (but not with an object) and induces a drift in self-localization toward the virtual body which occupies an extracorporeal position (Lenggenhager et al. 2007). (**c**) *Enfacement effect:* the same paradigm applied to faces, demonstrating a higher level of self-identification with morphed pictures of the subject and a partner's face when synchronous stroking is delivered to their cheeks and while they are sitting looking at each other in a mirror fashion (Sforza et al. 2010)

Lenggenhager et al. (2007), subjects observed the synchronous or asynchronous (i.e., delayed) stroking of their own backs, projected on head-mounted displays in front of them. Only after synchronous stimulation did they observe changes in self-localization (i.e., mislocalization of the position of their own body, in the sense of its being closer to their virtual body) in analogy with the proprioceptive drift that was found in the RHI experiments (see Fig. 15.2b). In this experimental situation, subjects also reported experiencing illusory touch on the virtual body, and they were keener to identify with it (irrespective whether the virtual body was their own filmed body or a fake one). This was not the case when an object, rather than a body, was projected and stroked synchronously with their own bodies. This result would seem to imply the influence of top-down cognitive constraints on multisensory integration, self-localization, and self-identification (see also Tsakiris and Haggard 2005 and Armel and Ramachandran 2003).

While comparing their results with the clinical manifestations during OBEs, Lenggenhager et al. (2007) observed how the illusion was neither associated with overt disembodiment nor with quantitative changes in the first-person perspective (see also Blanke and Metzinger 2009). They argued that only some aspects of OBE had been elicited in this experiment, and that an additional conflict between visual and vestibular information may be required to induce a more complete OBE (see Ionta et al. 2011). Thus they concluded that the FBI would rather seem to resemble HAS, in which patients tend to report seeing themselves from behind, and to identify with the illusory body (Blanke and Mohr 2005).

Ehrsson (2007) complemented these results by showing physiological changes related to embodiment of the virtual body as a consequence of multisensory integration: he reported significantly greater skin-conductance responses in reaction to threats against the virtual body when the latter was stroked in a synchronous, (illusory) manner. Recently even more aspects of the FBI have been elucidated. Thus Aspell et al. (2009) reported systematic alterations in the mapping of tactile stimuli during the FBI, as quantified through repeated reaction-time and accuracy measures. They found a greater visual capture of touch, in terms of a mislocalization of tactile stimuli toward the virtual body (measured through the visuo-tactile cross-modal congruency effect; see Pavani et al. 2000) in conditions associated with stronger changes in self-location and self-identification with the visually perceived body (synchronous condition). More recent data have shown that during the FBI, pain thresholds tend to be altered (Hänsel et al. 2011), a feature which has also been found in association with spontaneous OBEs. Moreover, muscle vibrations applied to the legs of subjects involved in FBI experiments were found to decrease the classical dependency of self-identification and congruency effects on the synchrony of stroking (Palluel et al. 2011). Finally, Petkova and Ehrsson (2008) demonstrated how critical visual information from the first-person perspective is for the experience of owning a body. Subjects in their experiments were wearing a head-mounted display (HMD) connected to a camera placed on a mannequin's body. Thus they were made to perceive the mannequin's body where they expected to see their own. Such a manipulation of the first-person perspective, in combination with the application of correlated multisensory information from the body (synchronous

visuo-tactile stimulation), turned out to be sufficient to trigger the illusion that someone else's body – or an artificial body, for that matter – was their own, irrespective of the concomitant execution of synchronous or asynchronous voluntary movements (i.e., the shaking of hands), and even when the subjects were directly facing their own real body (body-swapping illusion). These data on the first-person perspective were recently extended by Ionta et al. (2011), who used robotic stroking during functional magnetic resonance imaging (fMRI), and thus were able to induce experimental changes in the experienced self-location and direction of the first-person perspective during FBIs. These changes were reflected in the increased activity of the bilateral TPJs. The authors corroborated their findings by comparing the fMRI results with a lesion analysis of a large group of patients experiencing OBEs, whose brain damage was also localized at TPJ (although mainly on the right side). As regards the neural underpinnings of the FBI, Lenggenhager et al. (2011) recorded high-density electroencephalograms (EEGs) during the FBI and described differential alpha-band power modulations in bilateral sensorimotor cortices following synchronous and asynchronous stimulation of the virtual body, as well as a correlation of the alpha power in the medial prefrontal cortex, a brain region associated with a large variety of self-related cognitions, with the degree of drift in self-location.

Collectively, these studies indicate that self-identification (or the feeling of ownership of an entire body), self-location, and the first-person perspective are the results of a consistent pattern of spatially and temporally congruent visuo-tactile and sensorimotor signals that are integrated with additional visuo-vestibular mechanisms related to perspectival coding in a distributed network.

15.2.3 From Embodiment to "Enfacement": Challenging the Sense of Identity

Obviously our face is crucial for our sense of identity and constitutes our most distinctive external feature: when we look into a mirror we immediately know that the reflected image is ours. The face is also a special body part because, while we can inspect other body parts directly, we can only see the face when it is reflected in a mirror or some other reflecting surface. The self-identification of seen faces has been demonstrated only in a limited number of species: they include humans and apes, and recently it has also been possible to demonstrate signs of self-recognition in dolphins, elephants, magpies, and pigeons (Keenan et al. 2003; Plotnick et al. 2006; Prior et al. 2008). It develops in children around the age of two, in the same period of language development characterized by the first use of the pronouns "me" and "you" (Keenan et al. 2003). Moreover, for what concerns AP, in several cases of AH, patients reported to see only the face or the upper part of the trunk of the autoscopic body (Zamboni et al. 2005; Hécaen and de Ajuriaguerra 1952), suggesting a potentially different involvement of the upper and front-facing own body in bodily self-consciousness, likely due to different multisensory mechanisms.

Despite the relevance of self-face recognition for self-consciousness (Gallup 1982), experimental research in healthy subjects in this area has been sparse, and self-face recognition studies have focused primarily on visual mechanisms related to the perception and retrieval of one's own facial characteristics (Keenan et al. 2000). Recent research explored the impact of multisensory stimulation on self-face recognition, an ability that has been shown to be largely impenetrable in cases of brain damage. Indeed, even when transient difficulties in recognizing one's own face were reported by normal subjects (e.g., when looking at old pictures; see Brédart and Young 2004), persisting deficits in own-face recognition (not extending to other familiar faces, as in cases of prosopagnosia) have only rarely been reported and almost exclusively in patients with severe neurological disorders (such as the mirrored self-misidentification sign, i.e., the inability to recognize one's own reflected image, as shown by some patients at an early stage of dementia; see Breen et al. 2001) or psychiatric disorders (Kircher et al. 2007). Recent studies have extended procedures from the RHI and FBI experiments to the study of the perception of the own face and manipulated self-identification with one's own face experimentally (Sforza et al. 2010; Tsakiris 2008; Paladino et al. 2010). By using conflicting visuo-tactile information, Sforza et al. (2010) induced a modulation of self-face recognition associated with higher self-identification when participants were asked to rate morphed pictures. In particular, touching the faces of subjects who were viewing synchronous touches on a partner's face was shown to induce illusory self-identification or "enfacement" (Sforza et al. 2010), in the sense that the partner's facial features became incorporated into the representation of the participant's own face. As confirmed by psychophysical measurements, people participating in the experiment judged that morphed images of themselves and their partner contained more "self" than "other" only after synchronous, but not asynchronous, stroking (see Fig. 15.2c). Moreover, the incorporation of other's facial features into the self-face representation depended on the facial attractiveness of the other as well as on the participants' empathic abilities. Paladino et al. (2010) observed that such visuo-tactile facial stimulation not only leads to facial self-other merging (resemblance or bodily self-consciousness) but also extends its effect to the domain of social perception. In line with previous studies on bodily self-consciousness, these findings suggest that the visual capture of facial touch updates central representations of one's own physical facial appearance, maybe thus allowing us to update any slow physical changes related to the passage of time (Sforza et al. 2010; Arzy et al. 2009). Evidence that self-face representation might well be more malleable than previously believed also comes from a recent study exploring mirror gazing under specific light conditions (Caputo 2010). Thus, after a period of own-face observation in a mirror (in a sparsely illuminated room), individuals reported perceiving their own face as deformed, unknown or strange, and even as belonging to another person. Similar effects have been described by Barnier et al. (2008) with the aid of hypnosis. Collectively, these self-face effects are reminiscent of mirrored self-misidentification syndromes (see Breen et al. 2001).

15.3 Conclusion

Understanding the foundation of our sense of self has been a major ambition for science, philosophy, and religion since time immemorial. Only recently, however, has cognitive neuroscience started an attempt to clarify the psychological and cerebral mechanisms underlying the sense of self. The studies reviewed so far focused on an elementary sense of awareness that is strongly linked to bodily processing and body representation. Studies of hallucinations involving one's own body perception on the one hand, and experimental studies seeking to replicate these phenomena in healthy subjects on the other, suggest that the integration of visual and multisensory bodily signals from the entire body is important for three major aspects of bodily self-consciousness, namely self-location (i.e., the volume in space where humans experience the location of the self: "Where I experience to be"), first-person perspective (i.e., the directedness of conscious experience: "From which vantage point I experience to perceive the world"), and self-identification (i.e., the degree to which humans identify with their own bodies: "What I experience as my body") (Blanke and Metzinger 2009). Recently, a multisensory integration model has been proposed for the sense of identity as regards the representation of one's own face, challenging its relative stability and stressing the continuous need to update our facial representation through multisensory inputs (Sforza et al. 2010; Tsakiris et al. 2008).

Future studies will need to aim at integrating own-body and own-face representations to allow us to understand to which extent the sense of self in cases such as these has any neural and functional mechanisms in common. In this sense, the various phenomenological features of autoscopic phenomena offer a tantalizing model to be tested within the context of the paradigms described. Can multisensory conflicts applied to the bodies as well as the faces of patients with out-of-body experiences, heautoscopy, and autoscopic hallucinations modulate their hallucinatory experiences in such a way that they can be found to differ for each type of autoscopic phenomenon? Bolognini et al. (2011) provided the first important example of this approach by testing the effects of sensory and motor stimulation in a patient experiencing prolonged autoscopic phenomena. As those phenomena are rare, and mostly of a paroxysmal nature, we believe that, especially, laboratory work – based on such clinical observations – will allow for a scientific understanding of self-consciousness in health as well as in disease.

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Chapter 16
Phantom Limb, Phantom Body, Phantom Self: A Phenomenology of "Body Hallucinations"

Peter Brugger

16.1 Introduction

Behavioral neurology has a strong focus on deficits: It deals with functional breakdowns in the language system, with the many ways memories can be lost, and with the various impairments of action and perception. Hallucinations are intriguing examples of perceptual impairments. They are unique in that something is added to, rather than falling apart or falling entirely away from our perceptual experience. In the domain of the perception of our body, such productive symptoms of experience can take many faces, collectively being subsumed as "phantom experiences." These can be defined as experiences of bodily functions spatially dissociated from the objective body on the level of "flesh and blood." In the various types of phantom-limb experience, physically or phenomenally lost body parts continue to live on in corporeal awareness. But a phantom may also replace one lateral half of a person's body, most typically after a stroke in the hemisphere controlling that side has rendered it hemiplegic (i.e., paralyzed and devoid of any sensory functions). Finally, the complex experience of oneself as a phantom is known as a "hallucination of the double." This chapter is a guide to phantom experiences on all these levels, from single-limb phantoms to hemibody phantoms, and finally to phantoms of the entire body and self.

16.2 Phantom Body Parts

Phantom body parts are most frequently experienced after the physical loss of a limb. In a first section, we will review the history and phenomenology of amputation phantoms and emphasize their meaningfulness for theories of neural plasticity

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and reorganization. The question of innate components of the shape and functionality of our canonical, four-limbed body will be addressed in two subsequent sections; the first dealing with phantom experiences in people born without limbs and the second with a condition arguably consisting of the absence of an innate representation of one or more limbs. A further section will discuss phantom body parts that are experienced despite the fact that the relevant parts are still present, at least physically. One subsection will focus on the experience of such "supernumerary phantoms" in patients with spinal cord injury, another on patients with brain damage. Yet another one will deal with the experimental evocation of phantom body parts in healthy volunteers.

16.2.1 Phantom Body Parts After Amputation

Reports about phantom limbs are probably as old as survival from the loss of an arm or a leg. Already in the tenth century, soldiers who had lost an extremity in combat described that they continued to feel its presence. Folk psychology took these accounts as evidence for a divine resurrection of the limb, in analogy with the purported resurrection of the entire body after death (Price and Twombly 1976). It is a sad fact that medical knowledge about phantom limbs is also primarily based on what we learned from war experiences (Solonen 1962; Weeks et al. 2010). This was already the case in the sixteenth century, when Ambroise Paré (1510–1590), a barber by training, had advanced to be the most successful military surgeon. The Frenchman, whose diverse contributions to medicine are compiled in a work of ten volumes, stated in 1551 that "the patients, long after the amputation is made, say they still feel pain in the amputated part. Of this, they complain strongly, a thing worthy of wonder and almost incredible to people who have not experienced this." (Paré 1840/41, p. 221). As Paré's reports remained largely descriptive, they did not stimulate much dispute among professionals, and the topic of the phenomenal persistence of lost limbs vanished from the medical literature for more than three centuries. It resurfaced in the late nineteenth century in the work of the American neurologist Silas Weir Mitchell (1829–1914). Mitchell was confronted with the "sensory ghost" of lost limbs in the course of the American Civil War, and it is to him that we owe the term "phantom limb."

In conventional textbooks, much emphasis is given to *painful* phantom sensations. This may be a consequence of the severity of phantom-limb pain which, if present, is mentioned spontaneously by an amputee, while painless phantom-limb phenomena such as posture, weight, or movement sensations are not given comparable priority (see Fig. 16.1 for an illustration of both painful and painless phantom phenomena). Furthermore, phantom-limb pain is largely resistant to treatment. This holds for physiotherapeutic manipulation of the stump to a broad range of pharmacological interventions and invasive techniques involving thalamic stimulation or removal of cortical tissue (see Chap. 14). Not one single method has proven effective for all amputees, and once they yield relief, this tends to be only

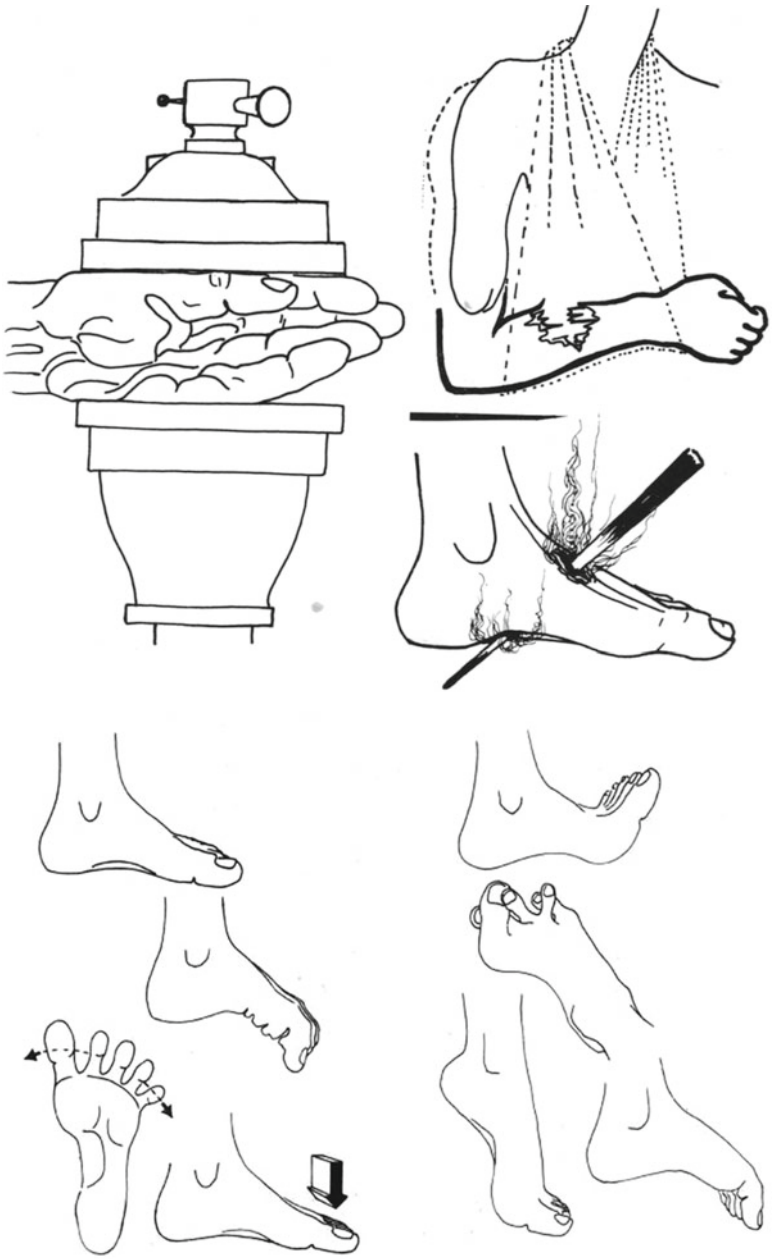


Fig. 16.1 Painful (*top*) and painless (*bottom*) phantom sensations. Pain can be clenching, burning, and/or stabbing, and even preamputation pain may persist. Non-painful phantoms mainly represent posture, weight, and movement. They can also comprise temperature and distinct impressions about paraphernalia, like for instance, rings or wristwatches (not shown) (Reproduced, with kind permission of the editors of *Acta Orthopaedica*, from Solonen 1962)

transient. As will be evident from the remaining sections of this chapter, any overemphasis on phantom *pain* does not adequately reflect the phenomenological richness of phantom experiences. The narrow focus on pain in a lost limb is comparable to a unilateral treatment of, say, color in a discussion of visual hallucinations. Color may predominate in single reports, but brightness, contrast, texture, form, and the occurrence of specific visual cues such as faces or places are of equal general importance.

During the first half of the twentieth century, one prominent theoretical question was whether the origin of phantom-limb sensations had to be sought in the amputation stump ("peripheral theories") or rather at the level of the brain ("central theories"). Propagators of peripheral theories pointed out that manipulations of the stump (e.g., massage, thermal and electrical stimulation, local anesthesia) would sometimes lead to a reduction of phantom-limb pain. Conversely, an argument for central factors involved in phantom generation is the observation that a phantom limb may cease to be felt after a stroke in brain areas that represent the particular limb. From today's perspective, the question of an exclusively peripheral or central determination of the phantom-limb percept is moot. Center and periphery are interconnected, i.e., any changes at the level of the stump will necessarily be accompanied by changes in the brain. The focus of current-day research on phantom-limb phenomena is almost entirely directed at the cerebral cortex – arguably as a consequence of the powerful technologies available to directly monitor the brain's reactions to gross changes in the periphery of our body (see Ramachandran and Hirstein (1998) and Giummarra et al. (2007) for overviews). And yet we should never forget that great thoughts of past centuries preceded the dominating technologies of today: For René Descartes (1596–1650), for example, it was already evident that the origin of phantom sensations was the brain (Finger and Hustwit 2003).

16.2.2 Phantom Body Parts in People Born with Incomplete Bodies

As the major theories of phantom limb focus on the amputation phantom, and thus conceive of phantom sensations as sensorimotor memories of previous limb use, it was long assumed that people born without a limb (a condition called "amelia") would not experience any phantom sensations. In fact, despite approximately 60 published cases of phantom limbs in amelia (see Price (2006) for an overview), this assumption had once almost reached the status of an axiom (Brugger and Funk 2007). It was also dominating the present author's views on the genesis of phantom experiences when he first met A.Z., a then 44-year-old woman born without legs and forearms who claimed vivid phantom experiences of all missing body parts. This view was thoroughly shaken after an extensive research collaboration initiated to substantiate these claims. A variety of methods, from clinical observation to behavioral testing and functional neuroimaging, showed that the phantom sensations reported by A.Z. were more than just wishful thinking, and reflected a cortical representation of body parts that had never physically developed (see Table 16.1).

Table 16.1 Methods used to substantiate claims about phantoms of congenitally absent limbs in A.Z., a person born without forearms and legs

Method	Main findings	Reference
Clinical observation: A.Z. was asked to fold her phantom arms, and clasp her phantom fingers (a) in a habitual way, and (b) reversed, i.e., the other arm/thumb on top	Reverse folding/clasping elicited a spontaneous reaction of postural discomfort and made A.Z. emphasize that she would never fold her arms /clasp her hands that way	Brugger and Funk (2007)
Clinical observation: A.Z. was asked to mimic finger postures as displayed on drawings of hands	A.Z.'s vividness ratings for the imagined postures reflected the degree of anatomical awkwardness of the postures	Hilti and Brugger (2010)
Behavioral testing: A.Z. was shown photographs of hands and feet in varying degrees of rotation. She provided laterality decisions of these body parts ("a left or a right limb?")	A.Z.'s reaction times of correct laterality decisions were a function of the rotation angle of the displayed limb, i.e., she showed the same constraints in this task as normally limbed observers do	Brugger et al. (2000), Funk and Brugger (2008)
Behavioral testing: A.Z. was shown pairs of photographs of a limb in two different postures eliciting an apparent motion percept	A.Z.'s apparent motion trajectories were a function of the flash rate; like for normally limbed observers, apparent motion percepts were influenced by anatomical joint constraints	Funk et al. (2005)
Behavioral testing: A.Z. had to sort labels of body parts and activities based on whether she considered them related or not. Sorting was achieved in a hierarchical splitting paradigm	Structure dimensional analysis revealed that some of the sorting characteristics by A.Z. reflected the presence of her phantoms, while others reflected peculiarities in her daily activities (e.g., writing with her mouth)	Bläsing et al. (2010)
Functional magnetic resonance imaging: repeated opening/closing of a phantom hand	Bilateral activation of premotor and parietal cortex; no activation of the primary sensorimotor area of hand representation	Brugger et al. (2000)
Transcranial magnetic stimulation: single-pulse magnetic stimuli were applied over areas anterior and posterior of the vertex, bilaterally. Verbal reports of phantom sensations were recorded verbatim	Phantom-hand sensations were elicited by contralateral stimulation. They were mostly reported when there was a simultaneous motor-evoked response from the deltoid muscle in the stump. Phantom movements were experienced also after stimulations posterior to the central sulcus and without accompanying motor-evoked potentials	Brugger et al. (2000)

Control experiments in an aplasic person born with a body similar to that of A.Z., but who had never experienced any phantom sensations, showed that these representations were specific to the presence of the phantom percept (Bläsing et al. 2010; Funk and Brugger 2008; Funk et al. 2005).

How can phantom sensations of limbs that have never been physically developed be explained? Do we have to assume that a four-limbed body as a canonical form of the human body is hardwired in our genes (Abramson and Feibel 1981)? As we have already proposed in our first report on the work with A.Z. (Brugger et al. 2000), the assumption of a genetic basis of "body schema" as a central representation of the body is not warranted by the present data. What must be considered are theories of the tight interplay between action observation and action execution (Gallese and Goldman 1998). It is now firmly established that a "mirror-neuron" system codes for both the motor execution and the visual observation of limb movements. Thus, in the absence of a physical substrate for the execution of an action, i.e., in the (congenital) absence of limbs, an individual can still activate networks mediating visuomotor limb representations while observing conspecifics moving their extremities. We admit that we are unable to explain why only a minority of aplasic people (up to 20% according to Melzack et al. (1997)) experience phantom limbs. However, given the very large heterogeneity in appearance and etiology of congenital limb deficiencies, it does not seem too farfetched to assume large interindividual differences in matching observation and (imaginary) execution of parts of the body. Contemporary authors agree that prospective studies of the mirror-neuron system in persons born without limbs are badly needed (Price 2006; Giummarra et al. 2007; Wood and Stuart 2009). Equally important is a consideration of intrauterine life events. In many amelic persons, the ultimate reason for a (non-teratogenically caused) limb deficiency remains unknown. While fetal limb movements have been studied to infer possible factors responsible for the genesis of congenital phantoms (Gallagher et al. 1998), the problem of matching the "incarnation" of a limb (i.e., its realization on the physical level) to its "animation" (i.e., the phenomenal experience of owning that limb) has not yet been sufficiently explored by current-day neuroembryology.

16.2.3 "Wannabe Amputees" and the Concept of "Negative Phantom Limbs"

The previous section dealt with the failed incarnation of a limb that is still animated in the sense of being experienced as a phantom. In the present section, we will very briefly address the question of whether the converse case can be observed: Is it possible that incarnation of a limb has taken place flawlessly, but animation has failed? Our answer is yes, and the condition we have in mind is called "body-integrity identity disorder" (BIID). People with BIID complain about being "overcomplete." They suffer from having four limbs and desire to get rid of one or several of them to match their physical appearance with the idea they have about how their body should

have been shaped. Typically, this desire for amputation has been around "as long they can think," quite similar to the phantom awareness in people with congenitally missing limbs. We have contrasted these two phantom-limb phenomena: the one designating an "animation without incarnation," the other, BIID, an "incarnation without animation" (Hilti and Brugger 2010). Unpublished data on the dreams of people with BIID who have realized their desire (i.e., succeeded in having the non-animated limb removed) indicate that the time they need to dream themselves amputated is much shorter than that for persons with traumatic amputations. This may indicate that their amputation desire was based on a central representation of their body, which diverged from the canonical four-limb format right from the beginning of their lives. Viewed as an instance of a "negative hallucination" in the domain of corporeal awareness, BIID needs to be considered in any comprehensive work on hallucinations.

16.2.4 Supernumerary Phantom Body Parts

A "supernumerary" phantom is the phenomenal experience of a body part in the absence of its peripheral loss (or congenital absence) but *in addition to* the respective physical limb. In former times, the condition was described as an "illusory reduplication of body parts" (Weinstein et al. 1954) and thought to occur only in cases of psychosis or organic brain damage. We propose here to label "supernumerary" also those phantom limbs experienced by patients with a dissected spinal cord or by healthy participants subject to procedures that elicit a phantom-limb percept.

16.2.4.1 Supernumerary Phantom Body Parts After Spinal Cord Injury

Spinal cord injury (SCI) produces a disconnection between brain and peripheral body parts. Thus a complete section of spinal nerve fibers leads to a "deafferentation" (no sensory information reaches the cortex) and a "deefferentation" (no central motor commands reach the peripheral organ). The reports about phantom limbs in this state of "functional amputation" are too numerous to be cited here (for some references, see Ettlin et al. (1980) and Drysdale et al. (2009)). In a neuroimaging approach, we have shown that the vividness of phantom-foot movements in patients with paraplegia correlates highly with the activation volumes of relevant cortical regions during motor imagery tasks (Alkadhi et al. 2005). A recent observation in a patient with an incomplete tetraplegia (paralysis of all four extremities) described spontaneous bilateral phantom-arm sensations that occurred exclusively in a reclined position (Curt et al. 2011). However, subjected to a "rubber-hand illusion" paradigm (Botvinick and Cohen 1998; see Sect. 16.2.4.3), a sudden supernumerary right-hand phantom occurred also in a sitting position, and remained as long as the rubber hand remained in view (see Fig. 16.2). This observation supports theories of

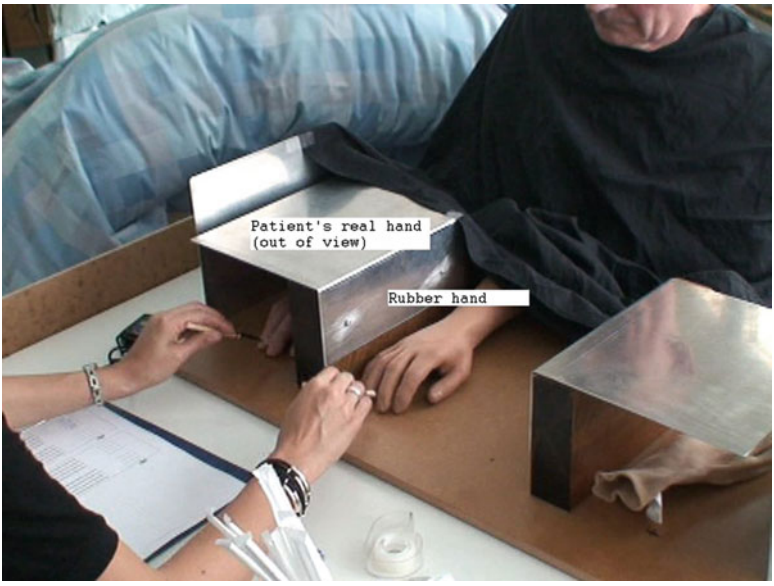


Fig. 16.2 The setup for inducing the "rubber-hand illusion" (*RHI*) in a patient with incomplete quadriplegia after a ski accident (Curt et al. 2011). While in healthy volunteers the RHI leads to a displacement of the unseen hand, touched in synchrony with observed touches to a rubber hand, in this patient the procedure resulted in inducing a supernumerary phantom-hand percept. See text for details (Reproduced, with kind permission of the editors of *Spinal Cord*, from Curt et al. 2011)

the rubber-hand illusion as reflecting a mismatch between visual, tactile, and proprioceptive information (Tsakiris and Haggard 2005), and illustrates the potential usefulness of illusion paradigms in clinical settings.

16.2.4.2 Supernumerary Phantom Body Parts After Brain Damage

Supernumerary phantoms are also observed after a deafferentation and/or deefferentation at subcortical or cortical levels. A recent study found the prevalence of supernumerary phantoms in patients with a stroke to be higher than 50% (Antoniello et al. 2010). Although phenomenologically similar, supernumerary phantoms after stroke and phantoms after the loss of a limb differ in important respects. First, pain is frequently associated with the latter but is only exceptionally an attribute of the former. Second, as "real" as amputation phantoms may feel, they are always recognized as illusory percepts. Reality monitoring is less perfect in the case of supernumerary phantoms after brain damage, the presence of which is often commented on in delusional ways. Thus patients sometimes refer to the phantom as a "spare limb" or claim that they "grew it for protection" (Weinstein et al. 1954, p. 50). Alternatively, hostile actions have been ascribed to supernumerary, but not to amputation phantoms (Hari et al. 1998). Third, amputation phantoms are never

visualized by mentally healthy amputees, whereas some patients with supernumerary phantoms have reported a visual, in addition to a somesthetic, awareness of their "extra" limb (Critchley 1953; Khateb et al. 2009). This visual component constitutes an important argument for the conceptual similarity between phantoms of single limbs and the "phantom double," which will be the subject of Sect. 16.4.

16.2.4.3 Supernumerary Phantom Body Parts in Healthy Participants

A rather painful method to induce supernumerary phantom limbs in healthy subjects involves the transient deafferentation of a limb by intravenous regional anesthesia or pressure-cuff ischemia of one limb. Brasil-Neto et al. (1992) used this method combined with a measurement of the functional reorganization of the corticospinal tract. They found a very rapid adaptation of the nervous system to this experimental, transient, and reversible "amputation" of a limb. "Vibratory myesthetic illusions" were described by Lackner (1988) to evoke phantom sensations of various body parts. Biceps vibration, for instance, fools the brain in believing that the forearm is extended, and as a result the subjects (as long as blindfolded!) feel the hand and forearm in extracorporeal space. One intriguing modification of this type of biceps vibration requires the subject to touch her nose with the fingers during the vibration period. A conflict arises: The hand is felt some 30 cm away from the face, yet the sensation of contact with the nose is maintained. As a consequence, subjects report a phantom nose, up to 30 cm long! (Lackner 1988). Apparently, the brain "fills in" the gap between the perceived hand location and the spatial position of the tip of the nose. This so-called Pinocchio illusion offers a tool for the investigation of short-term brain plasticity but may also aid in understanding individual differences in the susceptibility to experience spontaneous perceptual aberrations regarding one's own body (Burrack and Brugger 2005). Finally, the rubber-hand illusion paradigm, first described by Botvinick and Cohen (1998), and mentioned already in Sect. 16.2.4.1, produced an unanticipated interest by the neuroscience community (see Tsakiris and Haggard (2005) for an overview). Briefly, the observation of touch delivered to a rubber hand while one's unseen real hand is touched simultaneously (see Fig. 16.2) leads to the "incorporation" of the rubber hand, or, in other words, to a dislocation of one's own hand toward the rubber hand. This dislocation of a body part into extracorporeal space can be quantified by assessing the proprioceptive drift (Tsakiris and Haggard 2005) or the decrease in hand temperature (Moseley et al. 2008).

16.3 Hemiplegic Twins and Invisible Phantom Bodies

In the presence of brain damage, a supernumerary phantom limb is often no longer recognized as belonging to the own self. Either its actions seem alien (and often threatening, see Hari et al. 1998) or altered sensations are interpreted as a sign that

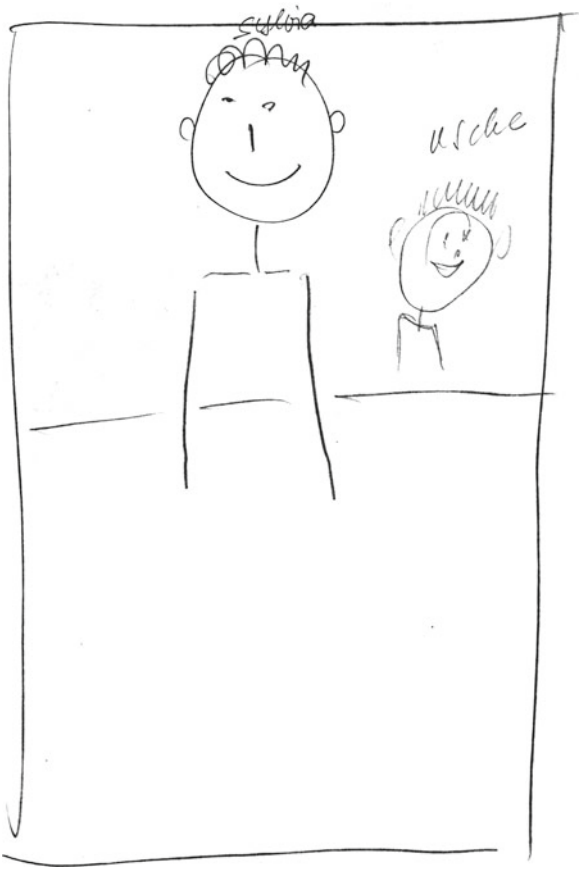
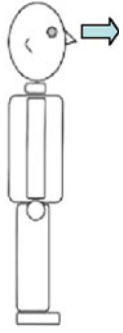
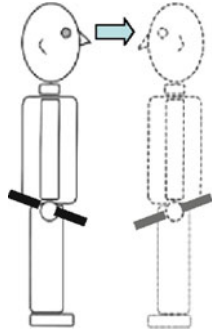
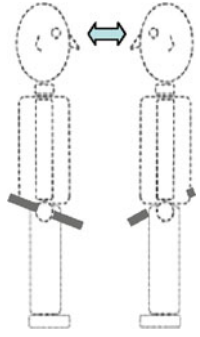
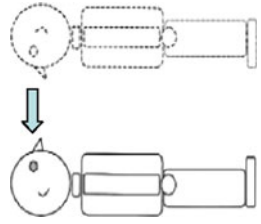


Fig. 16.3 Drawing by a 57-year-old, right-handed woman, showing herself and a phantom hemibody to her left side. The patient had suffered a large intracerebral bleeding in the right hemisphere, which produced a dense hemiplegia for which she remained anosognosic. The phantom hemibody was initially experienced as comforting, but then as an intruder. The patient attempted to expel the phantom from her bed by biting it – the bite marks on her left upper arm required medical treatment

the limb in fact belongs to another person. Likewise, hemiplegic patients, paralyzed along an entire half side of their body, sometimes fail to recognize the paralysis (a condition called "anosognosia") but conceive of their numb hemibody as another person ("personification anosognosia" or "somatoparaphrenia"; see Vallar and Ronchi (2009) for an overview; see also Fig. 16.3). This disownership of large parts of one's body and its simultaneous attribution to someone else's form a conceptual link between the phantom limb and the various shades of "phantom body" that will be discussed in Sect. 16.4. Common to phantom limb is the state of deafferentation, common to phantom body the conviction that another person is nearby.

The perhaps most obvious difference between the "hemiplegic twin" (Critchley 1953) and the phantom double is that the former is not usually visualized, but just "felt to be around." However, not all types of phantom body usually subsumed under the heading of "autoscopic phenomena" (see Chap. 15) manifest themselves in the visual domain. There is one type of phantom body (see Table 16.2) that is not visualized at all, even if it is sometimes felt to be "just at the fringe of vision." There is

Table 16.2 Four main types of autoscopic phenomena. Sketches adapted from Blanke et al. (2004), original taxonomy after Brugger et al. (1997)

Autoscopic phenomenon	Invisible phantom double	Autoscopy	Heautoscopy	Out-of-body experience
				
Sensory modality involved	Only somesthetic	Only visual	Somesthetic and visual	Somesthetic and visual
Core brain region affected (in case of brain damage)	Parietal	Occipital	Parieto-occipital	Parieto-temporal
Experience and localization of self	One self; within body	One self; within body	Two selves; primarily within body	One self; completely out of body
Reports about an experimental induction (key references)	Arzy et al. (2006)	Kitamura (1938) and Schilder (1935)	–	Stratton (1899), Ehrsson (2007), Lenggenhager et al. (2007), and Altschuler and Ramachandran (2007)

a vast and most heterogeneous literature on this invisible phantom (see Geiger 2009), and the bewildering terminological variety gives testimony to the prescientific state of its understanding. It has been referred to as an "invisible *doppelgänger*," a "felt presence," or a "shadow person" (Arzy et al. 2006), and explorers and mountaineers know it as the "third man" (see Brugger et al. (1997) for a more comprehensive list of terms). Unilateral forms and auditory variants of the phenomenon have been described, and famous writers' accounts have put it into most uncanny contexts (see Brugger et al. 1994 and 1997 for the literature). To be sure, with the invisible phantom body, we reach the borderlands between tales of the supernatural and the scientific study of hallucinations. What sense is it anyway, in which we hallucinate, if we feel the presence of another being close by, at a precise distance from our body, yet without reliance on visual, auditory, tactile, or olfactory cues? We argue that it is the sense of having a body, although some authors are reluctant to consider it a perceptual phenomenon at all (e.g., Thompson 1982). In any case, all visualization characterizing the phantom experiences to which we now turn is rather secondary to any changes in corporeal awareness.

16.4 Visible Phantoms: Autoscopic Phenomena

Autoscopic phenomena involve an illusory duplication of the own body. As the motif of the double, or *doppelgänger*, they are well known to students of the literary arts. There is a vast literature on the folklore and ethnology of the subject (see Brugger et al. (1997) for overview), and a considerable interest by philosophers, who feel that whole-body phantoms, whether observed in a clinical context or induced experimentally, may help us gain significant insights into the nature of the human self (Metzinger 2009).

Four main types of autoscopic phenomena need to be distinguished. We already mentioned the invisible phantom double in the previous section; the duplication may not be immediately apparent in this type, as the "sensed presence" (as it is called, see Chap. 17) is not usually experienced as a second self. However, the fact that "the other" typically imitates own body movements and sometimes "shares one's thoughts" makes clear that the invisible companion is a projection of one's own somesthetic impressions into extracorporeal space. An autoscopic hallucination is a unimodal, visual hallucination of one's own body, frequently only of the upper body or face. The perceived image is usually brightly colored, its duration very brief, and the defining feature is a mirror reversal, i.e., things carried in the right hand are displayed in the autoscopic double's left hand (Brugger 2002). This absence of a perspective transformation indicates the absence of parietal lobe involvement (Blanke et al. 2005) and constitutes the main difference with heautoscopy, another type of autoscopic reduplication, extensively researched by the Austrian neuropsychiatrist Erich Menninger-Lerchenthal (1898–1966), who wrote two monographs on the topic (Menninger-Lerchenthal 1935, 1946). Heautoscopy

literally means "seeing one's self" and thus underlines the presence of two selves, one seeing the other. This duality can lead to complex interactions between a person and her double; although supporting doubles have been reported, hostile interactions are the rule (Brugger 2007; Brugger et al. 1994) and make heautoscopy so attractive as a literary motif. Finally, the core feature of out-of-body experiences is the apparent separation of the self from what is considered the "empty body," usually observed from an extracorporeal vantage point (see Table 16.2). The recent neuroscientific literature has seen an upsurge of contributions that link this experience to certain parts of the brain (Blanke et al. 2002) or to distinct cerebral pathologies (Blanke et al. 2004). A topical issue is the experimental evocation of out-of-body states; among the methods introduced are mirror techniques (Altschuler and Ramachandran 2007; see Stratton (1899) for an early attempt) or full-body variants of the rubber-hand illusion (Ehrsson 2007; Lenggenhager et al. 2007). These methods allow the study of hallucinations of corporeal awareness under controlled conditions. We have to be aware, however, that experimentally induced phantom experiences, whether on the level of single limbs or the entire body, are phenomenally worlds apart from what they attempt to mimic.

16.5 "Phantomology": The Study of Body Hallucinations

Phantom experiences, the productive symptoms of corporeal awareness, form a heterogeneous class of hallucinations of one's own body. Borrowing a term from the Polish science-fiction writer Stanislas Lem (1921–2006), we could define "phantomology" (Lem 1964) as the science of the virtual reality of the body. Phantoms are "virtually real" in the sense of knowingly imaginary, yet phenomenally as convincing as the experience of our physical body. They help us recognize that it is by no means self-evident to "own a body" and make us aware that the concept of the self is largely grounded in basic sensorimotor processes (see also Chap. 13). One of the basic tenets of phantomology is that there is a continuum of phantom experiences – from phantom limb to phantom body. Phantomology can thus profit from circumstances not usually given in other fields of hallucination research: Most phantom limbs are experienced by persons who are healthy, wide-awake, and sober. In addition, they tend to be experienced almost continuously. This makes a laboratory approach feasible and has helped develop methods to investigate those phantoms that have hitherto been enshrouded in mysticism or regarded as too rare to be accessible to scientific explorations. As pointed out by Blanke and Metzinger (2009) and by Brugger (in press), the demystification of current-day concepts of "the self" will be among the foremost future prospects of phantomology. To this end, existing gaps between cognitive neurology and the philosophy of mind will have to be bridged.

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Chapter 17
Sensed Presences

James Allan Cheyne

17.1 Intuitions of "Something There"

> It is as if there were in the human consciousness *a sense of reality, a feeling of objective presence, a perception* of what we may call '*something there*,' more deep and more general than any of the more special and particular 'senses.'
>
> William James, *Varieties of Religious Experience*, 1902, p. 58

It is likely that the reader will have had an experience, in the absence of any tangible evidence, of sensing some unseen presence nearby: along the trail, around the corner, in another room. Such feelings may range from a vague and almost embarrassingly unwarranted suspicion to a feeling of absolute conviction. We associate such feelings most acutely with darkness, strange surroundings, and, very often, being alone. We may experience this when walking at night on a poorly lit street, or in darkly shaded woodlot, or alone in our own homes. For most of us and for the most part these episodes are subtle, fleeting sensations. Under certain conditions, however, such feelings can become protracted delusions accompanied by hallucinatory imagery.

Although the sensed presence has, in itself, no sensory components, it is more than an internal feeling state, being perceptually projected into extrapersonal space (Brugger et al. 1996; Cheyne and Girard 2004) often within precise and reliable coordinates (Girard et al. 2007; see Fig. 17.1). The sensed presence typically has a specific location and distance from the experient, usually within a few meters or less, behind or to one side just out of sight (Arzy et al. 2004; Brugger et al. 1997; Girard et al. 2007). In addition to such spatial specification, the presence is often explicitly understood to be an *intentional* agent with interests, wants, desires, and goals, ranging from altruistic through benign to strongly menacing (Geiger 2008; Cheyne 2001). With rare exceptions, only relatively recently have such strange and

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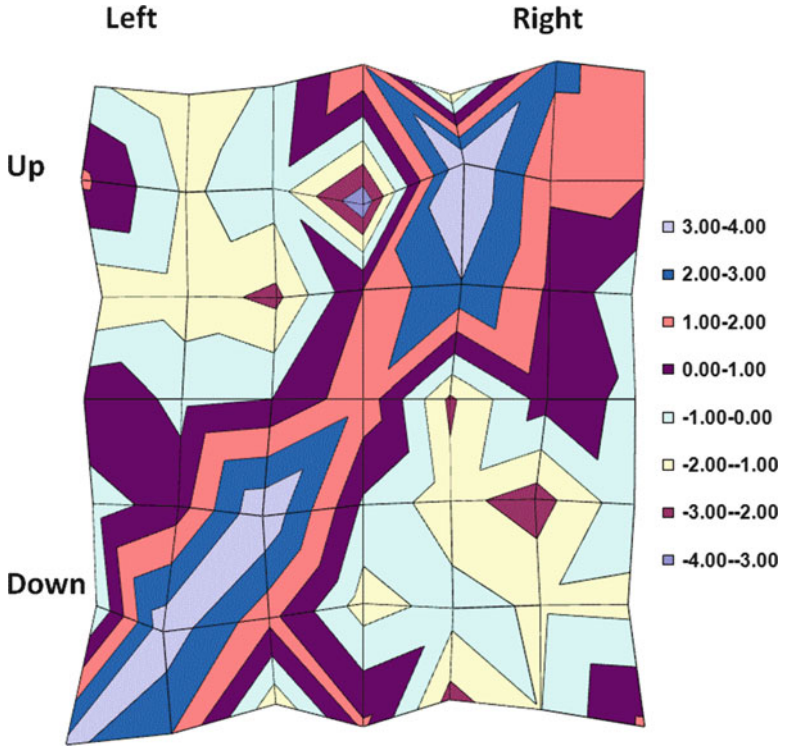

Fig. 17.1 The systematic spatial distribution of hypnagogic experiences of sensed presence and associated hallucinations. The numbers in the legend are residuals reflecting the spatial bias in locating the presence. Higher numbers (Z-scores) and peaks in 3-D surface chart indicate a stronger spatial bias (Adapted from Girard et al. (2007). Reproduced with permission)

apparently mysterious experiences been subjected to very close scrutiny by neuroscience. This chapter reviews a small selection of this recent work and its bearing on two neuropsychological hypotheses.

One dominant neuropsychological view is that the sensed presence is a reduplication of one's own body image (Blanke et al. 2008; Brugger et al. 1997) associated with neural events at the temporoparietal junction (TPJ) and sometimes in frontal motor and premotor areas of the brain resulting in the (dis)integration of bodily self-sensations (Blanke et al. 2003). Consistent with this hypothesis is the observation of striking parallels and transitions between sensed-presence and autoscopic experiences (seeing oneself in extrapersonal space, see Chap. 15), and that the presence sometimes seems to the experient to imitate her movements. Arguing somewhat against this hypothesis is that the presence is seldom recognized as self. In addition, the sensed presence, though itself without sensory qualities, is sometimes accompanied by visual hallucinations, which seldom resemble the experient, may be wearing different clothing, and be of a different age or sex. The body-image hypothesis also fails to explain the intentional nature of the presence or that, in some contexts, the other is experienced as something terrifyingly alien.

An alternative hypothesis is that the sense of presence is the activation of a distinct and evolutionarily functional "sense of the other" (Cheyne and Girard 2007a, b; Cheyne et al. 1999; Picard 2010) implicating structures deep within the temporal lobe specialized for the detection of cues for agency, especially those potentially associated with threat or safety. This hypothesis implies that the feeling itself is simply a dissociation of the normal feeling of the presence of others associated with the normal cues for their physical presence. The sense of the presence of others is pervasive and continuous when one *is* with others, but we rarely explicitly note or remark on it because, after all, there really are others present, and this is the normal feeling when they are there. We sometimes feel it explicitly when in intense relationships and interactions, but mostly it is just a background feeling. When this feeling becomes disconnected from explicit perceptual cues of the presence of others, we may then have the experience of the (disembodied) sensed presence (Cheyne 2009). This hypothesis has little to say, however, about the intriguing parallels between sensed presence and autoscopic hallucinations. Likely, neither hypothesis is adequate to explain all cases, though some combination of the two might come close.

This chapter will review several salient studies of sensed-presence experiences in four contexts selected because they bear upon these hypotheses and provide particular insights into the underlying sources of our experiences of sensed presence, self, and others. These contexts are: neurological and psychiatric conditions, brain stimulation, extreme environments, and sleep paralysis.

17.2 Neurological Cases: The Self-Interrupted

Sensed presences have been reported in neurological cases associated with tumors, lesions, and epileptic foci in occipital, parietal, and temporal lobes (Ardila and Gomez 1988; Brugger et al. 1996; Dening and Berrios 1994; Devinsky et al. 1989; Landtblom 2006). Recent theory and research on neurological cases of sensed presence have focused on paroxysmal somatognosic disorders (i.e., acute distortions of body image, see Chap. 13), often associated with temporoparietal dysfunction (Blanke et al. 2008). In addition, patients diagnosed with schizophrenia frequently demonstrate misattributions of their own actions (see Chap. 26), which also have been associated with the events in temporoparietal cortex (Farrer et al. 2004).

Brugger et al. (1997, see also Chap. 16) developed a useful taxonomy of *autoscopic phenomena* including autoscopic hallucinations, out-of-body experiences (OBEs), and heautoscopy, as well as the sensed presence. The sensed presence is, however, something of an anomaly in this taxonomy in that, on the face of it, it is neither *auto* nor *scopic*. That is, it is not experienced as a self, and it is not seen, in contrast to each of the other phenomena. Autoscopic hallucinations, for example, involve seeing a visual image of oneself in extracorporeal space. Heautoscopy, which also involves autoscopy, usually of a double of oneself, also includes somesthetic and vestibular sensations, which tend to contribute feelings of depersonalization (spatial and psychological detachment from one's body), and ambiguity about the location of one's self. The double can sometimes become transparent

Fig. 17.2 Artist's drawing according to a patient's description of four doubles. The patient's own body is shown as split, with the right side feeling slightly alien. All doubles were located to the right of the patient's body. Although the "double" immediately to the right did not resemble the patient, he was experienced still as belonging to the self. Other figures were also felt to belong to the patient's self, at least in a family sense. The degree of belonging decreased with increasing distance from the patient. An additional figure (not shown) was vaguely sensed about 20 m away (From Brugger et al. (2006). Reproduced with permission)

and "ghost-like" and tends to be referred to in the third person by experients (Brugger et al. 1997). Heautoscopy is, therefore, a potential bridge between autoscopic hallucinations and sensed presence.

Brugger and colleagues present a case that appears to illustrate a continuum from hallucinations of the self through increasingly distant and different identities resolving, over time, into a vague sense of an autonomous presence. A patient with a lesion in the left insula (implicated in interoceptive and vestibular processing) extending into the frontal-temporal cortex experienced hallucinations with three levels of dissociation from self (Brugger et al. 2006). Although the left half of the patient's body felt normal, the right half was emotionally and physically detached, though apparently still clearly interpreted as his own, while immediately to his right, he perceived another man, who, despite physical differences in appearance, still seemed to be a part of himself (see Fig. 17.2). The space further to the right was

populated by hallucinated individuals of different ages and sexes, whom he referred to as a "family," though not his own in reality. Eventually all of them faded until their presence was felt in "some hardly discernable sense." Despite the vagueness of the later experiences, he was able still to precisely localize them in the room. Picard (2010) also reports a case of a patient with epilepsy reporting the presence of multiple familiar persons. Although she could neither see nor hear them, she identified them as four family members.

17.3 Sensed Presence by Brain Stimulation: The Other as the Shadow of the Self

Arzy et al. (2004) report a case involving electrical stimulation of the cerebral cortex during presurgical evaluation of a patient with epilepsy. Stimulation applied at the left temporoparietal junction (see Fig. 17.3a) produced the sensation that there was somebody behind her. With further stimulation, the patient described the person as young and of indeterminate sex. During a subsequent stimulation, she was sitting with her arms around her knees and experienced the shadow person as sitting directly behind and embracing her (see Fig. 17.3b–d). She now referred to the presence as male and to the experience as unpleasant. Later during a naming task that required her to hold a card in her right hand, she complained that the presence "wants to take the card" and "doesn't want me to read." Given the importance of the region of cortex stimulated for the integration of bodily sensations, the authors reasonably concluded that the stimulation produced a disruption in the multisensory

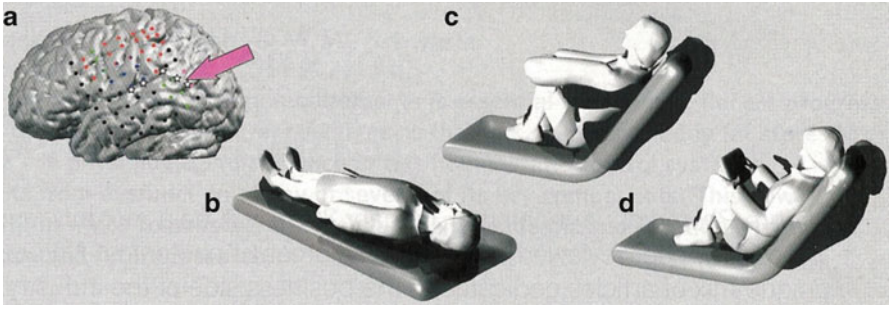

Fig. 17.3 **(a)** Three-dimensional reconstruction (*MRI*) of the left-hemisphere surface of a patient's brain. Subdural electrodes were implanted in the brain of a patient undergoing presurgical evaluation. The locations at which focal electrical stimulation evoked different responses are shown (*red*, motor; *blue*, somatosensory; *green*, language). The *arrow* indicates the site where the "feeling of a presence" could be induced; stars indicate the epileptic focus. **(b–d)** Positions and postures of the patient's body (*white*) and that of the "shadow" person during cortical stimulation. **(b)** The shadow "is behind me, almost at my body, but I do not feel it." **(c)** The shadow clasps the patient in his arms. **(d)** The shadow "wants" to take a book from the patient (From Arzy et al. (2004). Reproduced with permission)

processing of body-self information and that the shadow person was a result of disturbed perception of her own body (i.e., the shadow was the alienated sense of the self).

Brugger and colleagues cite a similar misattribution in Strindberg's self-recorded experiences in the course of probable schizophrenia:

> This unknown man never uttered a word; he seemed to be occupied in writing something behind the wooden partition that separated us. All the same, it was odd that he should push back his chair every time I moved mine. He repeated my every movement in a way that suggested that he wanted to annoy me by imitating me …. When I went to bed the man in the room next to my desk went to bed too…. I could hear him lying there, stretched out parallel to me. I could hear him turning the pages of a book, putting out the lamp, breathing deeply, turning over and falling asleep.

Like Strindberg, the patient in the Arzy study appeared not to draw the inference from the shadow's imitation of her own actions that she might be experiencing her own movements displaced. Perhaps from a first-person perspective, more compelling alternatives were available. For example, the patient also reported a definite impression that the presence was trying to take the card from her, suggesting that there were positive elements of otherness in her experience as in the case of Strindberg. This is not to deny that that she was sensing her own movements, but rather to suggest that she was construing these experiences as though their source were indeed another person. This might be taken as evidence that the senses of self and of others share certain brain mechanisms.

17.4 Illusory Companions in Times of Need

> Who is the third who always walks beside you?
> When I count, there are only two of you and I together
> But when I look ahead up the white road
> There is always another one walking beside you…
>
> T.S. Eliot, *The Wasteland*

Commenting on these lines, Eliot tells us that they "were stimulated by the account of one of the Antarctic expeditions [probably Shackleton's]…. It was related that the party of explorers at the extremity of their strength, had the constant conviction that there was *one more member* than could actually be counted." The Shackleton expedition experiences are prototypical of the "companion" version of the sensed presence in a number of ways. First, there were the rigors of a protracted Antarctic expedition gone awry, with members at the limits of their endurance. Second, the events occurred near the end of their ordeal while scaling mountainous terrain on the island of South Georgia. Third, although Eliot describes the experience as a visual hallucination, it was originally described by Shackleton merely as a "curious feeling" of an extra person. Finally, there was a strong conviction concerning the reality of the companion. An illusory companion may be a stranger nearby but out of sight, often just off to one side, or just behind one's shoulder, or

perhaps felt to be just a little way along the trail. Alternatively, the companion may be experienced as a familiar person: a friend, a favorite aunt, or sometimes a recently deceased actual companion, any of whom, in the guise of the presence, may sometimes provide, usually implicit, moral support and/or guidance (Geiger 2009).

Common precipitating events for companion presences are the misadventures of sailors, polar explorers, and especially mountaineers, that result in extreme conditions that include isolation, cold, injury, dehydration, hunger, fatigue, darkness, barren landscapes, and fear, as well as, in the case of mountaineering, high-altitude effects – all typically extreme, persistent, and in combination (Suedfeld and Geiger 2008; Suedfeld and Mocellin 1987).

17.4.1 Neurophysiological Effects of Altitude

Perhaps the most common and informative unusual context for companion experiences is extreme mountaineering, especially over 8,000 m (Geiger 2009). This is almost certainly related to the pervasive physiological and neuropsychological effects of high-altitude exposure (Maa 2010; Virtués-Ortega et al. 2004). Human physiology places fairly strict limits on our ability to thrive at high altitudes. A particularly distinctive feature of the stresses imposed by high altitude is the reduction in ambient pressure and resulting poor oxygen exchange in the lungs. Neural cells are greedy consumers of oxygen and hypersensitive to oxygen deficits. In addition, a well-known acute effect is high-altitude cerebral edema, which likely causes mechanical stresses because of the inelastic skull and resulting elevated intracranial pressure (Maa 2010). Although neurophysiological effects experienced by mountaineers in the form of acute mountain sickness have long been known, only recently have associated neuropsychological aspects been subject to detailed study including perceptual, motor, memory, and psychomotor deficits (see Maa 2010 for a review).

Using precise neuroimaging techniques and extreme samples, Paola et al. (2008) studied nine world-class mountaineers using quantitative magnetic resonance imaging (MRI) techniques prior to and following extreme ascents: Mount Everest and K2. These are, in terms of altitude, the most extreme possible test environments at 8,848 and 8,611 m, respectively, at less than 50% of sea level atmospheric pressure (Maa 2010). Paola and colleagues found their subjects, relative to controls, to have baseline (i.e., prior to their ascents for the study) reductions in white matter density/volume in the left pyramidal tract involving frontal cortex (primary and supplementary motor areas). Moreover, in comparison to their own baseline, the mountain climbers were found to have reduced gray matter in the region of the angular gyrus of the parietal lobe following the ascents (i.e., regions centrally implicated in the processing of multisensory body-related information, and hence in bodily self-perception and self-other distinctions). These results are not surprising as the brain areas in question were likely relatively poorly supplied with oxygen while being subjected to the most intense metabolic demands in mountaineering. On the supply side, these areas, called "watershed areas," are more removed from major arteries,

and hence tend to be most at risk for reduced available blood oxygen. On the demand side, part of the relevance of the localization on the supply side is revealed in just what mountaineers do when they climb mountains. They engage in extremely challenging motor activity and in considerable way-finding, thus making particular demands of parietal and motor cortex when oxygen availability is considerably reduced in those regions. Keeping track of motor planning, spatial location, whole-body orientation, and relative body-part arrangements are all high-demand activities during mountain climbing, activities in which the parietal angular gyrus is implicated. Brugger et al. (1999) also report a combination of somesthetic hallucinations, neuropsychological impairments, and EEG and MRI abnormalities among high-altitude climbers. Moreover, it is worth noting that the laboratory observations were of the relatively modest residual sequelae of the neurophysiological stresses experienced during climbs that, though extreme, were likely much less acutely stressful than the events that produce companion experiences (see Geiger 2008).

17.5 Night Creatures: The Theme of the Intruder

Arguably the most common and almost certainly the most terrifying context for the sensed presence is the group of hallucinatory experiences associated with sleep paralysis. Sleep paralysis is classified as a REM-related parasomnia or sleep disorder in which someone, when falling asleep or waking, experiences a brief episode of complete paralysis of the major muscles. The paralysis is often, though not always, accompanied by a variety of frightening experiences, the most common of which is the sensed presence (Cheyne and Girard 2007a). There is something profoundly malevolent and evil inherent in this instance of the presence. The uncanny dread and impending doom associated with this presence sometimes generates supernatural themes of "the grim reaper" or "the angel of death" (Cheyne 2001). In the sleep-paralysis context, the sensed-presence experience is often elaborated into explicit visual, auditory, and tactile intruder hallucinations (see Fig. 17.4a). Although – in modern industrialized societies – these presence experiences are often interpreted as human intruders, in numerous cultures around the world, nocturnal visitation by a sensed presence is experienced as an oppressive night spirit with a variety of specific names that equate with ghost, demon, hag, witch, *djinn*, and so on (Adler 2010; Hufford 1982).

Initially, and often exclusively, the experience is merely of a "watcher," i.e., a monitoring presence (see Fig. 17.5). Even simply being stared at can, of course, be quite disconcerting. Staring is seldom a neutral act but rather is viewed as a threatening gesture across cultures and among most primates (Eibl-Eibesfeldt 1989). That the intruder present in our room during sleep paralysis is staring at us is an obvious inference to draw. Yet this seems not a deduction consciously arrived at – one experiences the threat as an event, not as an inference.

Frequently, a complex scenario subsequently unfolds as the presence approaches and climbs onto the bed. Sometimes a presence will simply stop at some point,

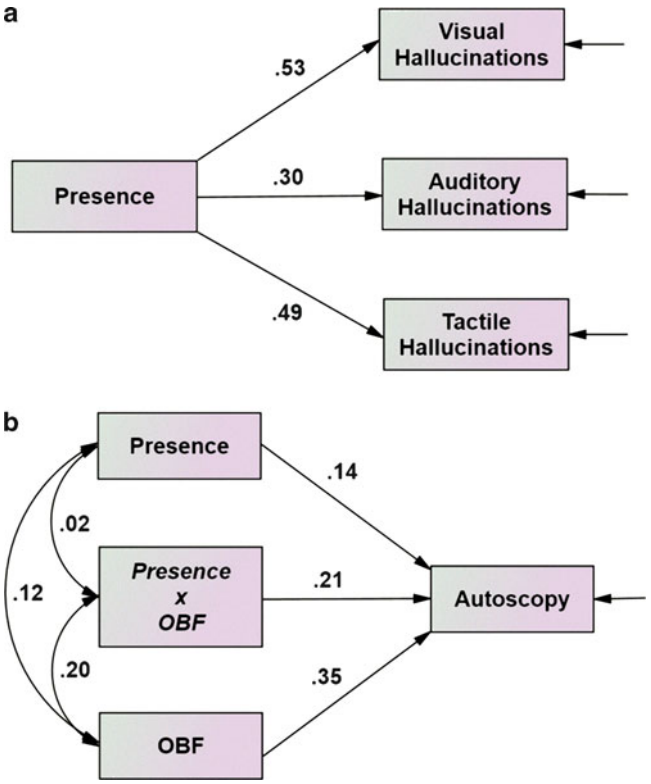

Fig. 17.4 Presence as others and as self: Path analyses of presence experiences during sleep paralysis. **(a)** Path coefficients with presence as predictors of visual, auditory, and tactile intruder hallucinations. **(b)** Path coefficients with presence experiences, vestibular-motor out-of-body feelings, and their interaction predicting autoscopic experiences (Based on data from Cheyne and Girard (2007a, b, 2009). Reproduced with permission)

leaving the anguished experient in a state of considerable suspense. A feeling perhaps preferable to the alternative experience of the mattress being pressed down as one realizes that one's bed is being shared with the presence. Frequently, the presence will be experienced as sitting on one's chest (the incubus experience: see Fig. 17.5), smothering and otherwise physically, and sometimes sexually, assaulting the experient.

17.5.1 Detecting Threatening Agents

Throughout evolutionary history, and into the present, for the large majority of humans, the world has been filled with ambiguous and unseen agents (see also Chap. 18); and often, just those presenting the greatest threat are cryptic, elusive, and, as

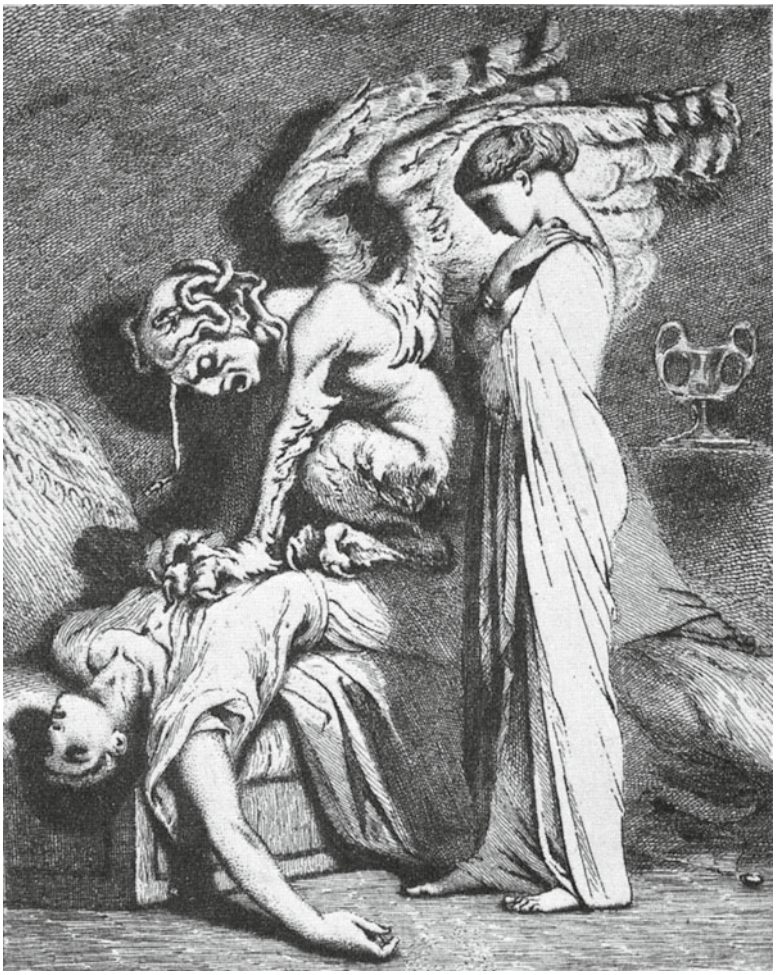

Fig. 17.5 Smarra: The watcher and the incubus. The tradition of the presence as watcher or threatening/assaulting intruder is an old one in the Judeo-Christian tradition. The feeling of being watched by an unseen presence is one of the more common experiences of the waking nightmare (Lithograph after Tony Johannot (1845). Paris: Bibliothèque Nationale)

the adage, *Homo homini lupus*, reminds us, often members of our own species (Keeley 1996; LeBlanc 2003). Shape, color, shade, immobility, and stealth conceal these agents from detection. Hence, agency detection must become very sensitive under presumed threat, even at the risk of false positives (see also Chap. 4). Rustling leaves or shadowy movements are at such times sufficient for us to experience the presence of agency, even without bodily signs of the agent. The experience of disembodied threatening agents is therefore intrinsic to our collective and individual evolutionary, historical, and developmental histories. Hence, evolutionary scientists

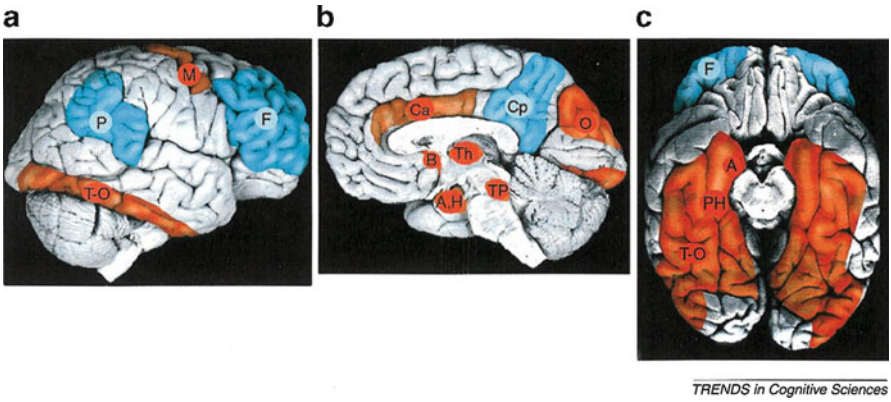

Fig. 17.6 Schematic representation of the relative increases and decreases in neural activity associated with REM sleep. *Red* regions indicate increased, and *blue* regions decreased, regional cerebral blood flow (*rCBF*) during REM sleep. *F* prefrontal cortex, *A* amygdala, *PH* parahippocampal gyrus, *T-O* temporo-occipital extrastriate cortex, *P* parietal supramarginal cortex, *M* motor cortex, *Ca* anterior cingulate gyrus, *Cp* posterior cingulate, *Oc* occipital lateral cortex, *B* basal forebrain, *Th* thalamus, *H* hypothalamus, *TP* pontine tegmentum. (**a**) Lateral (**b**) Medial and (**c**) Ventral (From Schwartz and Maquet (2002). Reproduced with permission)

have argued for evolved special perceptual sensitivities and biases (see Chap. 2), suggesting that experiences of unseen agents such as spirits and gods simply reflect our hypersensitive agent detectors (Barrett 2004; Guthrie 1993). On our view, in the threat simulation mode of sleep paralysis, such agency-detection devices come especially to the fore as criteria are lowered, and agency-detection bias is increased via activation of the amygdala and related structures (Cheyne et al. 1999).

17.5.2 The Role of REM State

As a REM phenomenon, the sensed-presence experience during sleep paralysis shares a number of relevant features with the previously discussed contexts, but it also has some unique features. In contrast to the earlier contexts, for example, the sensed presence during sleep paralysis is overwhelmingly associated with intense fear. During REM, and consistent with the previous contexts reviewed, activity of temporoparietal and frontal cortex is suppressed (Schwartz and Maquet 2002). Hence, integration of body sensations and orientation are compromised during REM states. In contrast, the activation of structures associated with the amygdala, including the anterior cingulate cortex, is enhanced (see Fig. 17.6). These areas appear to constitute a threat-activated vigilance system (TAVS, see Cheyne 2003) playing an important role in affective and strategic responses to threat (Whalen 1998) and hence likely to contribute to the sense of threat so particularly associated

with the presence of sleep-paralysis episodes. Exacerbating this hyperactivation of the TAVS is REM deactivation of prefrontal cortex, which normally modulates amygdalar activity. Finally, that one is supine, paralyzed, often alone, and in the dark during episodes must further heighten the sense of terror and uncertainty, further activating the TAVS (Cheyne and Girard 2007a, b).

The TAVS hypothesis suggests the further possibility that individual differences in fear-detection thresholds would lead to differential susceptibility to threatening presence experiences. The limited evidence bearing on this hypothesis is, however, not very consistent. A number of studies have implicated heightened stress and anxiety in sleep-paralysis experiences, though few have precisely defined either stress or anxiety or related either specifically to the sensed presence during sleep paralysis (see Simard and Neilson 2005; Solomonova et al. 2008). Simard and Neilson as well as Solomonova and colleagues did assess various aspects of social anxiety and various sleep-paralysis experiences, and reported correlations with sleep-paralysis experiences, but found no more than suggestive evidence that social anxiety is uniquely associated with sensed presence during sleep paralysis.

Although many people do imagine the intruder to be demonic and otherworldly, the threatening presence is not always subject to such supernatural interpretations. Often, people make assessments of the situation in terms of very material sources of danger: prowlers, robbers, and rapists, as well as simply accepting them as hallucinations (Cheyne 2001). It is important to realize, however, that *rational assessments need not detract from the vividness or realism of the experiences*. The compelling nature of the threat during sleep paralysis is such that we have suggested that it constitutes a paroxysmal paranoid delusion (Cheyne and Girard 2007a, b). The resistance of such experiences to alteration by rational assessment is consistent with a primitive modular source, such as the TAVS, that is highly immune to being overridden by higher-order cognitions (see also Chap. 26).

17.6 Reconciling Sensed Presence as Self and as Others

Despite the apparently absolute sense of otherness of the night creature, there is an aspect of the threatening presence that is consistent with the notion that it is somehow linked to the sense of self. The presence is sometimes taken to be a demonic entity intent on "taking over one's body" or "possessing one's soul." People thus tend to regard themselves as locked in a desperate struggle for the very integrity of their innermost self. Yet, how can something so utterly alien and other share any aspect of the self?

A beginning of an answer might be found in the observation that a good deal of human motor and perceptual learning throughout development occurs in the context of coordinated interactions with others. James Mark Baldwin (1861–1934) was one of the first, at the end of the nineteenth century, to consider seriously the parallels between the imitation of others and the repetition of one's own actions ("circular reaction") and hence that whenever we learn something about another person we

learn something about ourselves, and whenever we learn something about ourselves we learn something about others. Another early developmental psychologist, Lev Vygotsky (1896–1934), also noted that a child's early skills typically begin as shared capacities with adults, who "fill in" the gaps in the child's performance. Both Baldwin and Vygotsky implied that our own sense of ourselves as intentional agents developed in tandem with, and under the guidance of, the actions and implied intentions of others. With such a social background, we cannot help but understand ourselves as others do, or perhaps more accurately, understand ourselves very much as we understand others in a very embodied sense.

Recent evidence corroborates these early intuitions that the perception and interpretation of implicit and overt bodily self-activity and the actions of others are very closely linked across multiple shared systems. These include observations as diverse as infant facial imitation (Melzoff and Moore 1977), automatic imitation (Stürmer et al. 2000), the social Simon effect (Sebanz et al. 2003), and the existence of mirror neurons responsive to similar own and other actions (Rizzolati and Craighero 2004).[1] Interestingly, given the inherent intentionality of the sensed presence, in both the case of mirror neurons and automatic imitation, the awareness of the implicitly inferred intentions of the partner or model appears to be as or more important than concrete behavioral cues (Liepelt and Brass 2010; Vlainic et al. 2010). Moreover, the parameters during movement imitation map onto the physical topography of the bodies of model and imitator (Chartand and Bargh 1999). The locations of mirror neurons in frontal premotor areas and inferior parietal areas (Iacoboni et al. 1999) clearly correspond to the general areas most often implicated in sensed presence across many of the contexts considered here (Buccino et al. 2001; Chaminade et al. 2005). Thus, the anomalous activation of mirror neurons may sometimes obscure the distinction between self and others. Companion experiences and the presence experiences reported by neurological patients appear to involve these same shared motor and perceptual systems. The observation that the presences in neurological disorders and elicited contexts sometimes imitate the movements of corresponding body parts is consistent with the everyday interactions with others, and therefore should not automatically lead to the inference that an anomalous imitating agent is just a projection of our bodily selves. Companion experiences, in particular, might reflect a bias introduced by the intense need for companionship and assistance. TAVS-activated threatening presences would conversely bias interpretation to an external source of threat.

It is important not to omit, however, to mention that sleep-paralysis experiences also include some very dramatic anomalies of the bodily self (Cheyne and Girard 2009). These bodily self-experiences include vestibular and motor hallucinations such as flying, floating, falling, and spinning (see Chap. 13), as well as out-of-body

[1] The fact that the very primates in which mirror neurons were first observed do not appear to be capable of imitation suggests that the close linkage between the observed actions of self and others precedes the ability for explicit imitation, and may find its roots in the need to coordinate the activity of self and others.

experiences (OBEs), which include both kinesthetic out-of-body dissociative experiences and out-of-body autoscopy, and all of these have always formed a separate factor from the intruder hallucinations. Thus, in the sleep-paralysis context, we have consistently found a clear separation of the bodily self and threatening-other hallucinations. Nonetheless, we recently found tentative evidence that the sensed presence when combined with strong bodily sensations can contribute to hallucinations of self as well as of others (Cheyne and Girard 2009). Within the bodily self-experiences, we have found evidence for a potential path from vestibular-motor hallucinations to out-of-body dissociative experiences to autoscopic experiences. Although the sensed-presence experience itself is not strongly correlated with any of the OBE phenomena, we have found that the combination of sensed presence and out-of-body dissociation does significantly improve the prediction of autoscopic experiences (see Fig. 17.4b).

17.7 Concluding Remarks

The neuropsychological hypotheses concerning sensed presence admittedly remain tentative and crudely formulated, limited not only by our imagination but also by the paucity of empirical data. Moreover, our knowledge of brain functioning and its relation to everyday normal action and experience remains only very roughly worked out despite enormously exciting discoveries coming almost daily. In addition, as empirical phenomena, sensed presences remain elusive and comparatively rare, and hence challenging to observe under controlled conditions. As sensed-presence experiences constitute subjective experiences, investigating them is always limited on the phenomenal side by the challenge for the experients to describe what are, for all their gripping vividness, unfamiliar and fleeting sensations. Yet, as I hope this brief and selective review illustrates, the last decade has seen some fascinating progress in understanding this elusive and mysterious phenomenon from a neuropsychological perspective. More generally, and perhaps more importantly, however, is the potential for this work to help untangle the curiously intertwined oppositions of self and others.

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Chapter 18
Djinns

Jan Dirk Blom and Cor B.M. Hoffer

18.1 Introduction

"Djinn" and "hallucination" are very different notions. Deriving from widely divergent discourses, the two are hardly commensurable (Fig. 18.1). And yet the present chapter is devoted to djinns, in a book dealing with hallucinations. The reason for including this topic is that individuals with an Islamic background show a marked tendency to attribute any hallucinatory experiences they may have to a djinn, and therefore seek help from religious healers (see Fig. 18.2) before ever consulting a biomedical practitioner. Biomedical practitioners, in turn, and particularly those in Western societies, tend to know preciously little about djinns and Arabic-Islamic healing methods. When their Islamic patients finally show up on their doorstep, they establish diagnoses in conformity with their own psychiatric classifications, prescribe state-of-the-art pharmacological or psychotherapeutic treatments, and then almost invariably have to see with disappointment how these patients fail to recover and silently slip out of their treatment programs. In an increasingly multicultural society such as ours (i.e., the Netherlands),[1] this is an undesirable situation for patients and their families, as well as for the mental health practitioners involved. A second reason for addressing this topic is that hallucinations attributed to djinns would seem to possess quite extraordinary phenomenological characteristics,

[1] In 2010, 907,000 people in the Netherlands (i.e., 6% of the population) were Muslims, with 329,000 of them being of Turkish origin, and 314,000 of Moroccan origin (FORUM 2010).

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Fig. 18.1 *Djinn*. Oil painting by Marten Blom (Copyright 2010) (Reproduced with permission)

Fig. 18.2 Religious healer at Sidi Harazem, Morocco (Photograph by Cor Hoffer 2007)

setting them apart from the types of hallucination we tend to encounter in Western patients diagnosed with a psychotic disorder. As these characteristics are as yet largely uncharted, and the biomedical literature on the subject is limited (Khalifa and Hardie 2005; Sheikh 2005), this chapter also draws on anthropological and religious sources to arrive at a characterization of this niche phenomenon in the area of hallucinations research.

18.2 What Are Djinns?

Djinn is Arabic for spirit or ghost. It literally means "that which is concealed from people's sight" (Al-Ashqar 2005). Alternatives for "djinn" are *jinn*, *jin*, *jinni*, *cin* (in Turkish), and *shed* (in Hebrew). In the plural, it is *djinns*, *jins*, *jinn*, *dzjenoun*, *djnoun*, *jnoun*, *jenoun*, *jnûn*, *cinler*, and *shedim*. According to traditional Islamic faith, djinns were created by Allah out of smokeless fire (Qur'an 15:27). As such, Muslims generally consider these creatures part and parcel of the living world and believe that they actively participate in the lives and social interactions of humans, as do angels and *Iblis* (i.e., Satan) for that matter. Although often endowed with malign intentions, good djinns are also believed to exist. The latter are considered capable of helping humans to attain valuable goals in life and of coexisting with them in the form of djinn companions (*qareen*).

Being made out of fire, djinns are considered bodiless and hence invisible. And yet they are deemed capable of perceiving human beings (Qur'an 7:27) and of manifesting themselves to humans in a variety of shapes, including a vapor, cloud, cat, dog, snake, vulture, camel, donkey, onager, dragon, or human form. One of the Moroccan patients in our hospital used to see an old, female djinn hovering over the bed, reminiscent of her mother, but shorter, and with her feet bent backward in an anatomically impossible position. Another patient described to us a small, dark cloud that zoomed across the room, jumped off the furniture and walls, and sometimes disappeared through closed doors, whereas a third patient reported snakes and black dogs crawling and jumping up his legs and biting him in the thighs and belly. It is believed that djinns have a life cycle not unlike our own, in the sense that they are born, grow up, breathe, laugh, speak, eat, drink, urinate, defecate, have sexual intercourse, form families, appoint leaders, and so on, the only difference being that they get much older than we do before they die (Sakr 2001). Their preferred meal is said to consist of bones and dung (Al-Asqar 2005). In analogy with human demographics, djinns are classified according to gender, ethnicity, religious affiliation (i.e., Muslim, Jewish, Christian, pagan, or other), social class, political affiliation, moral standards, and so on (Bilu 1979). Some djinns are believed to be nameless, whereas others have names, such as the notorious female djinn Aisha Qandisha in Morocco and Alkarisi in Turkey (Crapanzano 1973; Hoffer 2000). Djinns are deemed to have humid, impure places as their natural habitat, including rivers,

wells, cemeteries, caves, ruins, market places, garbage dumps, bathrooms, and the vicinity of humans who neglect their personal hygiene. And yet they are also associated with fire, darkness, and blood. Reportedly, they feel particularly attracted to individuals going through transitional phases such as birth, circumcision, marriage, pregnancy, and the process of dying (Bilu 1979). According to some, the vulnerability to djinns is highest in cases of blood loss, extreme affective states, and negligence of prayer (Ghubash and Eapen 2009).

Like humans, djinns are considered sensitive to offense. It is believed that they can be easily provoked by insults and inadvertently disturbed by simple actions such as turning a stone or stepping over it (Stein 2000), killing a snake indoors, or pouring boiling hot water into the kitchen sink without saying "*bismillah*" ("In the name of Allah"). It is widely held that djinns can be conjured up by magicians and sent out to gather information from remote places with incredible speed – according to some, even from the gates of heaven – or to transport heavy objects from one place to another (Sakr 2001). Religious scholars distinguish many techniques used by djinns to influence humans, including seduction (*nazagha*), temptation (*azalla*), presenting something as attractive (*zayyana*), driving one astray (*aghwā*), beguilement (*fatana*) (Maarouf 2007), and marrying a person who has remained single for too long (El-Zein 2009), although the latter is considered extremely rare (Al-Ashqar 2005). They also distinguish three basic modes of interaction with humans: from a relative distance, for example, by whispering in one's ear (*waswasa*), by striking a person (*Ṣira*), and by entering the body and possessing it (*aslai*) (Maarouf 2007). The following two cases illustrate how versatile and intrusive those perceptual experiences can be.

18.3 Two Cases

Patient A is a 45-year-old Tunisian man who used to work as a chef in various restaurants. Fifteen years ago someone startled him by pushing him in the back while he was working, and at that very moment he had the feeling a djinn had gotten into him. Ever since he has felt inexplicable movements, as if the djinn were relocating itself from one arm to the other, and down to his chest, belly, and legs. After 5 years, he started seeing the djinn too, in the shape of a blond woman in her twenties, dressed in a white robe and surrounded by a soft white light. She moves the way real people do and looks him in the eye when she addresses him. Patient A tends to listen to her intently, believing she has an important message to convey, but he can seldom understand what she says. Sometimes he hears in Dutch, "We will destroy your life" or "You will never get married," but most of the time, he hears a language he does not master. Sometimes the woman changes shape, ending up with multiple feet or a half-animal appearance. The sight of her tends to be accompanied by the smell of rotting cadavers, a sour taste in the mouth, pinches in an arm or a leg, and the sensation of a strong wind. During nights, he often sees the woman sitting on his chest,

and feels her exerting pressure. At times, he even feels her having sexual intercourse with him. He always feels wide awake and yet unable to move or scream, and in the morning he often finds that he has ejaculated. Since the time he experienced the djinn, patient A lost his job, got into quarrels and fights, spoiled three marriages, and became socially isolated. He consulted various imams, who advised him to pray, visit the mosque, read Qur'anic texts, and undertake a pilgrimage to Mecca. After 10 years, he consulted a biomedical practitioner who diagnosed him with borderline personality disorder and prescribed antidepressants. Finding no avail, patient A discharged himself after 2 years and, after three more years, turned to our hospital. He was interviewed and offered an EEG and an MRI scan to rule out temporal epilepsy, but backed out once again and never returned.

Patient B is a married, 26-year-old Moroccan woman, a former cashier and mother of a single daughter.[2] Four years ago, she fell down from the lavatory pan at work, dislocated her pink, and lost consciousness for half an hour. Believing that such a curious incident in such an unhygienic place must have been the work of a djinn, she set out to consult physicians and myriad other health professionals and even had herself admitted to a rehabilitation center, initially because of limb dysfunction resulting from the dislocation, but soon thereafter also because of depression, headache, stomachache, and fainting. After 1.5 year, she started hearing a male voice which commanded her to steal, smoke, drown herself, cut herself, and jump off a balcony or in front of a running train. At this point, she consulted an imam, who confirmed that she had been attacked by a djinn and treated her by reading Qur'anic verses out loud. Meanwhile she consulted the outpatient ward of our psychiatric hospital, where she was diagnosed with borderline personality disorder and treated with antidepressants, benzodiazepines, and antipsychotics. Her behavior deteriorated to the extent that she had to be admitted several times a week because of self-mutilation, suicide attempts, and physical aggression toward members of her family. Upon reexamination, it turned out that she did not only hear voices but also saw a dark figure facing her and talking to her. In addition, she turned out to suffer from mood swings and nonepileptic seizures. A neurological examination, blood tests, an EEG, and an MRI scan did not reveal any underlying pathology. Patient B's diagnosis was adjusted to schizoaffective disorder, and she was treated with clozapine and valproic acid. A second imam, working in the service of our hospital, said that he doubted whether she had been stricken by a djinn. Nevertheless, he took time to pray with her and read the Qur'an. Patient B recovered insofar that the seizures, aggression, and self-mutilating behavior came to a halt, and that after 2 years of hospitalization, she was sufficiently stable to be transferred to an open long-stay ward, from where she could regularly visit her daughter and other family members.

[2]The case of patient B was described before in Blom et al. (2010).

18.4 Descriptive Psychopathology

In Muslim societies, many people consider their lives so much intertwined with those of djinns that any kind of illness, misfortune, and unconventional behavior can be attributed to them (Drieskens 2008). From this vantage point, it is quite understandable that the two patients described above would see such entities as an explanation for their experiences, but does this also explain their phenomenological characteristics? Our own phenomenological and anthropological studies of the beliefs of Islamic healers and their clients (Hoffer 2000, 2009) as well as the medical examination of some 30 clinical patients – most of them diagnosed with psychotic disorder – indicate that hallucinations experienced by Islamic patients in the Netherlands tend to be multimodal in nature (as opposed to the predominantly unimodal or bimodal hallucinations experienced by the majority of our Dutch patients), and that they tend to add up to *personifications*, i.e., compound hallucinations depicting human or humanoid beings (see Staudenmaier 1912). As we saw, patient A experienced somatic, tactile, visual, verbal auditory, olfactory, and gustatory hallucinations, as well as a possible aura (the sensation of a wind blowing against the body) and an incubus phenomenon, i.e., sleep paralysis combined with the lively and often multimodal sensation of a creature sitting on the chest (see Cheyne 2003, as well as Chap. 17, this volume). This array of hallucinatory phenomena combined to conjure up the image of a living being carrying out coordinated actions. In the case of our patient A, the clinical picture may well have been attributable to temporal epilepsy, but in many other cases, including that of patient B, epilepsy was ruled out with reasonable certainty whereas the hallucinations at hand were similarly elaborate in nature. One male patient described to us a female djinn walking toward him, touching his chest, disappearing into his body, delivering a baby inside, and then leaving, after which he heard the baby crying inside his head. A second man described to us the experience of a small, primordial creature attaching itself to his face, thus preventing him to speak or breathe. The same creature was experienced by him as sitting behind his back, anus to anus, forcing feces into his intestines, which he could only get rid of by forcefully straining back.

18.5 Traditional Islamic Versus Biomedical Interpretations

Thus far we have consistently spoken of "hallucinations" when we referred to the perceptual experiences of our Islamic patients. After all, we designate a percept as hallucinatory when it is experienced by a waking individual in the absence of an appropriate stimulus from the extracorporeal world. But does this approach do sufficient justice to the topic at hand? In anthropology, it is customary to distinguish between "illness" (i.e., a feeling of not being healthy or normal) and "disease" (i.e., a diagnosable pathological condition), with "illness" predominantly reflecting the patient's perspective and "disease," the health practitioner's perspective. In the case of Islamic patients attributing their perceptual experiences to djinns, and biomedical health practitioners treating them with antipsychotic medication, illness

and disease have diametrically opposed ontological connotations. While the health practitioners attribute the percepts at hand to some neurophysiological aberration in the brain, the patients interpret them as testimony of the presence of actual living beings in the world "out there." If the health professionals were radical empiricists in the vein of William James (1842–1910), they might be willing to accept that the ultimate stuff of reality is pure experience, and that different perspectives therefore do not only entail different worldviews but also different worlds (James 1996). But a pluralistic universe is not what most of us have in mind when we think about the world "out there." On the contrary, we usually envisage the world as a singular, physical entity with objectifiable characteristics, which is probably the principal reason why it is so hard for us to accept the validity of more than a single explanatory model at a time (see also Chap. 2). While incommensurable explanatory models are a sure way to compromise the working relation between any two parties (Kleinman 1980), one cannot expect health practitioners to abandon their own model in favor of their patients', if only because they owe their professional skills to that model. Nor can we expect patients to simply give up their idiosyncratic beliefs in favor of their practitioners' worldviews. So the question here is how biomedical practitioners can bridge the gap between the Islamic religious model and their own biomedical model when it comes to the interpretation and treatment of perceptual phenomena attributed to djinns.

18.6 Religious Context and Folk Belief

To complicate things further, it should be noted that the term "Islamic religious model" refers to at least two different discourses, namely, the official Islam and the body of folk beliefs prevalent in Muslim societies. The official Islam comprises the Sunnite and Shi'ite faiths propagated by imams, *ûlamâ*, and *mullahs* in mosques and other orthodox institutions. Islamic folk beliefs, on the other hand, are rooted in historical medico-religious traditions such as Islamic-Arabic medicine, prophetic medicine, Sufism, and all sorts of local cultural traditions and folklore (Hoffer 2000), examples of which can be found in abundance on the internet and in the popular media (Drieskens 2008). The differences between the two discourses are of utmost importance for representatives of the official Islam, who consider many of the folk beliefs as superstitions. The majority of nonorthodox Muslims, however, tend to borrow elements from both discourses, mixing them up freely in their daily lives, and applying them whenever they see fit. As a corollary, many of them do not only believe in the existence of djinns but also in magic (*s'hour*), the evil eye (*l'ayne*), hagiolatry, and many other phenomena and practices not sanctioned by the official Islam (Hoffer 2000; Hermans 2007). Moreover, Muslims tend to see little harm in adding elements from the biomedical discourse, as testifies the consultation of a psychiatrist as well as an Islamic healer by patients A and B. In this sense, we may well ask ourselves the same question as Van der Geest (1985), who wrote, "Why all this fuss, one could ask, about integration? In their heads, clients of health care have already achieved an 'integration' of medical traditions."

18.7 Treatment

Traditional Arabic-Islamic treatment methods tend to fuse elements from the official Islam and Islamic folk medicine. Some of them are directed at the expulsion or ousting of djinns, whereas others aim to establish a state of peaceful coexistence between humans and djinns (Crapanzano 1973). Protection against djinns is offered by imams, *fuqaha* (religious teachers), *ashraf* (descendants of a holy family), and other religious healers in the form of prayer, Qur'anic verses (read out loud or recited), lavages, faith healing, the laying on of hands (see Fig. 18.3), magnetism, magical rituals, the induction of trance states, amulets (see Fig. 18.4), talismans (see Fig. 18.5), dietary measures, herbs, and fumigation.

Qur'anic verses are also written down in saffron, dissolved in water, and then offered to the alleged victims of djinns either to drink or to wash themselves (Hoffer 2000; Sengers 2000). Measures of a more sweeping nature include ecstatic dances, pilgrimages, visits to a holy shrine (see Fig. 18.6), animal sacrifices, the cursing of djinns, exorcism, incarceration, and caning (Crapanzano 1973; Hermans 2007; Lebling 2010). Various patients of ours had been locked up for 40 days, some of them chained to a wall. One of them told us that during that time, she underwent a foot whipping every Thursday, 40 strokes at a time, and another patient told us that he was thrown backward into a desert well, with the apparent intention of taking

Fig. 18.3 The laying on of hands by a religious healer in West Morocco (Photograph by Cor Hoffer 2007)

Fig. 18.4 Amulet (*nazarlik*) (Photograph by Cor Hoffer 2000)

Fig. 18.5 Leather talisman with Qur'anic verses (Photograph by Cor Hoffer 2000)

Fig. 18.6 Islamic holy shrine in West Morocco (Photograph by Cor Hoffer 2000)

him by surprise and thus ousting his djinn by frightening the life out of him.[3] As regards incarceration and immobilization, we gained the impression from our patients' accounts that these measures reflected the despair of all involved rather than any malign intentions. Caning, whippings, and beatings – which tend to be frowned upon by biomedical practitioners and Muslim scholars alike – were sometimes justified by our patients through the assertion that pain is thus afflicted to the djinn rather than to the possessed person. Here, too, the motivation to apply such measures would seem to be powerlessness rather than hostility (conform Hanley 2005). As noted by Dein et al. (2008) and Mölsä et al. (2010), today, many religious healers – especially those practicing in Western countries – are prepared to consider biomedical diagnoses first, to the extent that they adopt the idiom and accept the therapeutic techniques employed by psychiatrists, and that they reserve their more drastic techniques for cases where all else has failed, perhaps comparable to the way biomedical practitioners take refuge to electroconvulsive treatment (ECT).

Biomedical practitioners tend to treat their Islamic patients in conformity with biomedical diagnostic algorithms, using methods ranging from psychotherapy to antidepressants, antipsychotics, mood stabilizers, sedatives, anticonvulsants, and ECT (see Chap. 24). But unless they have the proper background information on their patients' attributional habits, their treatments are seldom successful (Hoffer 2009). This appears to be the rule rather than the exception, considering the

[3]This type of treatment, called water shock treatment, was also practiced in eighteenth- and early nineteenth-century European psychiatry (Guislain 1826; Kraepelin 1918).

prevalence of djinn attributions among Islamic patients, their reluctance to discuss them, and the unfamiliarity of many biomedical practitioners with the issue at hand (Dein et al. 2008). Our own experience is that it takes considerable effort and genuine interest to encourage Islamic patients to discuss the true nature of their concerns and to have them shed some light on the therapeutic strategies attempted so far. But when they do so, one is often able to obtain surprisingly detailed accounts. We, too, establish diagnoses in conformity with the Diagnostic and Statistical Manual of Mental Disorders (DSM) and offer biomedical treatments to match. But in addition, we offer our patients the possibility of consulting an imam in the service of our hospital, who establishes his own religious diagnoses, and offers religious treatments in the form of prayer, Qur'an reading, lavages, and sometimes dietary measures. This two-track policy is of a complementary nature, in the sense that both parties encourage the patient to adhere to both types of treatment, thus tolerating the coexistence of the explanatory models involved and offering a treatment program that addresses the biomedical as well as the religious issues at stake. An important benefit of this strategy is the improved compliance of our patients, in addition to an improved patient-physician relationship, which, after all, is the sine qua non for any therapeutic success.

18.8 Concluding Remarks

The prevalence of hallucinations attributed to djinns is unknown, but we estimate that in the Netherlands, some 80% of Islamic patients receiving a – biomedical – diagnosis of psychotic disorder consider djinns as an explanation for their condition (Blom et al. 2010). In conformity with the literature on the subject (Akerele 1987; Saeed et al. 2000; Khalifa and Hardie 2005; Sheikh 2005; Hoffer 2005), we advocate a culturally sensitive approach that involves medical and transcultural history taking, proper medical diagnosis, proper medical treatment, as well as the consultation of a qualified imam or religious healer for the purpose of dealing with any religious issues at stake. In doing so, however, one should take care to avoid conflicting – and potentially harmful – therapeutic approaches. As to future research, we recommend systematic studies of the phenomenological characteristics and neurobiological correlates of hallucinations attributed to djinns, in the vein of relatively recent studies on autoscopy and out-of-body experience (Brugger et al. 1997; Blanke et al. 2004; see also Chaps. 15 and 16). It does not take a Kant or Freud to appreciate the notion that we constantly project our own ideas onto the world we think we are perceiving, but there might well be more to this type of hallucination than the mere idea that we are dealing here with a "culture-bound syndrome."

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Part III
Research

Chapter 19
Structural Neuroimaging in Psychotic Patients with Auditory Verbal Hallucinations

Paul Allen and Gemma Modinos

19.1 Introduction

Over the last few decades, neuroimaging techniques have allowed us to investigate the structural correlates of symptoms in individuals diagnosed with schizophrenia and other psychoses. Brain scans, using computerised tomography (CT) or magnetic resonance imaging (MRI), are often used clinically to rule out focal lesions such as a tumour or a stroke in patients who present with psychotic symptoms. In a seminal study, Johnstone et al. (1976) were the first to use CT scans to show structural alterations in the brains of patients diagnosed with schizophrenia. Since then, a significant body of research has used neuroimaging to examine neuroanatomy in patients with psychosis (Ellison-Wright and Bullmore 2009; Glahn et al. 2008; Shenton et al. 2001). A smaller number of studies have used structural neuroimaging to examine the brain in patients diagnosed with schizophrenia who experience frequent hallucinations, usually in the auditory modality. In this chapter, a comprehensive overview of studies examining grey- and white-matter changes in patients experiencing hallucinations is provided. The focus will be predominantly on studies of patients diagnosed with schizophrenia or schizophreniform disorders who experience auditory verbal hallucinations (AVHs).

19.2 Hallucinations and Brain Lesions

Braun and colleagues reviewed case studies of post-lesion hallucinations in the visual, auditory, and somatic modalities. They observed that lesions are almost always located in the brain pathway of the sensory modality of the hallucination and

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suggested that the lesioned tissue must have contained a predominance of inhibitory over excitatory neurons for the sensory modality in question (Braun et al. 2003). These inhibitory neurons would normally be responsible for 'gauging down' brain circuits containing complex sensory representations. In addition to localised lesions and dysfunction to specific brain regions (topological), dysfunction related to connections between brain regions (hodological) has also been proposed since patients prone to hallucinations have complex, task-specific hodological abnormalities that persist between hallucination episodes (ffytche 2008). Despite the ostensible relationship between hallucinations and lesions in corresponding sensory regions seen in neurological patients, in psychiatric patients who experience hallucinations, no gross brain abnormalities can usually be seen on brain scans at the individual level. For this reason, it has been necessary to combine brain scans of groups of subjects with hallucinations and compare these to healthy individuals and/or patients diagnosed with schizophrenia without hallucinations in order to identify neuroanatomical changes associated with these symptoms.

19.3 Grey-Matter Changes in Patients with Hallucinations

Early region of interest (ROI) studies investigating hallucinations in patients diagnosed with schizophrenia showed that their brains were characterised by volume reductions of the superior temporal gyrus (STG) and lateral ventricles. In particular, hallucination severity was inversely correlated with left STG volume (Barta et al. 1990; Flaum et al. 1995). More recently, Sumich and colleagues assessed positive and negative symptomatology in 25 first-episode patients and its relationship with grey-matter volume (GMV) in the temporal lobe (Sumich et al. 2005). The study used linear regression to establish associations between symptom dimensions and stereological measurements of Heschl's gyrus and the planum temporale. Volume decrease in left Heschl's gyrus (primary auditory cortex) was associated with hallucinations, whilst increased volumes in the left planum temporale were associated with delusions. Onitsuka et al. (2004) reported that increased severity of AVH is correlated with reduced grey-matter volumes (GMVs) in the left anterior STG and middle temporal gyrus (MTG). A summary of research studies using an ROI approach is provided in Table 19.1.

More recently, voxel-based morphometry (VBM), a whole-brain, unbiased, semiautomated technique for characterising regional cerebral differences in structural MRI (Ashburner and Friston 2000; Mechelli et al. 2005), has been applied to investigate structural abnormalities associated with AVH. O'Daly et al. (2007) reported an association between AVH severity and GMV loss in a wider range of temporal regions than those typically included in ROI studies, including the right STG and fusiform gyrus, and the left inferior temporal gyrus. Martí-Bonmatí et al. (2007) reported GMV reduction also in bilateral STG and medial temporal gyri in 21 patients diagnosed with schizophrenia and experiencing persistent hallucinations. Nenadic et al. (2010) studied a relatively large group of 99 participants

Table 19.1 Studies investigating brain structure with a region of interest approach

Authors	Sample	Design	Findings
Barta et al. (1990)	15 SCZ, 15 HC	Correlation severity AVH	Less left STG
Flaum et al. (1995)	166 SCZ	Correlation severity AVH	Less left STG
Onitsuka et al. (2004)	23 SCZ, 28 HC	Correlation severity AVH	Less left STG, MTG
Shin et al. (2005)	25 SCZ (17 AVH, 8 no AVH)	Comparison AVH>no AVH	More temporal GMV and WMV, more frontal GMV
Sumich et al. (2005)	25 SCZ	Correlation severity AVH	Less left Heschl's gyrus
Hubl et al. (2010)	13 SCZAVH, 13 SCZ no AVH, 13 HC	Group comparisons	AVH more volume in the right, but not in the left Heschl's gyrus (WM and GM)

AVH auditory verbal hallucinations, *GMV* grey-matter volume, *HC* healthy controls, *MTG* middle temporal gyrus, *SCZ* patients diagnosed with schizophrenia, *SCZAVH* patients diagnosed with schizophrenia and auditory verbal hallucinations, *SCZ no AVH* patients diagnosed with schizophrenia without auditory verbal hallucinations, *STG* superior temporal gyrus, *WMV* white-matter volume

diagnosed with schizophrenia. Voxel-wise correlations with a score of AVH severity identified areas in the left and right STG (including Heschl's gyrus) and left supramarginal/angular gyrus, although it is not clear whether these correlations represent increased or decreased GMV. Together, these results are consistent with previous ROI studies demonstrating main effects of auditory hallucinations related to modality-specific superior temporal areas including primary and secondary auditory cortices.

Also using VBM techniques, a number of studies have reported structural alterations in non-sensory regions to be associated with AVH. Shapleske et al. (2002) analysed whole-brain grey and white matter in patients with and without hallucinations and age- and gender-matched controls. Relative to non-hallucinating patients, those with AVH showed reduced grey-matter volume in the left insula and adjacent temporal pole. Neckelmann et al. (2006) reported GMV reduction that correlated with hallucination severity in the thalamus and cerebellum as well as the left STG. Martí-Bonmatí et al. (2007) described GMV reductions associated with the severity of AVH in the right precentral, left Rolandic gyrus, left inferior opercular frontal and left superomedial frontal gyri, bilateral orbitomedial frontal, right posterior cingular, bilateral anterior cingular, right parahippocampus, right insula, and right precuneus. The VBM study by Nenadic and colleagues also reports GMV reduction associated with AVH in the left post-central gyrus and left posterior cingulate cortex. Modinos et al. (2009) reported that GMV in the left inferior frontal gyrus was positively correlated with the severity of AVH. Furthermore, hallucination severity influenced the pattern of structural covariance between this region and the left STG and MTG, the right inferior frontal gyrus and hippocampus, and the insula

bilaterally. Gaser et al. (2004) studied 85 patients diagnosed with schizophrenia, of which 29 experienced hallucinations. They found severity of hallucinations to be correlated with volume loss in the right dorsolateral prefrontal cortex as well as the left transverse temporal Heschl's and supramarginal gyri. The volume loss in the right prefrontal cortex is of interest given the role that has been ascribed to frontotemporal interactions in volitional auditory perception (Silbersweig and Stern 1998). In light of this evidence, impairments in this network could erase the volitional signature of subjective perceptual awareness that arises from frontotemporal interactions and thus explain why hallucinations are experienced as involuntary. Interestingly, the right prefrontal area described by Gaser et al. (2004) partially overlaps with the homologue of Broca's area. Homotopic brain regions are connected to each other by inhibitory tracts (Karbe et al. 1998), which are the densest of all the interhemispheric pathways (McGuire et al. 1991a, b). Impairment of one region may thus lead to hyperactivation of the homotopic region. Support for this idea comes from a recent functional imaging study that revealed activation in the right homologue of Broca's area in patients whilst experiencing hallucinations (Sommer et al. 2008).

Overall, the imaging literature has primarily focused on how brain structure relates to AVH using indices of its overall severity. A recent study, however, investigated how GMV relates to a specific characteristic of AVH, namely spatial location. Plaze et al. (2009) used VBM to examine the neural substrate of this clinical feature in two subgroups of patients according to the spatial localization of their hallucinations. Patients with only outer-space hallucinations (voices heard outside the head) and patients with only inner-space hallucinations (voices heard inside the head) were compared. Convergent anatomical differences (white-matter volume) were detected between the patient subgroups in the right temporoparietal junction (rTPJ). In comparison to healthy subjects, opposite deviations in white-matter volumes and sulcus displacements were found in patients with inner-space hallucinations and patients with outer-space hallucinations. The authors concluded that spatial localization of auditory hallucinations is associated with the rTPJ anatomy, a key region of the 'where' auditory pathway. The rTPJ plays an important role in spatial awareness and in self-processing and integration of personal and extrapersonal spaces. In this context, the authors speculated that, regarding the spatial localization of AVH, the reported differences in rTPJ anatomy could contribute to the differential attributions of spatial coordinates to hallucinations in an egocentric referential manner (external vs. internal).

Whilst the majority of studies using either ROI or VBM analysis have mainly reported *reductions* in grey matter to be associated with AVH, *increases* in grey- and white-matter volumes have also been documented in hallucinating relative to non-hallucinating patients. Using a semiautomated Talairach atlas–based parcellation method, Shin et al. (2005) compared 17 first-episode patients with AVH to 8 first-episode patients without. Larger temporal grey- and white-matter and frontal grey-matter volumes were found in hallucinating patients. The authors suggest that increased volumes may be due to patient characteristics, as their study comprised of unmedicated first-episode patients. However, the results from this study should be

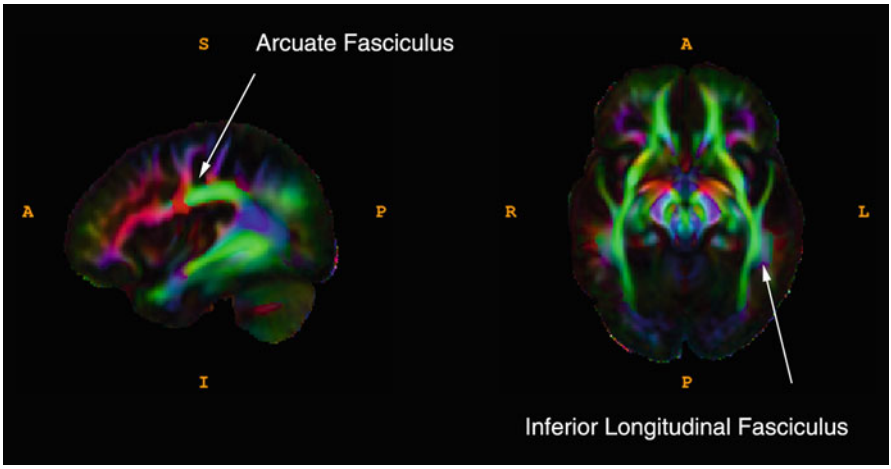

Fig. 19.1 The most consistently reported areas of grey-matter reductions in association with auditory verbal hallucinations in schizophrenia comprise the left superior temporal gyrus (*blue*) and the left middle temporal gyrus (*red*). The images depict the anatomical landmarks of these regions on the sagittal (*left*) and axial (*right*) views. They have been prepared with anatomically predefined masks according to the Talairach Deamon in the WFU_PickAtlas software in SPM5 and overlaid on the standard brain with MRICron

interpreted cautiously due to the small sample size. Hubl et al. (2010) also reported a bigger volume of Heschl's gyrus in the right hemisphere in hallucinating patients, caused by both grey- and white-matter increases, and Modinos et al. (2009) reported a positive correlation between volume in the left IFG and the overall severity of AVH. Such findings may be consistent with theories of increased connectivity between cerebral regions in hallucinating patients. This will be further discussed in the next section on white-matter studies, as increased integrity of frontotemporal white-matter bundles have been reported in hallucinators relative to non-hallucinators (Hubl et al. 2004; Shergill et al. 2007).

Despite the emergence of some clear trends in the findings, such as the apparent alteration in STG volume reported in patients, several studies have also been published that failed to find a relationship between STG volume and hallucinations (Cowell et al. 1996; DeLisi et al. 1994; Havermans et al. 1999; Plaze et al. 2006). In addition, and extending the findings from ROI studies, which are limited to the a priori selection of regions of interest, VBM studies have identified regions that have not been included in any of the main theoretical accounts of AVH (external misattribution of inner speech, modality-specific sensory cortical dysfunction, dysfunctional neural substrates of episodic verbal memory, see Seal et al. 2004; Waters et al. 2010; Northoff and Qin 2011) such as post-central cortical regions (García-Martí et al. 2008; Nenadic et al. 2010).

Overall, grey-matter reduction in the left STG/MTG, including the primary auditory cortex, is the most consistently reported finding in patients with AVH (see Fig. 19.1). This finding traverses methodological boundaries, as has been

repeatedly reported both by studies using stereological and studies using VBM data analysis methods. This finding is also consistent with lesion studies which report that the lesion is almost always in the brain region of the sensory modality of the hallucination (Braun et al. 2003). Furthermore, reduced grey-matter volumes in non-sensory regions have also been reported in a number of studies. Amongst these, there appears to be little consistency with regard to non-sensory regions showing significant abnormalities, although GMV anomalies in portions of the prefrontal cortex are reported by five studies. Volume reductions in the prefrontal and cerebellar cortices may be associated with impairments in awareness and volition of internal speech, and the assignation of a self-tag to the experience of AVH, as proposed by a recent review (Northoff and Qin 2011). Finally, the one study investigating a clinical feature of AVH, spatial location, reports that the spatial location of AVH is associated with right TPJ anatomy. A summary of research studies using VBM may be seen in Table 19.2.

19.4 White-Matter Changes in Patients with Hallucinations

White-matter (WM) changes are usually investigated with an MRI technique called diffusion tensor imaging (DTI) that assesses the directionality of water diffusion (anisotropy), which is restricted by boundaries such as white-matter fibres. Considered to reflect the underlying structural integrity (Basser and Pierpaoli 1996), reduced fractional anisotropy (FA) is believed to represent a loss of WM integrity. A recent meta-analysis identified two consistent locations of FA reduction in patients diagnosed with schizophrenia: one in the deep WM of the left frontal lobe and the other in the deep WM of left temporal lobe (Ellison-Wright and Bullmore 2009). The association between AVH and WM integrity has also been examined by a small number of studies. Using magnetic resonance DTI, Hubl et al. (2004) investigated the integrity of WM tracts in the brains of patients diagnosed with schizophrenia with and without AVH and a healthy comparison group. Patients with AVH were shown to have significantly higher FA values relative to both control groups in the lateral temporoparietal section of a major fibre tract known as the arcuate fasciculus. This tract connects language production areas (e.g. Broca's area) with auditory processing and language perception areas. The authors speculate that, during inner speech, the apparently stronger connectivity between such areas in patients with hallucinations may lead to dysfunctional coactivation of regions related to the acoustical processing of external stimuli, which may account for their inability to distinguish self-generated thoughts from external stimulation. Shergill et al. (2007) used DTI in patients diagnosed with schizophrenia to examine the integrity of the major WM fasciculi, which connects the frontal, temporal, and parietal cortices and the corpus callosum. Across all patients, there was reduced FA in regions corresponding to the longitudinal fasciculi bilaterally and in the genu of the corpus callosum. Within the patients group, AVHs were associated with relatively increased FA in the superior longitudinal fasciculi (SLF), which is a part of the arcuate fasciculus, and in the anterior cingulum. Seok et al. (2007) reported

Table 19.2 Studies examining brain structure with voxel-based morphometry

Study	Sample	Design	Findings
Shapleske et al. (2002)	41 SCZAVH, 31 SCZ no AVH, 32 HC	Comparison AVH>no AVH	Less left INS and adjacent temporal lobe
Gaser et al. (2004)	85 SCZ	Correlation severity AVH	Less left transverse temporal gyrus of Heschl, left (inferior) SMG, middle/inferior right PFC
Neckelmann et al. (2006)	12 SCZAVH, 12 HC	Correlation severity AVH	Less left STG (transverse), left THA, bilateral cerebellum
Plaze et al. (2006)	15 SCZAVH	Correlation severity AVH	No correlation GMD and severity AVH
Martí-Bonmatí et al. (2007)	21 SCZAVH, 10 HC	Comparison AVH>HC, correlation severity AVH	Less right precentral, left Rolandic gyrus, left inferior opercular frontal, left superomedial frontal, bilateral orbitomedial frontal, right PCC, bilateral ACC, both medial temporal gyri, both STG, right PHC, right INS and right PreC.
O'Daly et al. (2007)	28 SCZAVH, 32 HC	Correlation severity AVH	Less right STG, fusiform gyrus, left ITG
García-Martí et al. (2008)	18 SCZAVH, 19 HC	Comparison AVH>HC. Correlation severity AVH	Less in bilateral INS, STG, and left AMY. Severity AVH correlated with less left IFG and right post-central gyri
Modinos et al. (2009)	26 SCZAVH	Correlation severity AVH	More left IFG
Plaze et al. (2009)	45 SCZAVH (12 outer, 15 inner), 20 HC	Comparison outer>inner	Less WMV rTPJ. No difference GMV
Nenadic et al. (2010)	99 AVH	Correlation severity AVH	Less left/right STG (including Heschl's gyrus), left SMG/ANG gyrus, left post-central gyrus, left PCC

ACC anterior cingulate cortex, *AMY* amygdala, *ANG* angular gyrus, *AVH* auditory verbal hallucinations, *GMD* grey-matter density, *GMV* grey-matter volume, *HC* healthy controls, *IFG* inferior frontal gyrus, *INS* insula, *PFC* prefrontal cortex, *PHC* parahippocampal gyrus, *PCC* posterior cingulate cortex, *PreC* precuneus, *rTPJ* right temporoparietal junction, *SCZ* patients diagnosed with schizophrenia, *SCZAVH* patients diagnosed with schizophrenia and auditory verbal hallucinations, *SCZ no AVH* patients diagnosed with schizophrenia without auditory verbal hallucinations, SMG supramarginal gyrus, *STG* superior temporal gyrus, *THA* thalamus, *WMV* white-matter volume

that, in patients diagnosed with schizophrenia, FA of the WM regions was significantly decreased in the left SLF, whereas WM density was significantly increased in the left inferior longitudinal fasciculus (ILF). The mean FA value of the left frontal part of the SLF was positively correlated with the severity of AVH. Lee et al. (2009) used DTI to investigate altered structural integrity in STG grey and white matter in patients diagnosed with chronic schizophrenia compared with healthy controls. Relative to controls, the patients demonstrated reduced volume bilaterally in STG grey matter but not in white matter. For DTI measures, the patients showed increased mean diffusivity (a scalar measure of the total diffusion of the water molecules within a voxel, which is restricted by structures like membranes and myelin sheets), bilaterally, in STG grey matter, and in left STG white matter. In addition, mean diffusivity in left STG white matter showed a significant correlation with AVH. Lee and colleagues concluded that the increased water diffusivity in left-side STG, which was associated with auditory hallucinations, is due to a disconnection amongst auditory/language processing regions in patients diagnosed with schizophrenia. Ashtari et al. (2007) reported that adolescents with a diagnosis of schizophrenia or schizoaffective disorder and a history of visual hallucinations had lower FA in the left ILF than patients without visual hallucinations. Using a white-matter parcellation technique, Makris et al. (2010) compared the volume of brain fibre systems between patients diagnosed with schizophrenia ($n=88$) and matched healthy controls ($n=40$). White-matter regions of local and distal associative fibre systems were significantly different in the patients, and there were significant positive correlations between volumes (larger) in occipital, cingulate, and sagittal temporal regions and positive symptoms, in particular hallucinations. Table 19.3 shows a summary of research studies using DTI.

Based on the evidence accumulated to date, Whitford et al. (2010) proposed a direct link between WM abnormalities seen in patients diagnosed with schizophrenia and mechanistic accounts of AVH proposed by Frith (Frith et al. 1991, 2000). Specifically, it is proposed that abnormalities in frontal myelination of white-matter fasciculi result in conduction delays in the efference copies initiated by willed actions. These conduction delays cause the resulting corollary discharges to be generated too late to suppress the sensory consequences of the willed actions. The resulting ambiguity as to the origins of these actions represents a phenomenologically and neurophysiologically significant prediction error. On a phenomenological level, the perception of salience in a self-generated action leads to confusion as to its origins and, consequently, passivity experiences and auditory hallucinations.

In summary, a number of studies now show an association between white-matter alterations and hallucinations in patients diagnosed with schizophrenia. Although both increases and decreases in FA are reported, the majority of studies examining white matter report an increase in FA or white-matter volume associated with hallucinations. Furthermore, whilst there is considerable variation in the regions of reported white-matter alterations, the inferior and superior longitudinal fasciculi (or arcuate fasciculus) have been reported in three studies, implicating a disruption amongst cerebral networks supporting language and attentional processes (Fig. 19.2).

Table 19.3 Studies examining white-matter characteristics with diffusion tensor imaging

Authors	Sample	Design	Findings
Hubl et al. (2004)	13 SCZAVH, 13 SCZ no AVH, 13 HC	Comparison SCZAVH > SCZ no AVH + HC, SCZAVH > SCZ no AVH	SCZAVH > SCZ no AVH + HC = FA lateral parts, TP section of the arcuate fasciculus, and in parts of the ACC SCZAVH > SCZ no AVH = FA left hemispheric fibre tracts, including the cingulate bundle
Ashtari et al. (2007)	23 SCZ (9 SCZvisualH, 12 SCZnovisualH), 21 HC	Comparison SCZvisualH > SCZnovisualH	Less FA in left ILF
Seok et al. (2007)	15 SCZAVH, 15 SCZ no AVH, 22 HC	Correlation severity AVH	More mean FA value of the left frontal part of the SLF
Shergill et al. (2007)	33 SCZ, 40 HC	Correlation severity AVH	More FA in SLF and AC
Lee et al. (2009)	21 SCZ, 22 HC	Correlation severity AVH	More mean diffusivity in left STG
Makris et al. (2010)	88 SCZ, 40 HC	Correlation severity AVH	More WM volume in occipital, cingulate, and sagittal temporal regions

AC anterior cingulum, *AVH* auditory verbal hallucinations, *HC* healthy controls, *FA* fractional anisotropy, *TP* temporoparietal, *ILF* inferior longitudinal fasciculus, *SCZ* patients diagnosed with schizophrenia, *SCZAVH* patients diagnosed with schizophrenia and auditory verbal hallucinations, *SCZ no AVH* patients diagnosed with schizophrenia without auditory verbal hallucinations, *SCZvisualH* patients diagnosed with schizophrenia and visual hallucinations, *SCZnovisualH* patients diagnosed with schizophrenia without visual hallucinations, *SLF* superior longitudinal fasciculus, *STG* superior temporal gyrus, *WM* white matter

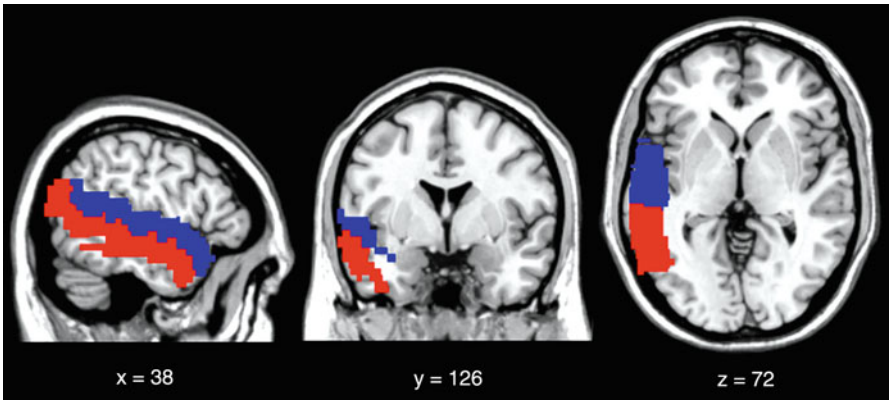

Fig. 19.2 Diffusion tensor imaging studies have most commonly reported white-matter abnormalities in association with auditory verbal hallucinations in schizophrenia which comprise the arcuate fasciculus (*left*) and the inferior longitudinal fasciculus (*right*). The image has been prepared using the IIT2 template (Described by Zhang et al. (2011). Enhanced ICBM diffusion tensor template of the human brain. Neuroimage, 54, 974–984)

19.5 Lateralisation and Gyrification Studies

Reduced cerebral lateralisation of language in patients diagnosed with schizophrenia has been documented in a substantial number of studies (Sommer et al. 2001). More specifically to patients with AVH, four studies have reported altered lateralisation. Shapleske et al. (2001) compared structural brain asymmetry of the planum temporale (PT) and sylvian fissure (SF) of patients with no history of hallucinations ($n=30$) and patients with a strong definitive history of AVH ($n=44$), in addition to 32 matched healthy volunteers. They failed to find differences between the groups on these measures. The only significant finding was a modest correlation between leftward asymmetry of the SF and hallucinations within the prominent hallucinator group. A recent functional imaging study also failed to find widespread lateralisation differences that were specific to AVH. Although patients with AVH did show decreased functional lateralisation, healthy individuals with AVH did not (Diederen et al. 2010).

One study examined cortical folding abnormalities in patients with treatment-resistant AVH. Cachia et al. (2008) used an automated method to extract, label, and measure the sulcus area in the whole cortex. They reported that for both hemispheres, patients diagnosed with schizophrenia had a lower global sulcal index. The local-sulcal index decrease was not homogeneous across the whole cortex and was more significant in the superior temporal sulcus bilaterally, in the left middle frontal sulcus, and in the left SF (Broca's area). It was hypothesised that sulcal abnormalities in language-related areas of the cortex might underlie these patients' particular

vulnerability to hallucinations. A limitation of this study, however, was that a non-hallucinating control group was not studied.

19.6 Conclusions

From the six region-of-interest studies on patients diagnosed with schizophrenia and experiencing auditory verbal hallucinations, four have reported volumetric decreases in sensory regions, mainly the superior temporal gyrus. From the ten voxel-based morphometry studies, seven found less grey-matter volume in the superior temporal gyrus. From the six diffusion tensor imaging studies examining white-matter connectivity in patients with auditory verbal hallucinations, five reported an increase in fractional anisotropy or mean diffusivity indices. In terms of the directionality of the results, the earlier lesion studies showed tissue loss in sensory regions. Region-of-interest studies suggest volume reductions in sensory regions. Voxel-based morphometry analyses are largely consistent with lesion and region-of-interest studies, whilst also showing significant effects in non-sensory regions such as areas of the prefrontal cortex, and areas of the neuronal circuitry underlying emotional processes (insula, amygdala, anterior cingulate cortex, parahippocampal gyrus). The majority of connectivity studies reported enhanced integrity of white-matter tracts relevant to language processing (arcuate fasciculus and inferior longitudinal fasciculus), indicating increased coactivation of language-processing regions in auditory verbal hallucinations. Hence, despite some divergence between studies, abnormalities in the auditory cortex and language-related brain regions seem to be the most replicated finding, consistent with evidence from functional neuroimaging studies in auditory verbal hallucinations (Jardri et al. 2011). In addition, there are abnormalities in white-matter integrity, indicating perturbed connectivity, particularly between frontal and temporal regions involved in language and attention processes. This aligns well with a recent comprehensive review of structural and functional MRI studies on brain connectivity in patients diagnosed with schizophrenia, which evidenced that the symptoms attributed to schizophrenia are associated with connectivity reductions, across all stages of the disorder and regardless of the neuroimaging methodology employed (Pettersson-Yeo et al. 2011).

The structural evidence reviewed can be linked to a model put forward from functional neuroimaging studies postulating bottom-up dysfunction through overactivation in secondary (and occasionally primary) sensory cortices that lead to the experience of vivid perceptions in the absence of sensory stimuli (Northoff and Qin 2011). Subsequently, hallucinatory experiences may be augmented by a weakening of top-down control from the ventral anterior cingulate, prefrontal, premotor, and cerebellar cortices, which, through a breakdown in monitoring and volitional assignment, may further lead to the experience of externality (Allen et al. 2008). Finally, structural alterations in regions involved in the experience and regulation of emotion (parahippocampal gyri, cingulate, orbitofrontal cortex, insula) may be implicated in the often affect-laden characteristics of hallucinations. It has been proposed

that it is not the presence of hallucinations per se but rather their negative emotional content and the perceived distress that appear to constitute an important difference between more benign positive experiences and psychopathology in healthy populations with hallucinatory predisposition (Sommer et al. 2008). Finally, aberrant structural and functional connectivity between sensory cortices and frontal regions may be central to this dysregulation.

Interestingly, a fourth conceptual framework for auditory verbal hallucinations has been put forward by Northoff and Qin (2011), which proposes that the brain's resting state activity prior to onset of auditory verbal hallucinations enables and predisposes to auditory verbal hallucinations, and thus tentatively provides an explanation for the initial overactivation of sensory regions (bottom-up dysfunction). There is some support for this theory as structural abnormalities have been reported in voxel-based morphometry studies in regions of the default-mode network (including the anterior and posterior cingulate cortex and the prefrontal cortex) (Raichle et al. 2001).

To conclude, for any theoretical framework of auditory verbal hallucinations to be comprehensive, it is important to integrate findings implicating relevant brain regions involved in bottom-up sensory and top-down monitoring processes, self-referential and emotional processing, and dysconnectivity between these networks. Future studies should aim at the integration of imaging data from different modalities (functional, structural, neurochemical), with large-enough samples (including patients with and without hallucinations as well as healthy individuals with and without subclinical hallucinatory experiences), in order to illuminate the mechanisms by which the human brain is capable of generating an auditory verbal hallucination.

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Chapter 20
Functional Neuroimaging of Hallucinations

André Aleman and Ans Vercammen

20.1 Introduction

The first functional neuroimaging studies of hallucinations appeared in the mid-1990s, just after PET and functional MRI began to be widely used as techniques for "capturing the brain in action." Positron emission tomography (PET, see Fig. 20.1) is a nuclear-medicine imaging technique that produces a three-dimensional image of functional processes in the body. The system detects pairs of gamma rays emitted by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in three-dimensional space within the body are then reconstructed by a computer. If the biologically active molecule chosen for PET is fludeoxyglucose (FDG), an analogue of glucose, the concentrations of tracer then reflect tissue metabolic activity in terms of regional glucose uptake. For brain-activation studies, radiolabeled water is also frequently used (Cherry and Phelps 2002). Functional magnetic resonance imaging (fMRI) is a technique based on changes in local blood oxygenation that accompany neural activation (Huettel et al. 2004). This is referred to as the blood-oxygen-level-dependent (BOLD) signal. The advent of those neuroimaging techniques has spurred attempts to localize brain areas involved in the puzzling experience of hallucination. Sixteen years after the first study (Silbersweig et al. 1995), there are now dozens of studies that have indexed brain activity during the experience of hallucinations. In this chapter, we summarize the main findings of these studies and discuss their implications for our understanding of the neural basis of hallucinations. We will also briefly address the studies' implications for cognitive models of hallucination.

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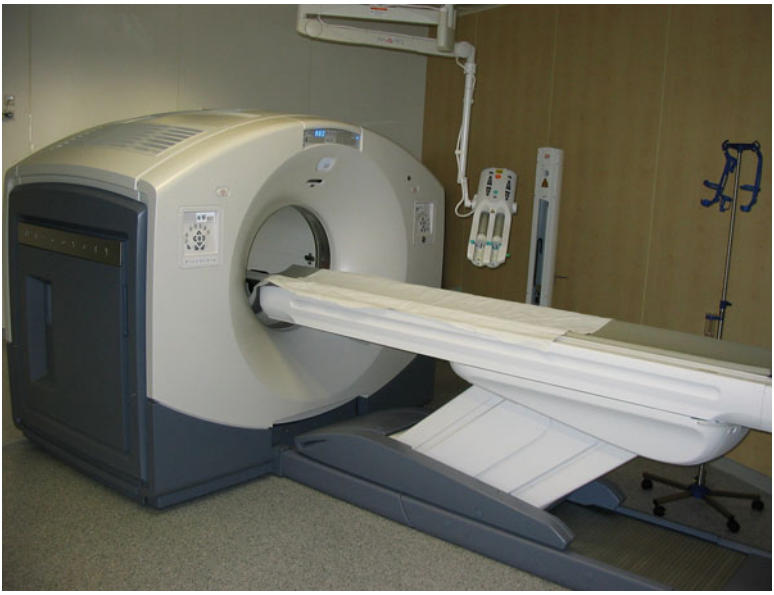

Fig. 20.1 Positron emission tomography (PET) scanner (Photograph courtesy of Wikimedia Commons, 2009. Reproduced with permission)

With regard to the neural basis of hallucinations, four different types of study can be distinguished. First, a significant number of studies have attempted to measure brain activity that directly correlates with the ongoing experience of hallucinations, as indicated by the patient with the aid of button presses. In such designs, a patient typically experiences intermittent hallucinatory episodes, which allows the investigator to contrast scans made during the hallucinatory episodes with those made during nonhallucinatory episodes. A second type of study is the perceptual-interference study in which auditory or visual stimuli are presented to patients who are actively hallucinating, as contrasted to patients without any hallucinations. This procedure allows researchers to determine to which extent hallucinations and external sensory stimuli utilize shared resources in brain areas involved in perception. A third type is the cognitive-activation study in which a particular cognitive task (e.g., speech monitoring) is carried out by groups of patients with and without hallucinations. This allows for the investigation of cognitive processes involved in the disposition toward hallucinations. Studies such as these can also be conducted in healthy individuals with a propensity to hallucinate. Finally, studies can focus on the functional connectivity between various brain regions. Synchronization of spontaneous neural activity across the brain, as observed in the low-frequency spectrum of the BOLD fMRI signal, is considered indicative of functional connectivity between those areas. Alternatively, correlations between time courses of different areas can be calculated. We will discuss these four types of study below. Most emphasis will be on studies of auditory hallucinations in patients diagnosed with

schizophrenia (see also Chaps. 8–10), as these are the most prevalent ones in the published literature. Whenever possible, however, we will also discuss findings regarding visual hallucinations, e.g., as experienced by patients with Charles Bonnet syndrome (see also Chap. 6).

20.2 Brain Activity During Hallucinations

The first study to report on the activity of brain areas during episodes of hallucinations was published by McGuire et al. (1993). They obtained patterns of brain activity from 13 patients diagnosed with schizophrenia during periods when they experienced hallucinations and compared them to patterns obtained at a later occasion when the patients did not experience any hallucinations. The neuroimaging method they used was SPECT (single photon emission computed tomography), which is based on the same principles as PET, providing information about regional blood flow in the brain, although yielding images with a somewhat limited spatial resolution. McGuire et al. observed stronger activity in Broca's area in the hallucination condition than in the control condition. Two other areas, i.e., the anterior cingulate and left temporal cortex, also showed increased blood flow in the hallucination condition, although to a lesser extent than Broca's area. Suzuki et al. (1993) investigated a group of five patients and also used a design in which periods of hallucinatory activity were contrasted with those without. Their SPECT scans showed increased activity in left temporal cortex in the hallucination condition. A limitation of these studies is that when patients are scanned during hallucination-free episodes, other symptoms may also have improved, as well as the patients' general level of functioning. Therefore, the established differences in brain activity may not be exclusively attributable to differences in hallucinatory activity. The first study to circumvent this problem was published by Silbersweig et al. (1995), who were the first to use the so-called button-press method. This method involves the pressing of a button by the patients inside the scanner while they are hearing voices or experiencing visual hallucinations, and the release of the button when the hallucinations are subsiding. This allows the researcher to distinguish periods of hallucination-related activity from nonhallucination-related activity. However, as this method requires that patients experience various discrete periods of hallucinations during their stay in the scanner (typically an hour), only small groups can generally be included in such studies. As a consequence, the power of those studies tends to be limited, and their results should be interpreted with some caution. In their study of five patients with auditory hallucinations, Silbersweig et al. (1995) used PET scans to index concomitant brain activity and reported the involvement of a network of regions comprising the bilateral parahippocampal gyri, the right anterior cingulate gyrus, the left orbitofrontal cortex, the thalamus, the putamen, and the caudate nucleus. On the basis of their findings, the authors suggested that hallucinations may well originate from subcortical structures that spread activity toward cortical perceptual areas, which in turn determine the specific content of the percepts at hand.

Publications that appeared after these landmark studies generally confirmed the involvement of higher-order sensory areas (e.g., the superior temporal gyrus in the case of auditory hallucinations) and the involvement of a distributed network comprising multiple cortical and subcortical structures. For example, Lennox et al. (2000) reported activity in the bilateral superior temporal gyri in four patients who were diagnosed with schizophrenia and experienced auditory hallucinations, along with activity in left inferior parietal cortex and the left middle frontal gyrus. A minority of studies found activity in primary auditory cortex (Heschl's gyrus) during auditory hallucinations (Dierks et al. 1999; Van de Ven et al. 2005), whereas the involvement of the superior temporal gyrus was ubiquitous in all those studies. Shergill et al. (2000) argued that the results of button-press studies may perhaps be compromised by activity in those regions involved in the monitoring of voices (i.e., a task requirement). To overcome this drawback, they used a random sampling method in which a large number of individual scans were acquired at unpredictable time intervals in intermittently hallucinating individuals. Immediately after each scan, the subjects were asked whether they had experienced any hallucinations during that session. Thus participants retrospectively reported whether or not they had experienced any hallucinations. With the aid of this procedure, Shergill et al. found activity in the bilateral temporal gyri, which was stronger in the right hemisphere. Other areas included inferior frontal and insular cortex, the anterior cingulate, the right thalamus and inferior colliculus, and left hippocampal and parahippocampal cortex. Using spatial independent component analysis, Van de Ven et al. (2005) observed involvement of the auditory cortex (including Heschl's gyrus) in three out of six patients diagnosed with schizophrenia. The largest study to date was published by Sommer et al. (2008). It presents 24 patients diagnosed with schizophrenia who were investigated with the aid of the button-press method. Group analysis revealed activity in the right-hemisphere homotope of Broca's area, the bilateral insula, the bilateral supramarginal gyri, and the right superior temporal gyrus. The patients also performed a language task (consisting of verb generation) during their stay in the scanner. In contrast to the hallucination-related activity, this task mainly co-occurred with activity in the left hemisphere, notably Broca's area and the left superior temporal gyrus. Interestingly, the lateralization of brain activity during hallucinatory episodes did not correlate with the lateralization of language activation, but rather with the degree of the negative content of hallucinations. The authors also investigated the time course of the BOLD signal associated with hallucinatory activity (Diederen et al. 2010), reporting deactivation of the left parahippocampal gyrus preceding the onset of hallucinations. In addition, significant deactivation preceding the onset of hallucinations was found in the left superior temporal, right inferior frontal, and left middle frontal gyri, as well as in the right insula and the left cerebellum. They interpreted the involvement of the parahippocampus as indicative of memory retrieval and the cortical activity as the subsequent reception of information from the hippocampus by the auditory association areas. In a study among six patients diagnosed with schizophrenia, Hoffman et al. (2008) reported that prehallucination periods co-occurred with activity in the left anterior insula and the right middle temporal gyrus, as well as with deactivation of the anterior cingulate and

parahippocampal gyri. Shergill et al. (2004) found increases in activity in the left inferior frontal and right middle temporal gyri 6–9s before the onset of hallucinations and no deactivations. Activity in the bilateral temporal gyri and the left insula coincided with the perception of the hallucination. The authors interpreted this as the generation of inner speech that may precede the engagement of areas implicated in the perception of auditory verbal material. Clearly, more studies are needed to establish the exact time course of hallucinatory activity, as well as the role of subcortical areas such as the thalamus (Silbersweig et al. 1995; Behrendt 1998; Aleman and Larøi 2008).

Jardri et al. (2011) integrated the evidence from ten neuroimaging studies indexing auditory-verbal-hallucination-related activity using PET or fMRI. For their meta-analysis, they used an activation likelihood estimation by combining the foci of activity reported across the various studies. Thus they assessed the combined findings in 68 patients diagnosed with a schizophrenia spectrum disorder and the stereotactic coordinates of 129 significant foci. Those patients who experienced auditory verbal hallucinations (AVH) showed significantly increased activation likelihoods in a bilateral neural network that included Broca's area, the anterior insula, the precentral gyrus, the frontal operculum, the middle and superior temporal gyri, the inferior parietal lobule, and the hippocampal/parahippocampal region. Although the network was bilateral, six out of eight activation clusters were found in the left hemisphere. The authors concluded that not only frontotemporal speech areas are involved in the mediation of AVH but also medial temporal areas associated with verbal memory.

In another meta-analysis, Kühn and Gallinat (2010) suggested a different neural substrate for state-versus-trait aspects of AVH. With "state" aspects, they meant the precise neural signature of hallucinations, as established by the comparison of periods of patient-reported hallucinations and absence of hallucinations in a within-subjects analysis (e.g., with the button-press method). With "trait" aspects, they referred to the comparison of brain activity among groups of patients with and without hallucinations, often during a cognitive task involving verbal material (we will discuss these studies in more detail in Sect. 20.3). Kühn and Gallinat (2010) included ten state and eight trait studies, and after meta-analytic integration of the results, they concluded that the state studies yielded activity in the bilateral inferior frontal gyri, the bilateral postcentral gyri, and the left parietal operculum. In contrast, the trait studies showed decreased activity in the left superior temporal gyrus, the left middle temporal gyrus, anterior cingulate cortex, and left premotor cortex. They suggested that the state of experiencing AVH is primarily related to speech-production regions such as Broca's area, whereas the trait that may render an individual prone to hallucinations is related to brain regions involved in auditory processing and speech perception.

With regard to visual hallucinations, studies (of which only a handful have been conducted) have consistently reported activity in extrastriate visual areas (Allen et al. 2008). For instance, ffytche et al. (1998) reported this in a study on visual hallucinations in patients with Charles Bonnet syndrome. Interestingly, they found that hallucinations of colors, faces, textures, and objects correlated with cerebral

activity in ventral extrastriate visual cortex; that the content of the hallucinations reflected the functional specialization of the regions at hand (i.e., area V4 in the case of hallucinations in color and the fusiform face area in the case of hallucinated faces); that visual consciousness is a product of complex neuronal sequences influenced by top-down processing; and that those top-down processes may well take place in specialized areas of the brain rather than in distributed brain regions.

20.3 Perceptual-Interference Studies

Perceptual-interference studies investigate to which extent hallucinations and external sensory stimuli share common resources in brain areas involved in perception. Thus auditory or visual stimuli (depending on the sensory modality under study) are presented to patients who are actively hallucinating and to those who do not. If, for example, auditory hallucinations share a processing system with auditory sense perceptions, one would not expect an increase in activity upon external auditory stimulation in the auditory areas of patients actively experiencing AVH. In contrast, nonhallucinating patients can be expected to show an increase in the activity of auditory perceptual areas in response to external auditory stimulation. David et al. (1996) and Woodruff et al. (1997) confirmed this hypothesis in studies in which speech stimuli were presented to patients diagnosed with schizophrenia who experienced AVH. They found evidence of reduced responsivity of temporal cortex, notably the right middle temporal gyrus, to external speech during hallucinations, as compared to hallucination-free episodes. The authors conclude that "the auditory hallucinatory state is associated with reduced activity in temporal cortical regions that overlap with those that normally process external speech, possibly because of competition for common neurophysiological resources" (Woodruff et al. 1997, p. 1676). In another study in which patients with AVH were scanned while they were listening to external speech, Copolov et al. (2003) reported limbic regions as being more active in hallucinators. This observed pattern of activity may be interpreted as consistent with models of auditory hallucinations as misremembered episodic memories of speech. Plaze et al. (2006) replicated this finding in 15 patients diagnosed with schizophrenia who experienced hallucinations on a daily basis and who were investigated with the aid of fMRI while they were listening to spoken sentences. The severity of their hallucinations correlated negatively with activity in the left superior temporal gyrus in the speech-minus-silence condition. This suggests that auditory hallucinations would seem to compete with normal speech for processing resources in temporal cortex. A similar effect has been reported for visual hallucinations. Howard et al. (1995) reported reduced activity in visual cortex upon the presentation of visual stimuli concurrent with the experience of visual hallucinations in a patient diagnosed with schizophrenia. In their study with patients diagnosed with Charles Bonnet syndrome, ffytche et al. (1998) also found a decreased response in occipital cortex upon external visual stimulation during hallucinatory episodes. When external stimulation was presented during hallucination-free episodes in the same subjects, a normal increase in visual activity was detected.

20.4 Cognitive-Activation Studies of Processes Associated with Hallucinations

A number of studies have investigated brain activity during certain cognitive processes, such as language tasks, that may differ among people with a disposition toward hallucinations as compared to people without. Those studies aim at underlying mechanisms that may contribute to the mediation of hallucinations. Most of them have been directed at speech processing and verbal imagery in patients diagnosed with schizophrenia who were experiencing AVH. For example, McGuire et al. (1996) studied the neural correlates of inner speech and verbal imagery in patients diagnosed with schizophrenia, some of who did, and some of who did not experience AVH. The inner-speech task required volunteers to imagine speaking particular sentences. In the verbal-imagery task, they were asked to imagine sentences spoken in another person's voice, which, according to the authors, entails the monitoring of inner speech. During the verbal-imagery task, the hallucinators showed reduced activity in the left middle temporal gyrus and the rostral supplementary motor area, regions that were strongly activated in nonhallucinating, healthy volunteers and nonhallucinating patients. The authors concluded that a predisposition toward verbal hallucinations in psychosis is associated with a failure to activate areas implicated in the normal monitoring of inner speech. In an analogous study using fMRI, Shergill et al. (2000) investigated the functional anatomy of auditory verbal imagery in patients with AVH. They scanned patients diagnosed with schizophrenia who had a history of prominent AVH – as well as a healthy control group – while generating inner speech or imagining external speech. The patients showed no increased activity while they were generating inner speech, but concomitant with verbal imagery they showed a relatively attenuated response in the posterior cerebellar cortex, the hippocampi, the lenticular nuclei, the right thalamus, the temporal cortex, and the left nucleus accumbens. The authors concluded that this pattern of activity correlated with the monitoring of inner speech. These results were consistent with previous findings but suggested that a more distributed network of cerebellar and subcortical areas may be involved in the comparator function than previously assumed. In a parametric study of inner-speech generation, this group again examined brain areas implicated in the processing of inner speech in patients experiencing AVH (Shergill et al. 2003). The participants were trained to vary the rate of words during their inner-speech task. When the rate increased, the patients diagnosed with schizophrenia showed a relatively attenuated response in right temporal, parietal, parahippocampal, and cerebellar cortex. These findings were again interpreted as evidence of defective self-monitoring of inner speech in patients experiencing hallucinations. The healthy volunteers in that study showed activity in brain regions involved in speech generation (i.e., left inferior frontal cortex) and perception (temporal cortex) during the generation and monitoring of inner speech (Shergill et al. 2000, 2001). However, verbal self-monitoring seems to be particularly associated with temporal, parahippocampal, and cerebellar activity (Frith and Done 1988). Consistent with the self-monitoring hypothesis, patients prone to hallucinations showed relatively attenuated activity in these regions as compared to the control participants.

The neural correlates of explicit source/self-monitoring have also been addressed in a more direct way in healthy individuals and patients with and without hallucinations. McGuire et al. (1996) implemented a verbal self-monitoring task in a PET study with healthy volunteers. In the first condition, the volunteers were shown written words and asked to read them out loud. In the second condition, they were asked to read the words out loud while they were hearing the investigator saying the same word (alien feedback). In one half of the trials, the alien feedback was distorted by elevating the pitch. Distortion of the volunteers' speech while reading out loud led to bilateral activity of lateral temporal cortex. A similar pattern of activity was evident in the alien-feedback condition. These data suggest that self-generated and externally generated speech are processed in similar regions of temporal cortex. A subsequent fMRI study applying the same task to a healthy control group confirmed these results (Fu et al. 2006). In the latter study, the use of an event-related design allowed correct and misattributed source-judgment trials to be analyzed separately. Thus Fu et al. (2006) established that correct source attributions for self-generated speech were associated with greater temporal activity than misattributions, which supports the self-monitoring theory that a mismatch between expected (signaled via a feed-forward signal or "corollary discharge" signal, see Chap. 21) and perceived auditory feedback leads to an increase in temporal activity.

Recently, however, Frith's theory of self-monitoring as an explanatory model for AVH and other passivity phenomena has been criticized (see reviews by Pacherie et al. 2006, and Allen et al. 2007). In short, the model proposes that the experienced passivity results from a lack of awareness of having initiated an action and that the sense of externality results from a lack of sensory self-attenuation. But the model does not explain why a particular external author is experienced (Pacherie et al. 2006). Frith proposed that the experience of externality may be due to a default belief system. An alternative account by Jeannerod and Frak (1999), and by Jeannerod and Pacherie (2004), proposes that the attribution of one's own actions to an external agent is due to abnormal activity in neural networks involved in representing the actions of the self and others. Functional imaging evidence of such a shared system in humans has shown a significant overlap in the neural circuits involved in action execution and action observation (see Grézes and Decety (2001) for a review).

In an fMRI study in which the participants made judgments (self/other) about the source of prerecorded speech, Allen et al. (2007) studied the neural correlates of source misattribution in patients with and without AVH and in healthy controls. The patients with AVH were more likely to misattribute their own speech to an external source than the nonhallucinating patients and controls. Moreover, compared to both control groups, the patients experiencing hallucinations showed altered activity in the superior temporal gyrus and the anterior cingulate when making misattribution errors. The authors therefore suggested that the misidentification of self-generated speech in patients experiencing AVH is due to abnormal activity in the anterior cingulate and temporal cortex and may well be related to an impairment in the explicit evaluation of auditory verbal stimuli. An important finding of this study is the confirmation of a role for the anterior cingulate gyrus in source-monitoring processes.

An important question is whether inner speech generated by healthy individuals also activates speech-perception areas (i.e., Wernicke's region in left temporoparietal cortex). We investigated that issue using a performance-based task in healthy volunteers (Aleman et al. 2005). The results showed that making metrical stress judgments of visually presented words co-occurs with activity in speech-perception areas in the left superior temporal sulcus. The volunteers were asked to imagine hearing someone else reading a word out loud. The speech-perception areas did not show any increased activity in a control condition in which they were asked to make semantic judgments of the same visually presented words. This study suggests that auditory verbal imagery relies in part on phonological processing involving not only speech-production processes but also receptive processes subserved by temporal regions. Using the same task, we investigated the correlates with the severity of hallucinations in 24 patients diagnosed with schizophrenia (Vercammen et al. 2011). The results indicated that louder AVH were associated with reduced task-related activity in the bilateral angular gyri, the anterior cingulate gyrus, the left inferior frontal gyrus, the left insula, and the left temporal cortex. This might well be due to a competition for shared neural resources. On the other hand, the perceived reality of AVH was found to be associated with reduced language lateralization. Therefore, we concluded that activity in the inner-speech-processing network may contribute to the perceived loudness of AVH. However, right-hemisphere language areas may well be responsible for their more complex experiential characteristics, such as their apparent source and their perceived reality.

AVH also occur in nonpsychotic individuals in the absence of psychiatric or neurological disorder and/or substance abuse (see also Chap. 28). As such, the examination of verbal-imagery processes and hallucinatory processes in these individuals from the general population could shed light on the underlying mechanisms of hallucinations in relation to "normal" auditory-verbal processes, and on the extent to which AVH in psychotic patients differ from these subclinical experiences. Recently, Linden et al. (2011) carried out a functional imaging study of AVH and auditory imagery in seven healthy voice hearers. Using the button-press method, they found activity in the human-voice area in the superior temporal sulcus during both hallucinatory and imagery episodes. Other brain areas supporting both hallucinations and imagery included the frontotemporal language areas in the left hemisphere and their contralateral homologues, as well as the supplementary motor area (SMA). As hallucinations tend to be distinguished from imagery by the percipient's supposed lack of voluntary control, which is in turn thought to be represented by the prefrontal cortex, Linden et al. investigated whether that difference would be reflected in the relative timing of prefrontal and sensory areas. Activity of the SMA indeed preceded that of auditory areas during imagery, whereas during hallucinatory episodes, the two processes occurred simultaneously. Therefore, they suggested that voluntary control might be represented by the relative timing of prefrontal and sensory activation, whereas the sense of reality of the experiences may be a product of the activity in the voice area. Notably, this study did not report on the dorsolateral prefrontal cortex, which is also an important area for the willful extraction of perceptual information from memory (Kosslyn 1994). Indeed, it is

remarkable that none of the functional neuroimaging studies of active hallucinations report on the involvement of the dorsolateral prefrontal cortex, whereas the mental-imagery studies generally do.

Although there appear to be some consistent differences between verbal imagery and hallucinations, new evidence suggests that subclinical hallucinations, as observed in healthy individuals, and the psychotic experiences of patients diagnosed with schizophrenia, are not easily differentiated on the basis of brain activity patterns. Diederen et al. (2011) conducted an fMRI study in 21 nonpsychotic subjects with AVH and 21 matched psychotic patients, who were asked to indicate the onset and offset of hallucinatory episodes with the aid of button presses. Interestingly, there were no significant differences in AVH-related brain activity between the groups. Common areas of activity for the psychotic and nonpsychotic groups during the experience of AVH comprised the bilateral inferior frontal gyri, the insula, the superior temporal gyri, the supramarginal and postcentral gyri, the left precentral gyrus, the inferior parietal lobule, the superior temporal pole, and the right cerebellum. These findings implicate the involvement of the same cortical network in the experience of AVH in both groups. It has been suggested that some experiential characteristics may still differentiate subclinical from clinical hallucinations. One such characteristic may be affective loading.

Escartí et al. (2010) focused on the emotional aspects of AVH in patients diagnosed with schizophrenia, by presenting emotionally laden words to patients with and without hallucinations, and to a group of healthy control subjects. In patients experiencing hallucinations, the parahippocampal gyrus and the amygdala were more strongly involved in the task-related network than in patients without hallucinations and in control subjects. This is consistent with the suggestion made by Aleman and Kahn (2005) that increased amygdala activation may well contribute to the mediation of positive symptoms in psychosis. Further research examining AVH in clinical and subclinical populations is warranted to clarify whether limbic contributions to AVH-associated activity can distinguish psychotic features from subclinical hallucinatory experiences.

20.5 Functional Connectivity and Hallucinations

Functional connectivity can be defined as a cross-correlation over time between spatially remote brain regions (Friston et al. 1993). Another concept is *effective* connectivity, which indicates the contributory influence of each region on a different one (Bullmore et al. 2000, Friston et al. 1996). In a study of functional connectivity by Lawrie et al. (2002), eight patients diagnosed with schizophrenia and ten control volunteers were studied with fMRI while they thought of the missing last word in 128 visually presented sentences. Although there were no differences in the regional brain responses among the two groups, correlation coefficients between left temporal cortex and left dorsolateral prefrontal cortex were significantly lower in the patients diagnosed with schizophrenia and were negatively correlated with the

severity of AVH. Thus frontotemporal functional connectivity may well be reduced in patients diagnosed with schizophrenia and may also be associated with auditory hallucinations.

As regards effective connectivity, Mechelli et al. (2007) studied patients with and without AVH, as well as healthy volunteers. Using the fMRI data previously reported by Allen et al. (2007), they tested the hypothesis that source misattributions are associated with poor functional integration within the network of regions that mediate the evaluation of speech. In the healthy volunteers and patients without AVH, the connectivity between left superior temporal and anterior cingulate cortex was found to be significantly greater for alien speech than for self-generated speech. In contrast, a reverse trend was found in patients experiencing AVH. The authors concluded that in the latter group, the tendency to misattribute one's own speech to an external source is associated with an impaired effective connectivity between left superior temporal and anterior cingulate cortex. Although this finding is based on external rather than internal speech, a similar mechanism may well underlie the default appraisal of inner speech in AVH.

Five other studies have investigated functional connectivity in relation with hallucinations. Gavrilescu et al. (2010) restricted their analysis to cross-hemisphere resting functional connectivity, linking primary and secondary auditory cortices. They reported reductions in the hallucinating patients when compared with non-hallucinating patients and healthy control subjects. Vercammen et al. (2010) assessed functional connectivity during the resting state relative to a bilateral seed region located at the temporoparietal junction to compare patients with active AVHs and healthy control subjects. The patients showed a reduced connectivity of temporoparietal cortex and the right inferior frontal gyrus. Within the patient group, the severity of AVHs was correlated with the degree of reduction in the connectivity of temporoparietal cortex and anterior cingulate cortex. A study by Raij et al. (2009) found that subjective ratings of the perceived reality of AVHs were positively correlated with enhanced coupling between the left inferior frontal gyrus and bilateral auditory cortices, as well as the posterior temporal lobes. Finally, Hoffman et al. (2011) found greater connectivity between Wernicke's and Broca's areas (Wernicke's being the seed region) for hallucinating patients, as compared to nonhallucinating patients, but not compared to healthy control subjects during the resting state. They also found some evidence for greater connectivity summed along a loop linking Wernicke's and Broca's seed regions and the putamen for hallucinating patients as compared to nonhallucinating patients and healthy control subjects. They suggested that higher levels of functional coordination intrinsic to a corticostriatal loop may be an underlying factor in the mediation of AVHs. Their findings are complicated, however, by the fact that various relevant connectivity parameters in the hallucinating patients did not differ from those in the healthy controls and that for others they did not differ from those in nonhallucinating patients.

To summarize, although studies do not converge in all details, all published studies provide evidence for disrupted connectivity between temporal, prefrontal, and anterior cingulate cortex. Thus, alterations in the functional integration of language networks and attentional networks would seem to be crucial to the neural substrates

of perceiving sounds that "are not there." These findings are relatively unsurprising, given the fact that schizophrenia has been described as a disorder of "disconnection" (Friston and Frith 1995), characterized by profound disruptions of larger-scale prefrontotemporal interactions. And yet further work is clearly required to parse out the exact nature of the disturbance. More research is needed to establish the nature of abnormalities in connectivity which may manifest as reduced versus increased connectivity depending on the networks studied and the task characteristics (or resting state) involved.

20.6 Conclusion

Functional neuroimaging techniques such as PET and fMRI have been employed successfully over the past two decades to reveal brain areas involved in the mediation of hallucinations. Numerous studies converge on the involvement of bilateral secondary sensory areas. Auditory verbal hallucinations in patients diagnosed with schizophrenia (and in those with schizophrenia spectrum disorders) have been studied most extensively. These studies have shown a central role for speech-production and speech-perception areas not only in the left hemisphere (see Fig. 20.2) but also their homotopes in the right hemisphere. The parahippocampal gyrus is also involved

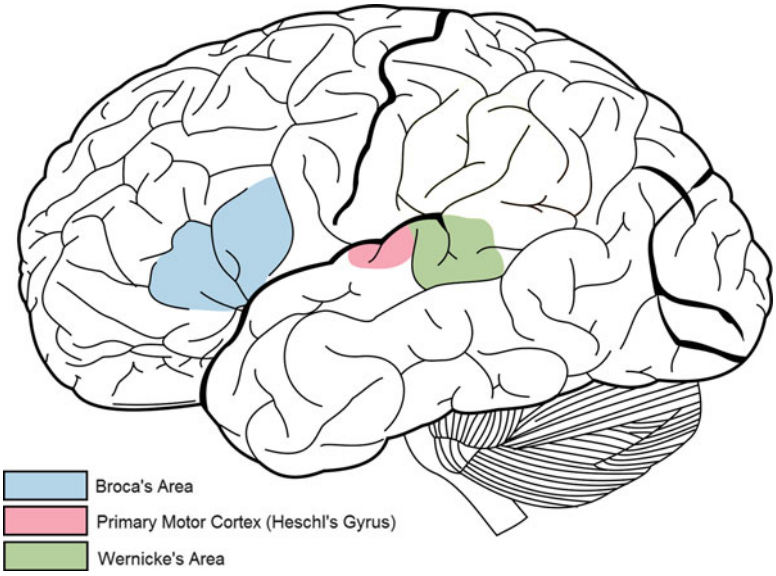

Fig. 20.2 Brain areas typically activated during language processing that have been implicated in various neuroimaging studies of auditory verbal hallucinations. Left frontal (Broca's area), temporal/parietal (Wernicke's area), and primary auditory cortex (Heschl's gyrus) (Brain map courtesy of the Free Software Foundation, 2010. Reproduced with permission)

in such hallucinations, presumably even in their initiation. Other relevant areas are the anterior cingulate, the insula, the cerebellum, and the thalamus. In conclusion, auditory verbal hallucinations would seem to depend primarily on distributed brain networks involved in perceptual attention and memory (which may well reflect top-down processing), in addition to various modality-specific sensory areas. Especially the role of monitoring systems and of the emotional connotations of hallucinations deserve further elucidation.

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Chapter 21
Neurophysiological Research: EEG and MEG

Remko van Lutterveld and Judith M. Ford

21.1 Introduction

Imagine you are driving your car through a quiet suburb. Suddenly a soccer ball bounces onto the street with a child chasing it. Visual information about the unfolding scene travels from your eyes to the visual processing centers in the brain, and after involvement of many other brain regions, the motor cortex sends a signal to your foot to slam the brakes. The electrical activity of the brain processes involved in your rapid response takes place in a flash. Electroencephalography (EEG) and magnetoencephalography (MEG) are the only noninvasive neuroimaging techniques that allow tracking of such fast-changing brain activity (see Figs. 21.1 and 21.2).

EEG measures the electrical signals produced by groups of neurons in the brain, and MEG measures the concurrent magnetic signals elicited by these electrical signals. Both EEG and MEG are able to track brain activity on a millisecond timescale, with the same temporal resolution as the neural activity itself. For source localization, however, MEG may be a more suitable technique than EEG. Electrical signals related to neuronal activity are smeared out by the skull, hampering accurate EEG source localization, while magnetic signals measured by MEG are not substantially affected by the skull.

The focus of this chapter will be on auditory hallucinations because they are reported more often than visual, gustatory, or somatic hallucinations, and are a cardinal symptom of psychosis. Over time, several approaches evolved to study auditory

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Fig. 21.1 Research subject wearing an electroencephalography (EEG)-recording cap

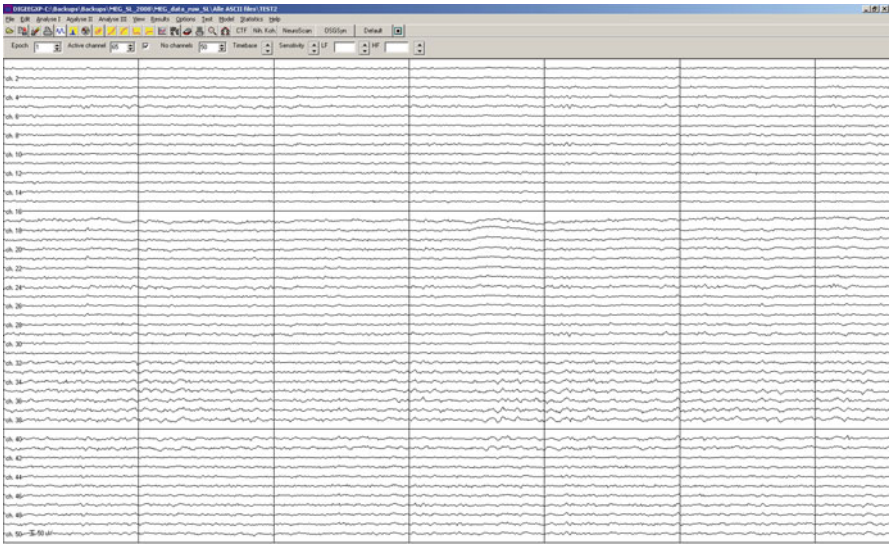

Fig. 21.2 Magnetoencephalography (MEG) recordings. Every line represents data from an MEG sensor. Electroencephalography (EEG) recordings look similar

hallucinations using neurophysiological methods. The most intuitive strategy is to use symptom capture, in which patients indicate the presence of hallucinations. Brain activity during hallucinatory episodes is then compared to hallucination-free episodes. A second approach is to combine symptom capture with event-related potentials (ERPs) to assess the processing of auditory information during the active "state" of an auditory hallucination.[1] A third approach associates ERPs with the tendency or the "trait" to hallucinate. In the latter approach, the severity of hallucinations is correlated with an ERP index of auditory processing. In a fourth approach, repetitive transcranial magnetic stimulation (rTMS, a method that applies magnetic pulses to the brain in order to activate or deactivate brain regions, see also Chap. 25) is used to study EEG measures in the context of hallucinations. A fifth approach is to study basic neurophysiological mechanisms that may underlie the tendency to hallucinate. Each of these approaches will be described in detail.

21.2 Symptom-Capture Studies

21.2.1 Early Symptom-Capture Studies

Before the era of antipsychotic medications, depth-electrocorticography (ECoG) studies were sometimes conducted in conjunction with neurosurgery for relief of severe psychotic symptoms. In one such ECoG study, Sem-Jacobsen et al. (1955) reported that "a close relationship between the patient's acute episodes of psychotic behavior and the electric activity was found." As they continued, "The findings in this study draw attention to the presence of focal spike discharges in some chronically psychotic patients during episodes of disturbance or hallucinations or both, and to the presence of changes in the activity of the temporal lobe and probably the frontal lobe during hallucinations."

Thirteen years later, Marjerrison et al. (1968) used scalp-recorded EEG for the first time to capture the electrophysiological signal associated with auditory hallucinations. They reported that newly admitted or readmitted patients diagnosed with acute schizophrenia, who experienced hallucinations during the experiment, had lower variation in EEG-related brain activity than similar patients who were not hallucinating during the experiment. In the next two decades, EEG studies investigating hallucinations were scarce. In the 1970s, Whitton et al. (1978) recorded the spectral power preceding an auditory hallucination in six unmedicated patients. This was compared to EEG power preceding a response in healthy controls performing tests of creativity. They reported that EEG power was predominant in the delta and theta bands in the 4-s interval prior to reports of hallucinations and creative responses, and suggested that the intrusiveness of the hallucinatory experience may be similar to the sudden internal experience of solving a creative task.

[1] ERPs are measured with EEG. Its MEG counterparts are called event-related fields (ERFs).

In a landmark telemetry study, Stevens et al. (1979) equipped patients diagnosed with schizophrenia with EEG electrodes, and the EEG signal was sent through radio waves to a base station. With this system, the patients were able to walk freely about the ward or dayroom. Hallucinatory behavior (e.g., muttering) was coded by a trained observer, enabling the comparison of hallucination episodes with nonhallucination episodes ("symptom capture"). In this study, Stevens and her team published EEG recordings of a hallucinating patient, reporting power increases during hallucinations in all frequency bands and scalp derivations with the exception of alpha in the left temporal region. In a follow-up study using the same paradigm, Stevens and Livermore (1982) reported that hallucinations correlated with the presence of ramp spectra in the EEG, i.e., spectra characterized by a smooth decline in power from lowest to highest frequencies. According to the authors, such spectra have previously been found in conjunction with subcortical spike activity of epilepsy, suggesting hallucinations were present subsequent to some abnormal subcortical discharge.

On a methodological note, Serafetinides et al. (1986) investigated the influence of verbal versus button-press methods to indicate auditory hallucinations on oscillations in the EEG. The method used to determine the presence of hallucinations had a marked effect on the EEG results. Verbal reporting was associated with a bilateral increase of high-frequency activity, while nonverbal reporting was associated with an asymmetry in power between the left and right hemisphere. After this report was published, no study made use of verbal reporting of hallucinations anymore.

21.2.2 Contemporary Symptom-Capture Studies

With the advent of better analysis algorithms and greater computing power, EEG and MEG data can be decomposed into precise information in the time-frequency domain, while also providing better spatial resolution than the older clinical EEG methods. However, modern EEG and magnetoencephalography (MEG) symptom-capture studies investigating hallucinations are scarce. To date, only one EEG study and three MEG studies have been published. In the EEG study, Sritharan et al. (2005) reported an increase in alpha band power in the left superior temporal cortex during auditory hallucinations in seven patients diagnosed with schizophrenia. Moreover, an increase in synchronization between the left and right superior temporal cortices was found during auditory hallucinations, suggesting an increase in functional coupling between these brain regions during hallucinations.

Ishii et al. (2000) were the first to investigate auditory hallucinations using MEG in a symptom-capture design. In a case study, they reported an increase in theta-band activity in the left superior temporal cortex during hallucinations. In another case study, the same structure was implicated, albeit in the beta band (Ropohl et al. 2004). Reulbach et al. (2007) studied five patients with nonverbal auditory hallucinations (e.g., noise, music) and three patients with command hallucinations. Hallucinations in the former group were associated with an increase in beta-band activity in the left superior temporal cortex, while hallucinations in the latter group were associated with the same

activation pattern extending into the left dorsolateral prefrontal cortex. According to the authors, these findings suggest that the lack of frontal-lobe involvement in nonverbal auditory hallucinations could be interpreted as a sign of diminished cortical involvement compared to the complex mechanisms involved in the generation of voices.

21.3 Combined ERP/ERF-Symptom-Capture Studies

Another approach to study auditory hallucinations is to combine symptom capture with EEG-based event-related potentials (ERPs). ERPs are evoked by a stimulus, and usually occur within 1 s after stimulus presentation. With the combined symptom-capture-ERP method, ERPs are studied during hallucinatory episodes and compared to ERPs during nonhallucinatory episodes. An ERP often used in this approach is the N100 component. The N100 is generated in the auditory cortex (Hari et al. 1984) and is considered to be a standard metric of auditory-cortex activation. As such, the N100 provides the opportunity to compare auditory-cortex activity during the hallucinatory state with activity during the nonhallucinatory state. Tiihonen et al. (1992) measured the N100 amplitude and latency to tones presented to two patients suffering from intense transitory auditory hallucinations. In both patients, the N100 was delayed during the experience of auditory hallucinations compared to when the patients were not hallucinating. In one of these patients, the N100 amplitude was also lower during hallucinations. In a larger study, Hubl et al. (2007) investigated the N100 amplitude in seven patients with a psychotic disorder with acute auditory hallucinations and found smaller amplitudes during hallucinations. Moreover, the largest differences in N100-source strength between episodes with and without hallucinations were located in the left superior temporal cortex. The authors concluded that these findings indicate competition between auditory stimuli and auditory hallucinations for physiological resources located in the primary auditory cortex and that abnormal activation of this brain region could be a component of auditory hallucinations.

Line et al. (1998) took advantage of the rapid timescale of EEG to study the timeframe surrounding auditory hallucinations. They presented eight patients diagnosed with schizophrenia with flickering visual stimuli, leading to the generation of electrical activity in the brain at the same frequency of the flashing stimulus. In the second before the onset of an auditory hallucination, patients showed a large and significant decrease in the latency of brain responses in the right temporoparietal area, suggesting involvement of this area in the genesis of hallucinations.

In a recent EEG study, transiently stable neuronal states were investigated (Kindler et al. 2011). The authors found that a so-called microstate associated with error monitoring was shorter during hallucinatory episodes compared to nonhallucinatory episodes. The authors speculated that the early termination of this microstate facilitated the misattribution of self-generated inner speech to external sources during hallucinations.

21.4 Associations Between Hallucinatory Trait and EEG/MEG Measures

Yet another strategy to study hallucinations is to investigate the association between EEG and MEG measures and the *tendency* to hallucinate. Lee et al. (2006) used quantitative EEG and source imaging to investigate 25 patients diagnosed with schizophrenia experiencing treatment-refractory auditory hallucinations and 23 who were hallucination-free for at least 2 years. Resting-state EEG in the hallucinating patients showed significantly increased beta-band activity in the left inferior parietal lobule and the left medial frontal gyrus compared to nonhallucinating patients. Moreover, gamma and beta frequencies were significantly correlated in hallucinating patients but not in nonhallucinating patients. The authors suggested that the strong correlation between gamma- and beta-frequency oscillations may indicate that the brains of hallucinating patients act as if they were experiencing real auditory stimulation, as previous studies have shown strong correlations between gamma- and beta-frequency oscillations in normal populations in response to auditory stimuli (Haenschel et al. 2000).

Various authors have used ERPs to study associations with auditory hallucinations. Still, the relationship between ERPs and clinical symptoms of psychosis remains controversial. Havermans et al. (1999) studied the P3b evoked potential, which is considered a standard measure of effortful attention, and reported reductions in P3b amplitude in chronic hallucinating patients compared to nonhallucinating patients. Turetsky et al. (1998) found a strong association between a frontal P3b subcomponent and the severity of auditory hallucinations. However, other studies failed to find any associations between P3b amplitude and positive symptoms (Eikmeier et al. 1992; Liu et al. 2004). As most patients diagnosed with schizophrenia who experience auditory hallucinations also experience other symptoms such as delusions, disorganization, and negative symptoms, the diverse P3b findings may be related to this diversity in symptomatology.

To circumvent this problem, Van Lutterveld et al. (2010) investigated P3b amplitude in nonpsychotic individuals experiencing auditory verbal hallucinations as an isolated symptom. Because a reduced P3b amplitude has consistently been demonstrated in patients diagnosed with schizophrenia, and hallucinating nonpsychotic individuals and patients share a single isolated symptom, the authors expected that the P3b amplitude would be reduced in these subjects compared to controls. Contrary to their hypothesis, however, they found an increase in P3b amplitude, which was interpreted as refuting a pivotal role of decreased effortful attention in the pathophysiology of auditory verbal hallucinations.

Finally, one study investigated the P3a event-related potential to speech sounds in hallucinating and nonhallucinating patients diagnosed with schizophrenia. Unlike the P3b, the P3a is not associated with effortful attention, but with involuntary shifts to auditory changes and the processing of novelties. Fisher et al. (2010) found that hallucinating patients had smaller P3a amplitudes than nonhallucinating patients, and that for the hallucinating patients, the P3a amplitude was negatively correlated

with auditory hallucination trait scores. The authors suggested that auditory verbal hallucinations are associated with an impaired processing of external speech sounds, perhaps due to competition between external and internal auditory verbal stimuli (i.e., hallucinations).

Other studies have investigated mismatch negativity (MMN) and hallucinations. Mismatch negativity is an event-related potential related to automatic auditory change detection. However, as with the P3b findings, the results of these studies are inconsistent. Some of them reported an association between MMN amplitude and auditory hallucinations (Fisher et al. 2008a, b; Youn et al. 2003), whereas others did not (Kasai et al. 2002; Schall et al. 1999). These diverse findings may be at least partly explained by the different methodologies used. For instance, Schall et al. (1999) presented visual and auditory stimuli simultaneously while others did not.

Recently, interest has been growing in auditory steady-state evoked potentials elicited by click trains. With this paradigm, a steady stream of clicks is presented (hence the adjective "steady-state"), and the brain's responses are measured during the presentation epoch (Uhlhaas and Singer 2010). Spencer et al. (2009) presented click trains pulsing at 40 Hz to patients and healthy controls. They found that patients with higher gamma-band activity (~40 Hz) in the left primary auditory cortex had a greater propensity for experiencing auditory hallucinations. Moreover, this activity was influenced by delta-wave activity. The authors raise the possibility that aberrant oscillatory synchronization in the temporal cortex might interact with dysfunctional corollary discharge mechanisms (i.e., a malfunctioning in neural signals originating in frontal speech areas that indicate to sensory areas that a forthcoming thought is self-generated), leading to the experience of auditory hallucinations. The reported correlations in this study were based on lifetime hallucination ratings, and the medicated patients were not actively hallucinating at the time of the study. Still, these findings extended earlier results of the same laboratory, in which a correlation between gamma-band activity and hallucination severity of first-episode psychosis patients was found (Spencer et al. 2008).

21.5 Electrophysiology and Repetitive Transcranial Magnetic Stimulation

In the last decade, repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential treatment option for auditory hallucinations. With rTMS, electromagnetic induction is used to noninvasively increase or decrease local brain activity (see also Chap. 25). Two studies have investigated the effects of rTMS on the EEG in the context of auditory hallucinatory activit (see also Chapt. 25). Jandl et al. (2006) reported that a subgroup of patients benefited from rTMS administered over the left superior temporal cortex, as revealed by a decrease in auditory hallucination severity, while no changes in whole-head EEG were reported. Horacek et al. (2007) applied rTMS to the left temporoparietal cortex for 10 days and reported a significant decrease in hallucination severity. TMS treatment caused a decrease in activity

in the beta-1 and beta-3 bands in the left temporal lobe, whereas an increase was found for the beta-2 band in the right temporal cortex and the inferior parietal lobule, indicating transcallosal signal transmission. A possible explanation for the divergent findings of the two studies is that the data-analysis procedures differed significantly. For example, a source-localization procedure was used in the latter study, whereas in the former study, the EEG was assessed on sensor level.

21.6 Studies of a Basic Neural Mechanism That May Underlie Auditory Hallucinations

Feinberg (1978) suggested that malfunctioning of the corollary discharge mechanism might underlie the experience of auditory hallucinations. Corollary discharge is a basic feed-forward system involved in suppressing the sensory consequences of self-generated actions (Sperry 1950; Von Holst 1950). It has been documented across the animal kingdom (Crapse and Sommer 2008), and its action allows all species to suppress sensations that result from their own actions and to tag them as coming from oneself. For example, someone else can tickle you, but you cannot tickle yourself, as the corollary discharge predicts the forthcoming sensations, preventing the sense of surprise, and suppressing the intensity of the sensation.

Such feed-forward systems have been well described in the visual and somatosensory systems but also serve the auditory system across species from crickets (Poulet and Hedwig 2002) to songbirds (McCasland and Konishi 1981) to primates (Eliades and Wang 2003) and humans (Ford et al. 2007b; Paus et al. 1996). Because the corollary discharge mechanism operates on a rapid timescale, this theory has been investigated most extensively using neurophysiological recordings. In humans, EEG (Ford et al. 2010) and MEG (Curio et al. 2000; Houde et al. 2002) have been used for studies of the auditory system, but only EEG-based methods have been used in studies among patients diagnosed with schizophrenia.

While this mechanism explains the suppression and tagging of sensations resulting from overt motor acts, Feinberg (1978) suggested that thinking may conserve and utilize the computational and integrative mechanisms that evolved for the purpose of dealing with physical movement. In a well-functioning corollary discharge system, a signal is sent from frontal areas involved in thought generation to temporal speech reception areas, tagging the perception as self-generated. When this mechanism is malfunctioning, a person may experience an auditory hallucination through misperceiving his or her own thoughts as being externally generated.

Several lines of research support the hypothesis of corollary discharge dysfunction in psychosis. The first line explored whether this system is deviant in patients diagnosed with schizophrenia versus healthy controls. In these studies, control subjects and patients first uttered syllables and then listened passively to a recording of their own speech played back. EEGs were recorded during both talking and listening conditions, and the amplitude of the N100 component of the ERP to speech

onset was used as a measure of auditory-cortical responsiveness. Consistent with the action of the corollary discharge system, the N100 amplitude was smaller during talking than listening in healthy controls. Interestingly, there was significantly less N100 suppression in the patients under study, suggesting aberrations in the corollary discharge system (Ford et al. 2001a, 2007a, b). In another N100 study, the effects of thinking on auditory-cortical responsiveness were investigated. It was shown that thinking affected the N100 amplitude in healthy controls but not in patients diagnosed with schizophrenia (Ford et al. 2001b).

In a second line of research, functional connectivity, as measured by coherence between frontal and temporal lobes in the gamma band, was found to be higher during talking than listening in healthy controls. This pattern was disrupted when the uttered syllables were pitch-shifted while the subjects were talking, resulting in a non-self experience of the spoken sounds. In patients diagnosed with schizophrenia, distortion of the auditory feedback did not result in alteration of gamma-band frontotemporal coherence, again suggesting a malfunctioning corollary discharge system (Ford and Mathalon 2005). In another coherence study, it was found that theta-band frontotemporal coherence was higher for talking than for listening in controls but not in patients diagnosed with schizophrenia. This effect was carried by the hallucinating patients, as the nonhallucinators tended to show the pattern seen in the healthy controls. The authors suggested that a failure in the frontal-temporal network during overt speech may also occur during covert speech, leading to a misattribution of self-generated thoughts to external sources (Ford et al. 2002). Given that the N100 recorded from auditory cortex is suppressed during talking, the net result of coherent communication between frontal and temporal lobes is to suppress auditory sensation.

The corollary discharge theory can also be investigated by examining the small time frame before the onset of speech. In one such study, prespeech neural synchrony was reported to be related to subsequent suppression of the N100 amplitude in healthy controls, but not in patients. Moreover, time-frequency analyses showed greater prespeech synchrony in healthy controls than in patients, especially those with severe auditory hallucinations. The authors interpreted these findings as suggesting that EEG synchrony preceding speech reflects the action of the corollary discharge system, which dampens auditory responsiveness to self-generated speech and is deficient in patients who hallucinate (Ford et al. 2007b).

Another line of research explored the influence of pitch-shifting auditory stimuli on auditory-cortex activation. In this paradigm, hallucinating and nonhallucinating patients diagnosed with schizophrenia as well as controls were asked to utter meaningless sounds. Simultaneously, they were presented with auditory feedback of their own sounds, pitch-shifted feedback of their own sounds, feedback of someone else's voice, or pitch-shifted feedback of an alien voice. It was found that the N100 amplitude to the unaltered self-voice was dampened relative to the altered self-voice and the alien auditory feedback. This pattern was not seen in hallucinating patients, and the degree of the imprecision correlated with the severity of hallucinations (Heinks-Maldonado et al. 2007).

Finally, in a recent study, subjects were asked to initiate auditory stimuli by button presses. It was found that the N100 suppression was normalized in patients after adding a delay of 50 ms in the presentation of the stimulus, suggesting a temporal delay in corollary discharge (Whitford et al. 2011). Moreover, this normalization correlated with white-matter integrity of the arcuate fasciculus, a fiber bundle connecting speech/motor initiation areas in the frontal lobe with the auditory cortex in the temporoparietal lobe. These data suggest that structural deficits of the arcuate fasciculus may lead to temporally delayed corollary discharges and that abnormalities in this fiber tract may be involved in the pathophysiology of auditory hallucinations. A recent study by De Weijer et al. (2011) supported this suggestion, demonstrating degraded fiber integrity of this bundle in hallucinating patients diagnosed with schizophrenia.

21.7 Electrophysiology and Auditory Hallucinations: What Does the Empirical Evidence Tell Us?

EEG and MEG studies of auditory hallucinations have yielded heterogeneous results regarding the involvement of various frequency bands. The theta, alpha, beta, and gamma bands have all been reported to be related to the experience of hallucinations. However, the results regarding location are more consistent. The area most consistently implied is the left temporal cortex. Symptom-capture studies, combined ERP-symptom-capture studies, and an rTMS/EEG study have consistently implicated this brain region. More specifically, most studies implicated the left superior temporal gyrus, consistent with the report that hallucinated voices sound loud and real. These results are in line with structural and functional magnetic resonance imaging (sMRI and fMRI) studies, in which this brain region is also frequently reported (Allen et al. 2008; Barta et al. 1990; Diederen et al. 2010; Dierks et al. 1999). As the left superior temporal cortex is implicated in speech perception, an aberrant corollary discharge mechanism may result in the experience of auditory hallucinations, leading to temporal-lobe abnormalities picked up by EEG and MEG studies. This idea is supported by studies that found alterations in the fiber bundle connecting speech/motor initiation areas in the frontal lobe with the auditory cortex in the temporoparietal lobe in hallucinating subjects.

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Chapter 22
Psychoactive Substances

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22.1 Introduction

This chapter discusses some substances that are particularly likely to induce hallucinations. Many such drugs are available in nature and have long histories of use; more have emerged from laboratories either accidentally or as the result of purposeful research. Many more substances than these *can* elicit hallucinations, given the natural corporeal variations among individuals. For example, antidepressants such as paroxetine (Shimizu et al. 2010) or citalopram (Capaldi and Carr 2010) occasionally induce auditory hallucinations, which tend to resolve quickly after the drug is discontinued. Even the lack of an ordinary biological component – such as water in dehydration – can cause similar effects.

This chapter focuses on a few substances often taken for the purpose of hallucination. Some effects that are typically sought by hallucinogen users are alterations of sensory perception, interpretation, and context. Changes in visual perception are perhaps the canonical hallucinogen-induced effect. For example, a normal aspect of human sight called "persistence of vision" enables us to perceive subsequent still images as a seamless motion picture, or a moving dot of light as a complete picture in a laser show. Some hallucinogens extend this ability so that a larger set of images is retained in perception – the line behind the laser dot becoming longer – an effect commonly known as "trailers." Spots or afterimages seen upon closing one's eyes

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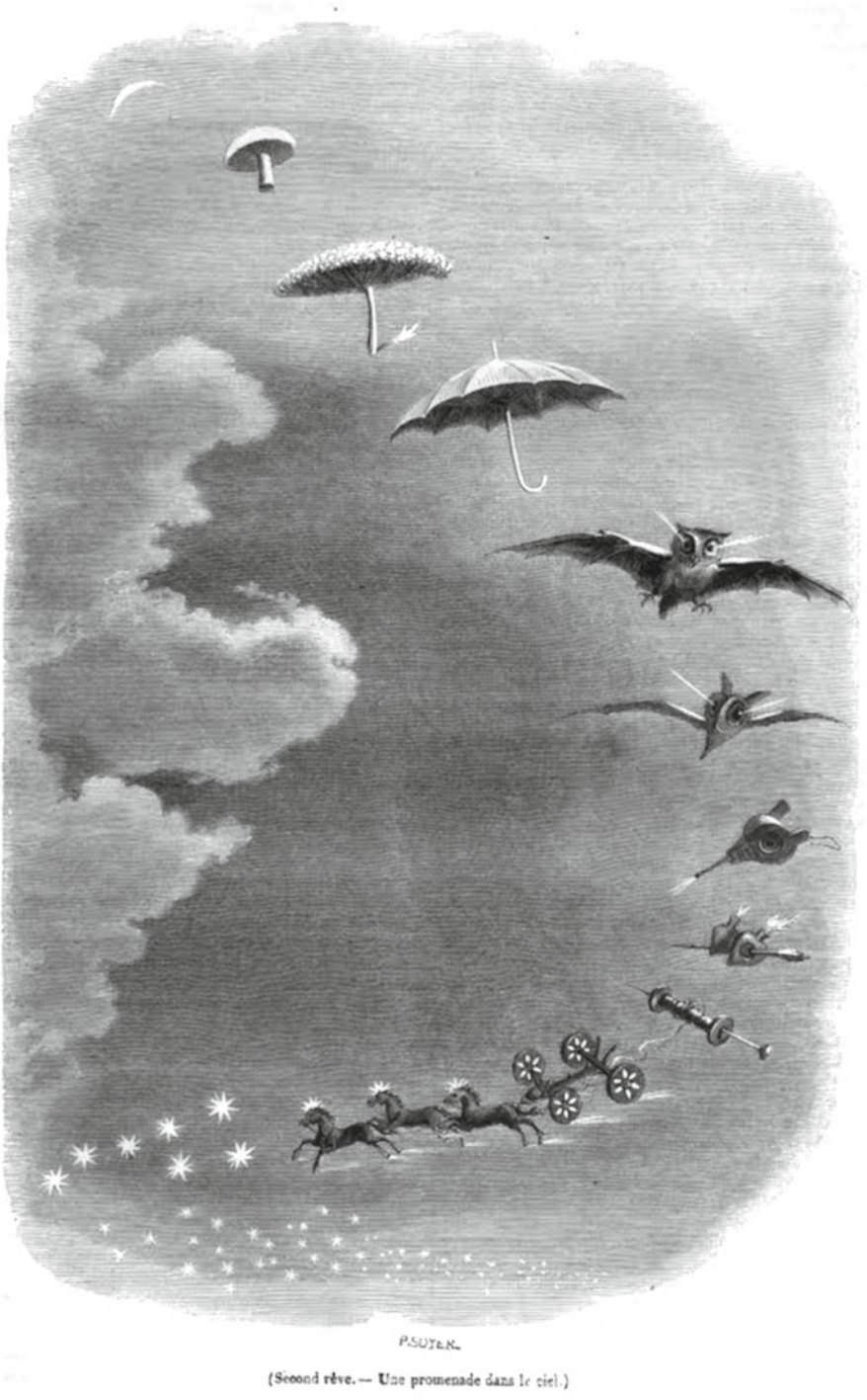

Fig. 22.1 *The Second Dream: A Stroll In The Sky*. Wood engraving by P. Soyer, after J.J. Grandville. Originally published in *Le Magasin Pittoresque*, 1847

may become elaborated into geometrical structures, architecture, faces, animals, or plants. Closed-eye visual effects are usually easier to discern and more elaborate than those perceived with eyes open, doubtless because of the lack of processing competition from ordinary sight. Alterations can also be found in the salience of signals, such as an increase in acuity or in the pleasure derived from visual stimulation – hence the common hallucinogen joke, "Wow, have you ever *really looked* at your hand?"

Auditory effects are less common than visual responses to hallucinogens, although there are substances that particularly evoke them (see Sect. 22.2.3.2). Other senses such as smell and touch are even less prone to their effects.

Most substance-induced alterations consist of "partial hallucinations" in which an actual sensory stimulus is involved; the hallucinator tends to be aware of the difference between the hallucinogen-affected experiences of that stimulus and of a usual sensorium. Sometimes a complete loss of contextual meaning is evoked, in which the hallucinator experiences an essentially different environment (i.e., a scenic or panoramic hallucination), and either loses awareness of his sensory surroundings or becomes unable to recognize them as such. In such cases, the hallucinator may appear to act upon such perceptions (e.g., by speaking to those who are not there) or may be apparently unconscious (in a state resembling dreaming sleep).

22.2 What Drugs Cause Hallucinations?

As noted earlier, many substances or chemical imbalances in the body *can* induce hallucinations. These substances are often ingested with hallucinogenic intent.

22.2.1 Historical Hallucinogens and Their Cultural Contexts

Many hallucinogens known today have long cultural histories, each with its own specific traditions and goals.

22.2.1.1 Mescaline

Mescaline occurs in substantive quantities in several types of American cacti, including the San Pedro cactus (*Echinopsis pachanoi*) in Peru, Argentina, Bolivia, Ecuador, and Chile. Its record of use dates back at least 2,000 years to the Moche culture. It is also present in *Lophophora williamsii*, the Peyote cactus native to southern Texas and northern Mexico. The Native American Church (NAC, see Fig. 22.2), established in the USA in the 1880s and incorporated in 1918, venerates peyote as its holy sacrament for all-night prayer services. In its religious context, the Peyote Road is a term for right living, emphasizing values such as love for others, devotion to family, hard work, and abstinence from alcohol (De Smet and Bruhn 2003).

Fig. 22.2 Native American Church (NAC) setting (Photograph by John Halpern)

The alkaloid mescaline is 3,4,5-trimethoxy-β-phenethylamine. It is known to cause nausea soon after onset, but the psychoactive effects are much longer lasting, up to 12 h. It increases the salience of music and intensifies colors and textures (see Fig. 22.3). Alterations of interpretation can also occur, such as seeing cars as having faces and personalities. Often users (even outside of a religious environment) report feeling a deepened sense of the divine in ordinary people and objects, a sense of the sacred within themselves and toward the world. Emotional effects increase with dose, although it is difficult to identify those as "hallucinatory" rather than genuine responses to the experiences.

Mescaline's neurological effects include blocking the release of acetylcholine and affecting the cell membrane's level of potassium ion conductance, as demonstrated in rat cortex and frog neuromuscular conjunctions (Ghansah et al. 1993). In live cats, behavioral changes in response to mescaline are blocked by pretreatment

Fig. 22.3 Mescaline-inspired artwork (Photograph by John Halpern)

with serotonergic or dopaminergic agonists, implying that those systems are involved in the perceptions and actions of those (and probably other) mammals (Trulson et al. 1983).

22.2.1.2 Psilocin and Amanitoxins

Mushrooms of many genera contain hallucinogens. By far the most common and well-known is psilocin (4-hydroxyl-dimethyltryptamine). Psilocin is a 5HT1A and 5HT2A/2C partial agonist, working in the brain's serotonergic systems. It can also be produced within the body as a dephosphorylated metabolite of the prodrug psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine).

Psilocin and psilocybin are present in the fruit bodies of many mushroom species (Guzmán et al. 2000). Often these mushrooms are small, brown, and bitter-tasting. Common examples in the United States' Pacific Northwest are *Psilocybe cyanescens*, *P. azurescens*, and *P. stuntzii*; *Psilocybe caerulipes* in the East; and *Psilocybe cubensis* along the Gulf Coast (also frequently cultivated worldwide). In Japan, *Gymnopilus spectabilis* is known as *o warai take* or "the big laughter mushroom," while mere *warai take* is *Panaeolus papilonaceus* (Sanford 1972). At least some of the

Fig. 22.4 Two *Amanita muscaria* (Public domain image picture, retrieved May 4, 2011, from http://www.public-domain-image.com/flora-plants-public-domain-images-pictures/fungi-mushrooms-public-domain-images-pictures/two-amanita-muscaria.jpg.html)

distribution of these mushrooms may be due to human migration. In Europe, however, such mushrooms may have never entered, let alone altered, human consciousness.

The hallucinogenic properties of Chinese and Japanese psilocin-containing mushrooms are well recorded, dating back at least to a report by Chang Hua in the Chin Dynasty (approx. 245–400 AD), stating that "[mushrooms] growing on the Feng tree, when ingested, cause people to laugh unceasingly." Remedies such as strong tea with alum were prescribed, although since a typical course of psilocin hallucination is less than 6 h long, it is difficult to tell whether these treatments were effective or merely incidental. In Japan, an illustration of *Panaeolus papilonaceus* adorned the cover of the 1918 *Journal of Japanese Botany*. However, these fungi never became integrated into either traditional Chinese medicine or any other known traditions of use. An old folktale describes Buddhist nuns dancing and singing after eating some mushrooms they found, who are then joined by woodcutters whose experiences are the same. But the story only goes so far as that anecdote. A scattering of other stories repeat similar incidents throughout the centuries. The closest they seem to have come to having a place in those societies was very recently, after psilocin became a worldwide phenomenon. "Magic mushrooms" were available in Japan by vending machine and in "head shops" until illegalization in 2002. But even preprohibition, there appear to be no records of any outcomes more exotic than inappropriate public behavior.

The other common mycological hallucinogen comes from showy species of *Amanita* – large, bright-capped mushrooms decorated with white spots (e.g., *A. muscaria*, *A. pantherina*, and *A. gemmata*, see Fig. 22.4). These contain the active compounds muscimol and ibotenic acid (metabolized to ibotenate), constituting

substrate analogues for gamma-aminobutyric acid (GABA) and N-methyl-D-aspartic acid (NMDA). The mycologist David Arora, in his classic work *Mushrooms Demystified*, describes their effects "on the central nervous system [as] confusion, mild euphoria, loss of muscular coordination, profuse sweating, chills, visual distortions, a feeling of greater strength, and sometimes hallucinations, delusions or convulsions. (An inordinate number of 'trippers' mistake themselves for Christ.)" (Arora 1990).

The human history involving the amanitas is likely vast, but laden with much mystery. They have been proposed as the basis for everything from the magical Soma of the Hindu Rig Veda texts to the Vikings' fearlessness in battle and also proposed as the original Tree of Knowledge. However, people who consume psychoactive amanitas often cannot recollect their experiences, perhaps as a result of the effects on the NMDA systems now known to regulate memory (Fei and Tsien 2009).

22.2.1.3 DMT and MAOIs

DMT – N,N-dimethyltryptamine – is widely found in nature, including in vines, barks, roots, a sea fan, and mammals. It binds nonselectively to at least eight subtypes of the serotonin receptor and is an agonist for at least three of them. It also shows affinity for the dopamine D1 and several adrenergic receptor subtypes, as well as for imidazoline-1 and trace-amine-associated receptors. Moreover, it is the only known endogenous sigma-1 opioid ligand (Fontanilla et al. 2009). It is a powerful and often context-altering hallucinogen. In traditional South American shamanism, it is sometimes intranasally insufflated. DMT is not orally psychoactive by itself, as monoamine oxidase (MAO) in the gut lining breaks it down. Intravenous injection, smoking, or inhalation of DMT can elude the body's MAO metabolism, but usually not for very long. Such experiences tend to span 30 min or less, while the effects experienced upon intramuscular injection last about 1 h.

DMT becomes psychoactive after oral ingestion when combined with a monoamine oxidase inhibitor (MAOI). Thus it is sometimes (though not always) an ingredient of a psychoactive beverage known as *ayahuasca*, along with reversible MAOI beta-carbolines from the vine *Banisteriopsis caapi*. The hallucinations produced by ayahuasca tend to last about 3 h. Typical effects include time dilation, visual and auditory hallucinations, and experiences that users cannot adequately render afterward, such as an "alternate reality" populated by "machine elves" or "beings of light" with whom they can interact (McKenna 1992).

Although DMT is illegal in much of the world, American members of the two largest Brazilian ayahuasca religions have won legal battles in Oregon and New Mexico protecting their right to practice their faiths freely and without government harassment. At present, the Santo Daime, the União do Vegetal, and the Barquinha are three of the best-known ayahuasca churches. Influenced by Christianity as well as South American indigenous shamanism and other religious traditions, their spiritual obligations include honoring nature in a personified way, such as in the following line from a Santo Daime hymn: "I venerate my sweet mama of the sky/ On the earth and in the astral." It is possible that such interpretations of the spiritual have a common neurological origin with the "machine elves" noted above.

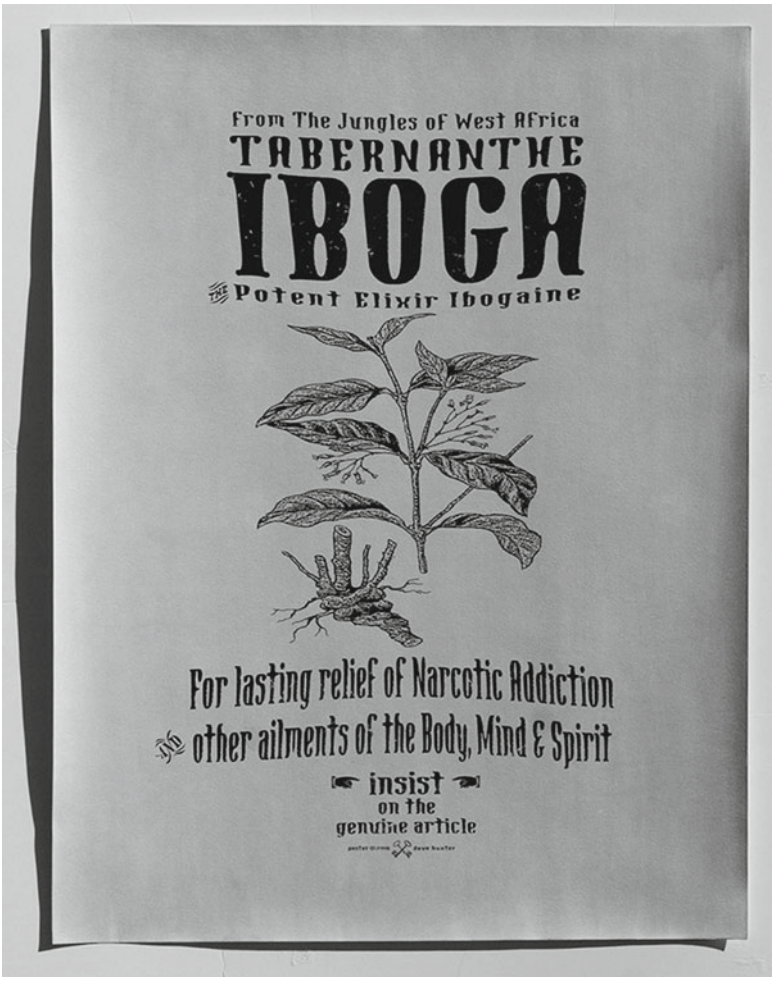

Fig. 22.5 *From The Jungles Of West Africa – Tabernanthe Iboga*. Hand-printed with dark chocolate brown ink on archival coffee hand-stained paper (Copyright 2010 Dave Hunter. Reproduced with permission)

22.2.1.4 Ibogaine

The hallucinogen ibogaine, an indole alkaloid, is found in the religious sacrament of practitioners of Bwiti, a religion practiced across greater West Africa. Some Bwiti scholars believe the iboga plant (*Tabernanthe iboga*, see Fig. 22.5) to be the Biblical Tree of Knowledge.

At first onset, ibogaine offers visual hallucinations, and then, in later hours, an apparently unique introspective state allowing visions of the "true self" and a

profound understanding of the consequences of one's actions. Here is an example of a user's account:

> I didn't see much. I travelled a red path and came to a village of one house with one door and one window. Two white men were sitting at either end of a table. They were writing. That was all. I returned then. But I was dissatisfied so I took a big dose of eboga again and this time I saw my mother and she was surrounded by many people. She died when I was young and I didn't recognize her. But men surrounding her said it was my mother. She came and stood at my right. Another woman came with a child and stood at my left. I reached for the child but she held it away from me. Then I became sick and had to pass out to the edge of the forest to throw up. As I came back I saw a host of small babies laughing and playing together in the air. That was all I saw.
>
> (Fernandez 1982)

During the 1880s, German soldiers in Cameroon did not fail to notice the stimulant effects of ibogaine: "Its exciting effect on the nervous system makes its use highly valued on long tiring marches, on lengthy canoe trips, and on difficult nightwatches." (District Officers from Kamerun 1888). From 1939 through 1970, it was marketed in France as *Lambarene* for fatigue, infections, and postdisease recovery. Incidentally, its hallucinatory effects were not discussed in this context.

During the 1960s, the Chilean psychiatrist Claudio Naranjo began to investigate ibogaine as an adjunct to psychotherapy, noting its utility in its particular tendency to evoke old memories associated with later-in-life bad choices, including addiction, and the opportunity to then decide to live differently (Naranjo 1974). Howard Lotsof unexpectedly achieved lasting abstinence from heroin dependence after an ibogaine experience himself in 1962 and subsequently obtained several US Patents for the "iboga cure" of addictions (Lotsof 1985, 1992, see also Fig. 22.6).

Ibogaine is not, as of this writing, an FDA-approved medication in the USA. This is unfortunate, as a potential goal and effect of ibogaine treatment is to end addictions, for which there are few useful techniques. Apparently, the tendency to see one's past in a detached way allows individuals to gain perspective on their needs and other ways to meet them. In this case, it is the drug's typical effects on thought that propel the cure. Other people's interpretations are secondary, although considerable support may be required to complete the process. There is also evidence that ibogaine and its long-lasting metabolites help suppress the physical symptoms of opiate withdrawal, making for a smoother transition to complete abstinence (Glick and Maisonneuve 1998). Supervised ibogaine treatment for addiction is presently available just south of the USA in Mexico and just north in British Columbia, as well as in many other parts of the world. Its legal status is variable and in some flux – at latest report ranging from the USA's Schedule I to no formal regulation in Canada, to government-licensed at certain treatment sites in the West Indies.

22.2.2 Psilocybes and the Saint Children: A Transition Between Traditional and Modern Hallucinogen Cultures

American hallucinogenic mushrooms have been part of Native American heritage since antiquity, though their origins and histories have been lost and cultural imperialism

Fig. 22.6 Poster recognizing Howard Lotsof's discovery of the antiaddictive effects of ibogaine (Copyright 2004 Dave Hunter. Reproduced with permission)

destroyed a tremendous amount of both practice and oral records. However, traditions were also preserved, under some secrecy, in relatively peaceful and isolated groups such as the Mazatec-speaking villages in Oaxaca, Mexico. In their groundbreaking publication *Mushrooms, Russia, and History*, Valentina and R. Gordon Wasson ("RGW") discuss a smattering of historical references for psychoactive mushroom use in Oaxaca, mostly from Christian clerics from around the sixteenth century (Wasson and Wasson 1957).

After they had heard about a living mushroom tradition from a Mazatec-speaking Bible translator, in 1953, the Wassons traveled to Mazatec communities and, eventually, were permitted to participate in a psilocin-focused ritual called a *velada*. The *curanderas* who conducted these were reverent and proud, considering the mushrooms a magical medicine. In 1955, the Wassons went to Mesoamerica to enter deep into

these practices and were introduced to María Sabina, said to be a *curandera* "of the first class." They wrote of RGW's first personal ingestion of the mushrooms:

> There was no inclination to sleep. At all times we [RGW and another American named Allan] were alert both to our subjective hallucinations and to the goings-on around us in the dark. RGW took imperfect notes intermittently and kept track of the hours. But he and Allan were both alive to the fact that they were not themselves. Though RGW had resolved to fight off any effects of the mushrooms and remain the detached observer, the mushrooms took full and sweeping possession of him. There is no better way to describe the sensation than to say that it was as though his very soul had been scooped out of his body and translated to a point floating in space, leaving behind the husk of clay, his body. 'Landslide', the designation of the Mazatecs for the mushroom we were using, had seemed to him a clumsy name before; now its awesome truth imposed itself. Our bodies lay there while our souls soared. We both felt nauseated; RGW twice made his way to the other room to vomit, and Allan three times. One or two others, not identified in the darkness, did likewise. But these episodes seemed of no moment. For we were both seeing visions, similar but not identical visions, and we were comparing notes in whispered interchanges. At first we saw geometric patterns, angular not circular, in richest colors, such as might adorn textiles or carpets. Then the patterns grew into architectural structures, with colonnades and architraves, patios of regal splendor, the stonework all in brilliant colors, gold and onyx and ebony, all most harmoniously and ingeniously contrived, in richest magnificence extending beyond the reach of sight, in vistas measureless to man. For some reason these architectural visions seemed oriental, though at every stage RGW pointed out to himself that they could not be identified with any specific oriental country. They were neither Japanese nor Chinese nor Indian nor Moslem. They seemed to belong rather to the imaginary architecture described by the visionaries of the Bible. In the aesthetics of this discovered world attic simplicity had no place: everything was resplendently rich.
>
> (Wasson and Wasson 1957)

Later, in discussing a second velada, during which the visions were quite different, they wrote,

> For the world our visions were and must remain 'hallucinations'. But for us they were not false or shadowy suggestions of real things, figments of an unhinged imagination. What we were seeing was, we knew, the only reality, of which the counterparts of every day are mere imperfect adumbrations. At the time we ourselves were alive to the novelty of this our discovery, and astonished by it.
>
> (Wasson and Wasson 1957)

These hallucinations must all be described as "partial," drawing primarily upon the visual senses, and on the interpretive levels of cognition, where they invited the participants to compare their visions with Elizabethan aesthetics, Platonic ideals, and the imagery of the Bible. At no time, however, were they lost to their actual surroundings; RGW describes touching the wall of the house to reorient himself, which always worked, though it also tended to occasion nausea.

In 1958, Albert Hofmann succeeded in synthesizing psilocybin. He gave María Sabina some capsules of his product, and she attested that they were as efficacious as the fungal forms (Schultes and Hofmann 1973). But later, after word of these mushrooms had spread throughout the world, she said,

> From the moment the foreigners arrived, the 'saint children' [i.e., mushrooms] lost their purity. They lost their force; the foreigners spoiled them. From now on they won't be any good. There is no remedy for it.
>
> (Estrada 1981)

RGW agreed with her. In 1980, he wrote, "Since the white man came looking for the mushrooms, they have lost their magic" (Wasson 1980).

22.2.3 Modern Hallucinogens: "Psychotomimetics" and Current Research Techniques

During the twentieth century, great advances were made in medical chemistry, including the discovery of an extensive variety of novel psychoactive substances (Shulgin and Shulgin 1991, 1997). At first it was hoped that hallucinogens (especially lysergic acid diethylamide or LSD) would provide insight into the mechanisms of psychosis and hallucinations in general (Hoffer and Osmond 1967), although it soon turned out that these processes are far too complex to be so simply modeled (Geyer and Vollenweider 2008).

Significant work was done with the hallucinogens psilocin and psilocybin (Vollenweider et al. 1997a; Gouzoulis-Mayfrank et al. 1999), DMT (Riba et al. 2006; Gouzoulis-Mayfrank et al. 2005), and ketamine (Vollenweider et al. 1997b; Krystal et al. 1994). Most of these substances activate limbic and paralimbic structures, heightening arousal and leading, in turn, to intensified and/or additional endogenous stimuli which may be experienced as hallucinations. From the 1990s through 2008, it was commonly considered that changes in cerebral informational interplay are responsible for these experiences (Vollenweider and Geyer 2001), but more recently it was found that some substances (e.g., LSD, psilocin, and DMT) exert hallucinatory and other effects by directly stimulating serotonin receptors on cortical pyramidal cells (Geyer and Vollenweider 2008). Still, most modern hallucinogens have not received the kind of scientific attention they might warrant.

22.2.3.1 LSD

LSD (lysergic acid diethylamide, see Fig. 22.7) was first synthesized in 1938 by Albert Hofmann in an investigation of ergot- and squill-based bioactive chemicals, particularly in the hopes of finding an analeptic. On April 16, 1943, Dr. Hofmann, led by his intuition (Hofmann 1969), resynthesized the substance for further investigation and accidentally absorbed a small amount through his fingertips. To quote from his description, he felt

> a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away.
>
> (Hofmann 1980)

"Fantasy pictures," "intense colors," and "dreamlike state" remain canonical for "hallucinogens" to this day.

Fig. 22.7 An LSD ampule (Photograph by John Halpern)

On April 19, 1943, Hofmann purposely ingested 250 micrograms of LSD, which he expected to be too little for any bioactivity. As the effects began, he asked a lab assistant to escort him home. Because of wartime restrictions on motor vehicles, they rode bicycles. On the way, he began to experience intense, disturbing sensations and thoughts, for example, believing his next-door neighbor was a witch. He was examined by a physician, who assured him that his only apparent issue was pupil dilation, and then Hofmann was able to relax and enjoy the "fascinating images [….] rearranging and hybridizing themselves in constant flux." He came away convinced that LSD had a future in psychiatry because it was so intense and introspective. He could not imagine any recreational use.

As Hofmann described, hallucinations with LSD are predominantly visual. All other sensory spheres can be altered by LSD's effects, but contribute relatively slightly to its range. In contrast, psychotic individuals experience mainly auditory hallucinations (e.g., voices). True or "full" hallucinations are very rare with LSD; it typically alters sights from the physical environment and leaves the individual aware that the effects are drug-induced. Within the lower dose range, users may see trailers and other elaborations of normal visual processes, or primitive forms that look like webs, lattices, tunnels, or geometrical designs. There may be many more complex hallucinatory phenomena during more intense experiences, sometimes unfolding

into mental fantasies or memories of life events. Most of LSD's hallucinogenic phenomena are described by knowledgeable users as rewarding and enjoyable, sometimes giving insights into their own psychological make-up and functioning.

LSD has a high affinity for serotonin receptors (mainly 5-HT2a and 5-HT1c) and a broad range of other receptors. Its complex pharmacodynamics are still not completely understood. Research has shown that the alterations of the serotonin system may play a major role in its hallucinatory effects (Passie et al. 2008).

22.2.3.2 DiPT

A member of the tryptamine chemical family, diisopropyltryptamine (DiPT) is a fascinating substance because, unlike most hallucinogens, its effects are predominantly auditory. It is also possibly less sensitive than other hallucinogens to the mindset of the user, the setting in which it is ingested, and other psychological considerations, perhaps because the auditory system has become less salient to the human organism as we have evolved into a vision-based species. In general, auditory pitch is perceived as lower than normal, and harmonious sounds lose their resonance with one another. This dissonance is even perceived by people with perfect pitch, which has some implications about where in the processing stream DiPT's effects occur. Voices are also altered and disharmonious with one another (Shulgin and Shulgin 1997).

DiPT has few other known effects; it would seem to call for further investigation from those interested in the neurology of sound, music, and verbal language processing. For example, it would be fascinating to know the effects of this substance on perceptions of tonal languages such as Chinese, Huichol, or Dogon; would it alter the words perceived as being spoken?

22.2.3.3 Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is a noncompetitive NMDA receptor antagonist first synthesized in 1962. Its tendency to cause dissociation from the body and its actual state (in particular for people in pain) makes it a valuable type of medication in anesthesia. Because of these psychoactive properties, it is termed a "dissociative anesthetic."

Because it disrupts the normal stream of input from the peripheral to the central nervous system, ketamine can vastly distort the perception of the body. Experience of time and space as well as thinking are typically gravely altered. At higher doses, users may sometimes feel entirely disembodied, existing as a "point of consciousness" somewhere in the universe. They may experience the world and themselves as one entity, particularly with eyes closed to break another bond between themselves and their ordinary self-monitoring processes (see Chap. 7). Synesthesias may occur, particularly in the form of sound sensations with visual experiences, but auditory and open-eye visual hallucinations are rare. Users are generally aware of the influence of the drug, even though their reality-testing abilities may be limited (Kelly 1999).

As ketamine is metabolized, the individual slowly reorient, perhaps passing through moments where they feel as if they are surrounded by nonhuman consciousnesses. These unusual experiences resolve as the drug's course completes, although as memories they may remain compelling.

Dissociative phenomena might be expected to be distressing, but as one study of it as a postoperative pain medication stated, "A close supportive relationship with the surgeon and operating room personnel is probably as important as any pharmacologic manipulation in avoiding psychological mishap with low-dose ketamine." (Cunningham and McKinney 1983). Indeed, some mental distance from one's painful body in illness, injury, or surgery may come as a psychological mercy.

Ketamine is regulated in the USA at Schedule III, recognizing it as having a current medical use and stating that it has a relatively low abuse potential. In Canada, however, it is rated a Schedule I narcotic. Meanwhile, the World Health Organization considers ketamine a core element of its Essential Medicines List, as a general anesthetic.

22.3 What Happens After Drug-Induced Hallucinations?

Drug-induced hallucinations generally have a clear and typical duration, usually quite brief, after which the person's perceptions return to their baseline. Such time-limited effects are utterly unlike most psychiatric diseases, which tend to be more progressive and open-ended.

22.3.1 Effects of Experience

Hallucinatory experiences run the gamut from entirely unmemorable, to frightening, to triggering extensive life changes. All that can be added is that certain types of hallucinogens are prone to causing or emphasizing certain types of experience. However, no matter what hopes or fears or drugs one may bring to an experience, "few battle plans survive contact with the enemy," and this is as true among psychoactive substances as in other realms of human experience and endeavor.

22.3.1.1 The Good Friday Experiment

In 1962, Walter Pahnke, then an MD and also a PhD student in Harvard University's Religion and Society Program, gave psilocybin to 10 of 20 white Protestant male divinity students during Good Friday services, asking questions about the mysticism of their experience to determine the differential effects of the chemical. As detailed in Dr. Pahnke's resultant doctoral dissertation (Pahnke 1963), the Good Friday experiment found many elements of "deep mystical" experience reported by those who had received psilocybin, as opposed to those who had ingested a placebo.

In 1991, Rick Doblin published a follow-up study for which he tracked down 16 of the original participants. From his conclusions:

> For the psilocybin group, the long-term follow-up yielded moderately increased scores in the categories of internal and external unity, sacredness, objectivity and reality, and paradoxicality, while all other categories remained virtually the same as the six-month data. Several decades seem to have strengthened the experimental groups' characterization of their original Good Friday experience as having had genuinely mystical elements. For the controls, the only score that changed substantially was that of alleged ineffability, which decreased.
>
> A relatively high degree of persisting positive changes were reported by the experimental group while virtually no persisting positive changes were reported by the control group. In the open-ended portion of the long-term follow-up questionnaire, experimental subjects wrote that the experience helped them to resolve career decisions, recognize the arbitrariness of ego boundaries, increase their depth of faith, increase their appreciation of eternal life, deepen their sense of the meaning of Christ, and heighten their sense of joy and beauty. No positive persisting changes were reported by the control group in the open-ended section of the follow-up questionnaire.
>
> There was a very low incidence of persisting negative changes in attitudes or behavior in either group at either the six-month follow-up or the long-term follow-up. However, the one psilocybin subject reported to have had the most difficult time during the experiment was the one who declined this author's request to be interviewed in person or fill out a questionnaire, placing in question the generalizability of this finding for the long-term.
>
> (Doblin 1991)

In 2006, Griffiths and colleagues published a similar experiment using a more modern design, including methylphenidate for the placebo and 8-h private sessions that were comfortable and supportive, but not overtly religious (Griffiths et al. 2006). They found that psilocybin "produced a range of acute perceptual changes, subjective experiences, and labile moods including anxiety. Psilocybin also increased measures of mystical experience. At 2 months [post psilocybin], the volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers. [….] When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously occurring mystical experiences." This supports the notion that religious or mystical feelings may be based in physiological levels of perception and cognition.

22.3.1.2 Schizophrenic Break, Drug-Induced Psychosis, and HPPD

One particularly persistent piece of disinformation promoted by the War on Drugs is that hallucinogens make you mentally ill. This is not the case. Schizophrenia, for example, is remarkably consistent in its epidemiology at affecting 1% of the population all over the world (Patel et al. 2008).

However, it remains possible to have a hallucinogen-related experience so awful that it results in post-traumatic stress disorder, particularly if say one is victimized, arrested, or hospitalized during the process. The same is true of any traumatic experience, such as a car accident or rape, and in none of these cases is it appropriate to blame the victims. A difficult hallucinogenic experience may be helped with

supportive care, potentially including medicine, though "talking through" is typically sufficient, as Bwiti and NAC clergy can attest.

Investigation is currently underway to discover if the so-called flashback syndrome, also known as hallucinogen persisting perception disorder (HPPD), is in fact a distinct clinical entity, or merely an interpretive change in ordinary peculiarities and individual differences in vision. In general, HPPD phenomena resolve spontaneously after the last exposure to a hallucinogen (over a time course of weeks to perhaps as long as a year), although there are also individuals reporting essentially permanent changes to visual perception. A number of HPPD patients describe milder forms of visual disturbance prior to hallucinogen exposure, suggesting that some individuals are more premorbidly susceptible to these rare adverse effects than others and that they may be related to changes in perceived salience as well as basic visual perception processing.

22.3.2 Effects of Society

Set, what persons bring of themselves to an experience, and setting, the environment in which the experience occurs, are critical to what happens in hallucinatory experiences (Zinberg 1986). This truism applies to other human undertakings as well, and in medicine in particular. The placebo effect depends heavily on the patient's expectations, whether for pain relief, the healing of a wart, or bronchodilation, or even unwholesome outcomes such as nausea and hypertension. This is unsurprising; we are a social species, and clues as to the appropriate metabolic state can be strongly affected by information from a trusted source – a physician, a priest, a parent. Brain structures such as the amygdala and neurochemicals such as endorphins can be regulated by social information as well as individual expectations and perceptions (Amanzio et al. 2001). Interestingly, those suffering from Alzheimer's disease lose the ability to respond to placebos, likely because their prefrontal cortices have lost the ability to form and maintain expectations (Benedetti et al. 2006).

Such varied sociobiological contexts may explain why a single substance such as psilocin can become an idle folktale in China and Japan, revered in Mesoamerica, and linked to criminality in the USA.

22.3.2.1 Religious Contexts

One common cultural response to hallucinogens is to treat them with reverence and surround them with ritual. Psilocin (as a psychoactive metabolite of administered psilocybin) increases mystical experiences relative to methylphenidate as an active placebo in drug-naïve adults, suggesting that this response is not arbitrary. Religions can also provide social support and control for experiences, such as the Bwiti iboga initiations, which can be physically and emotionally challenging, if also potentially rewarding. The Native American Church, with more than half a million adherents in the USA and Canada, attests to the scalability of this approach.

22.3.2.2 Illegal Contexts

In the majority of modern societies, the consumption of hallucinogens is illegal and socially stigmatized. Even in those subcultures in which it is not considered somehow immoral or dangerous, there is an outstanding threat that the hand of the law will descend upon a person who chooses to self-induce a hallucinatory state, depriving them of freedom, diminishing their social standing, and marking them as criminal.

Given this, it is nearly impossible to discuss a contemporary hallucinogenic experience without a certain amount of fear, except for those few which are protected by laws relating to freedom of religion, which necessarily fall into a class of their own. These fears must be recognized as part of the set and setting of modern hallucinogen consumption, but not as inherent to the substances or the experiences themselves.

While some cultures surrounded hallucinogen consumption with rules about appropriate usage, and others have essentially dismissed them as occasional aberrations in the course of daily life, modern Western culture is unique in its extent and breadth of condemnation. Disinformation distributed through both official and popular channels has been claimed as acceptable despite its untruth, simply because it might discourage potential consumption of a hallucinogen. The fear of hallucinations is quite powerful, as it can prevent general agreement on basic, empirically investigable scientific facts.

These factors must be considered in any analysis of psychoactive substances undertaken in the here and now. These stigmata may cause research subjects to lie, or researchers desirous of funding to spin their results to suit the dominant paradigm, whether by minimizing the hallucinatory potential of a drug in development or exaggerating the dangers of hallucinogen use. Needless to say, these tendencies can only hamper scientific understanding of hallucinogenic substances and their properties and endanger the health, safety, and freedom of society's members who might desire to experience hallucinations.

It can only be hoped that science's endless curiosity will continue to press the societal restraints upon these matters, and knowledge continue to accrue. The scientific process has tremendous resilience; those of us who would practice it need only to retain our faith and do our jobs. Further pursuit of such research may reveal that drug-induced hallucinatory phenomena offer a systematized route to observe not just how the brain processes hallucinations, but better clarify how our awareness of reality is consistently distorted.

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Chapter 23
Examining the Continuum Model of Auditory Hallucinations: A Review of Cognitive Mechanisms

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23.1 Introduction

Faced with mounting evidence that auditory hallucinations occur both in health and in psychosis (Daalman et al. 2011; Sommer et al. 2010; Stip and Letourneau 2009; Van Os et al. 2009), the continuum model of psychotic symptoms has become the "accepted dogma" (David 2010). We would like to begin, however, by making a distinction between the term "auditory hallucinations," which we consider a symptom of psychosis, and "hearing voices," an experience that also occurs outside of the psychosis context (see Chap. 28). We would moreover like to make a distinction between the experience of hearing real voices (in the physical sense) and nonreal "voices" in the absence of an acoustic signal. Thus, we have used the terms auditory hallucinations, "hearing voices," and hearing voices to denote similar phenomenological experiences in patients diagnosed with schizophrenia and in individuals in the general population – in the absence and presence of a speech signal, respectively.

Despite the dominant influence of this model, careful phenomenological comparison suggests both similarities and differences between nonpsychotic and psychotic "voice hearers." For example, Daalman's study found that while the perceived location of the "voice" was the same in both groups, patients with psychosis experienced a more diminished sense of control (Daalman et al. 2011).

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The emotional characteristics of the experience also distinguished the two groups, with a more negative valence for "voices" experienced by individuals with psychosis. An intriguing (but also somewhat surprising) finding was that 78% of healthy "voice hearers" attributed the location of their "voices" to an external source, while only 58% of patients did so. Such differences begin to raise some doubts about the dimensional nature of these experiences; nonetheless, the influence of this model now extends to clinical care. For example, it is now recognized that the majority of hallucinations in the general population are transitory and do not necessitate a need for care, but those that persist are associated with an increased risk of developing psychosis (De Loore et al. 2011; Dominguez et al. 2011) – implying a continuum of disability. In practice, therefore, it makes sense that symptoms such as auditory hallucinations are used (e.g., in the clinical staging model) to ascertain an individual's risk for developing a psychotic illness (McGorry et al. 2007). Importantly, the continuum model of psychosis has also encouraged the view that auditory hallucinations and "hearing voices" in psychotic and nonpsychotic groups, respectively, rely on similar underlying cognitive and neural mechanisms. As a consequence, an increasing number of studies are being conducted on healthy "voice hearers," on the assumption that such studies will uncover the basic etiological mechanisms underlying all experiences of "hearing voices" – including symptoms of hallucinations in those diagnosed with schizophrenia – while confounding effects arising from medication, hospitalization, and illness duration are avoided.

Alternatively, phenomenological differences in psychotic and nonpsychotic groups suggest that some significant differences in the respective cognitive and neural mechanisms causing "voices" might also be expected. We decided, therefore, that a critical appraisal of this aspect of the continuum model would be timely and may have important clinical, etiological, and empirical implications. Consequently, we examined a range of studies from a variety of theoretical perspectives, including bottom-up, top-down, and memory-based models, as well those more specifically focused on the role of language, seeking comparable evidence from individuals in both groups.

23.2 Language Lateralization

Auditory hallucinations experienced by individuals diagnosed with schizophrenia usually entail "voices" talking to, or about, the patient. Not surprisingly, therefore, a large body of literature has examined the role of speech and language lateralization in psychosis (Sommer and Kahn 2009). There is a large body of literature showing that in healthy individuals the left hemisphere is dominant for language in general, with evidence from behavioral (Hellige 1990), lesion (Lezak 1994), and functional neuroimaging (Petersen et al. 1988) studies. There is a corresponding large literature showing a similar left-sided lateralization for speech perception,

with evidence also from behavioral and neuroimaging studies (see Tervaniemi and Hugdahl (2003) and Cowell (2010) for reviews). Considering that the experience of "hearing voices" has, by definition, a profound perceptual characteristic, a straightforward prediction would be that a similar lateralization would be apparent for nonreal and real voice hearing. Studies of the lateralization of language and psychosis show, however, a complex picture, with both left- and right-hemisphere dominant activation. In a pioneering study Flor-Henry (1969) found that psychosis-like symptoms in patients diagnosed with temporal lobe epilepsy resembled those diagnosed with schizophrenia more when the focus of the epilepsy was in the left temporal lobe rather than in the right temporal lobe. Later studies have, however, not always replicated these original findings. Language processes seem to engage both the left (Hugdahl et al. 2008a, b) and right (Sommer et al. 2008, 2010; Sommer and Diederen 2009) hemispheres, or their disconnection (Ceccherini-Nelli et al. 2007) in patients diagnosed with schizophrenia, making it difficult to track down a primary pathology residing in one hemisphere or the other. However, in a recent review of both structural and functional brain-imaging data, Crow (2010) provides compelling evidence that a deficit of lateralization in patients diagnosed with schizophrenia in general seems to be associated with phonological rather than semantic/syntactic aspects of language. This observation would then nicely fit to a view of deficit in speech perception and phonology in patients diagnosed with schizophrenia as underlying the occurrence of auditory hallucinations. Such a view would, however, not be consistent with a continuum model of auditory hallucinations and "hearing voices" since there are no reports in the literature of a unique deficit in the lateralization of speech perception and phonology in "voice hearers" in the general population. A somewhat similar conclusion can be drawn from the study by Diederen et al. (2010), who compared brain activity in patients with auditory hallucinations with a group of nonclinical "voice hearers" and nonclinical non–"voice hearers." The results showed a reduced lateralization for language in the patient group, compared to the two nonclinical groups, which replicated previous findings of a deficit in left-hemisphere functioning in patients diagnosed with schizophrenia. More interesting, for the current discussion, is that there were no significant differences in language lateralization between the two nonclinical groups, thus supporting a noncontinuum view of auditory hallucinations in patients and "hearing voices" in the general population. The task used in the Diederen et al. (2010) study was, however, a verbal-fluency task requiring the subjects to covertly and overtly generate words that began with a certain letter shown on a screen in front of them. A word-production task will by its very nature also load on semantics in addition to phonology, which would engage different language processes and brain regions than a speech-perception task with a focus on phonology. Thus, it is still unsettled whether a patient group experiencing auditory hallucinations and a group of nonclinical "voice hearers" would differ in lateralization for a pure speech-perception, and thus pure phonetic task, for example, a dichotic listening task with presentations of simple consonant-vowel syllables that are devoid of semantic meaning (cf. Tervaniemi and Hugdahl 2003).

23.3 Bottom-Up Activity

The experience of "hearing voices" involves more than just speech. Voices, whether real or hallucinated, carry important information about the identity, emotion, and location of the speaker, which is processed in partially separable auditory pathways (Badcock 2010; Belin et al. 2011). Many patients report, for example, that they can identify the voice of another person, their gender or their accent, and phenomenological comparisons confirm that similar attributions to real and familiar people are made in healthy and psychotic "voice hearers" (Daalman et al. 2011). Consequently, it has been proposed that auditory hallucinations and "hearing voices" in patients and healthy individuals, respectively, may be viewed as the product of internal (bottom-up) activity in parallel voice-perception pathways which intrude into ongoing mental events (Badcock 2010; Hugdahl 2009).

In studies on cognition, such intrusive activity associated with auditory hallucinations has been examined in the guise of unwanted thoughts, images, and memories. Morrison and Baker (2000) were the first to examine the frequency of intrusive thoughts in patients diagnosed with schizophrenia, using the Distressing Thoughts Questionnaire (Clark and de Silva 1985). Hallucinating patients reported more frequent intrusions than nonhallucinating psychiatric or healthy controls, though subsequent studies – based on different questionnaires – have not consistently replicated this relationship (Linney and Peters 2007). Morrison (2005) has argued that auditory hallucinations can be conceptualized as a variation of normal intrusive thoughts, but that psychotic and nonpsychotic experiences differ as a result of the interpretation (or catastrophic misinterpretation) of intrusions that leads to distress and disability in individuals with psychosis. However, a recent meta-analysis has found little support for the role of metacognitive beliefs in hallucinatory experiences in either clinical or nonclinical samples (Varese and Bentall 2011). This is despite the fact that statistical modeling in healthy individuals prone to "hearing voices" has shown a strong and significant association with intrusive cognitions (Jones and Fernyhough 2009), suggesting that clinical and nonclinical "voice hearers" may indeed have a shared tendency to more frequent intrusive thoughts.

Auditory hallucinations have also been conceptualized as intrusive auditory imagery since both involve internal representations in the absence of external input. Initial reports suggested that individuals with clinical or nonclinical hallucinations experience more vivid auditory imagery. However, more recent evidence shows that mental-imagery vividness is independent of the presence of, or predisposition to, auditory hallucinations (Oertel et al. 2009). Following a critical analysis of the available data, Aleman and Larøi (2008) concluded that: "There is no convincing evidence of abnormalities in mental imagery ability in people who experience hallucinations. This does not imply that activation of mental images may not be central to hallucinations" (p. 91). In support of this conclusion, new evidence now shows that the neural networks engaged during auditory hallucinations show considerable overlap with those engaged during auditory imagery – both in psychotic and nonpsychotic individuals (Allen et al. 2008; Linden et al. 2011). Of note, this

includes similar activity in the human-voice area in the superior temporal sulcus and adjacent areas, which may, in part, explain why hallucinated "voices" in both groups are typically perceived as real. Importantly, increased activation in voice-perception networks during auditory hallucinations would also be expected to add internal "noise" to ongoing cognitive processes, and might, therefore, be expected to result in impaired recognition of externally produced voices. Consistent with this prediction, the ability to distinguish familiar and unfamiliar voices was found to be impaired in patients diagnosed with schizophrenia who experienced auditory hallucinations, compared to nonhallucinating patients and controls (Zhang et al. 2008). However, similar evidence has yet to be reported in healthy "voice hearers," leaving open the possibility that both similarities and differences in voice identification may be present in clinical and nonclinical groups.

Another possibility is that auditory hallucinations involve intrusive memories (Hemsley 1993; Waters et al. 2006). A recent quantitative review of functional-imaging data has shown that auditory hallucinations in psychosis are associated with increased activation in the medial temporal lobes (Jardri et al. 2011), the region most often linked to verbal episodic memory. Memory-based models have sometimes been criticized (Jones 2008) on the basis that they can only account for intrusive memories of traumatic events, which form only a small proportion of auditory hallucinations, and are rather associated with anxiety disorders such as posttraumatic stress disorder (PTSD). However, such criticisms may be unfounded since the data clearly show that intrusions in both clinical and nonclinical "voice hearers" also arise in emotionally neutral conditions of free recall (Brébion et al. 2009, 2010). Furthermore, Waters et al. (2006) have shown that patients diagnosed with schizophrenia who experience auditory hallucinations often fail to form an integrated representation of an event in memory. Together, the findings suggest that intrusive recollections may comprise either individual features (words, voice identity) or complete episodes (memories of abuse) from memory and could potentially account for the diverse phenomenology across the continuum of hallucinated "voices."

23.4 Source Memory

Bottom-up models emphasize the fact that hallucinated "voices" involve multiple components (words, voice identity, emotion, and location) that must eventually be combined. One of the defining features of episodic memory is that events (e.g., words) are encoded along with details of the context in which they occurred (Ranganath 2010) – such as spatial location or voice pitch. This combined set of information allows the source of a memory to be correctly recalled (e.g., who said what, where the speakers were) and depends on distinct brain circuits in the medial temporal lobe (Ranganath 2010). For example, the parahippocampal and hippocampal cortices – in the auditory "where" pathway – play a critical role in encoding and binding spatial information in context. Spatial-source memory has received considerably less investigation in psychosis relative to the large number of studies assessing

self/other source discrimination (reality monitoring) despite the fact that a recent meta-analytic review concluded there was no evidence for a differential deficit in reality monitoring in patients diagnosed with schizophrenia (Achim and Weiss 2008). Furthermore, phenomenologically, spatial-source memory has been identified as a key dimension of auditory hallucinations (Stephane et al. 2003), while structural brain imaging has shown that the perceived location of "voices" is associated with anatomical changes in the auditory "where" pathway (right temporoparietal junction) (Plaze et al. 2011). In contrast, other studies suggest that spatial-source memory is not impaired in healthy hallucination-prone individuals (Badcock et al. 2008; Chhabra et al. 2011; McKague et al. submitted). For example, Chhabra et al. showed intact integration of external voice and location information in memory in healthy adults predisposed to hallucinations, while McKague et al. manipulated the perceived internal/external location of auditory stimuli, and found no association between the accuracy or bias in performance and hallucination-proneness. Thus potentially important dissimilarities in spatial-source memory may exist in psychotic auditory hallucinations and "hearing voices," respectively, which clearly warrant further investigation.

23.5 Top-Down Control

It seems inevitable that intrusive activity associated with auditory hallucinations will require some form of top-down or "executive" control, and indeed this has been the focus of many cognitive accounts (Badcock 2010; Hugdahl 2009). Three key separable components of executive control have been identified, i.e., shifting between response sets, updating working memory, and inhibiting prepotent responses or response tendencies (Miyake et al. 2000). The notion that dysfunction of volitional inhibition may be a critical mechanism underlying auditory hallucinations has gained support from a variety of recent studies involving both patients diagnosed with schizophrenia (Badcock et al. 2005; Soriano et al. 2009; Waters et al. 2003) and healthy "voice hearers" (Paulik et al. 2007, 2008). For example, Soriano et al. used a directed forgetting task to measure the ability to suppress recently acquired information. The task involves the presentation of two lists of words for later recall. The first list is followed by an instruction to "forget" the items just learned, while the second list is accompanied by an instruction to "remember." At recall, the participants must remember words from both lists. Typically, fewer list-1 items are recalled in the forget condition than in the remember condition, indicating that suppression has indeed occurred. The results of the study by Soriano et al. (2009) showed that patients with auditory hallucinations failed to produce a reliable directed forgetting effect compared to patients without hallucinations, indicating a significantly impaired ability to intentionally suppress irrelevant information in memory. The degree of inhibitory failure was shown to be significantly correlated with the frequency of auditory hallucinations (but not with other symptoms), a finding that had previously been reported by Waters et al. (2003) based on

different measures of inhibitory function. It seems likely, therefore, that at least some forms of inhibitory control are *specifically* associated with hearing "voices" both in clinical and nonclinical populations. In addition, it seems likely that difficulties in executive control reflect underlying abnormalities in prefrontal cortex (Pomarol-Clotet et al. 2010; Hugdahl 2009) since this region is usually associated with inhibitory processing (Koechlin et al. 2003).

Finally, it must also be noted that although these cognitive studies point to similar mechanisms of top-down control in healthy and psychotic "voice hearers," these groups differed in their subjective sense of control (Daalman et al. 2011). Hence, the mechanisms underlying objective and subjective control both in health and in psychosis may well be far more complex than is currently understood.

23.6 Discussion and Conclusions

Although the continuum model of psychotic symptoms has been quite influential and has accumulated evidence for similar etiological mechanisms in clinical and nonclinical populations, there is a risk of accepting the continuum view unchallenged because alternative causal models or experimental designs – and more effective clinical interventions – may not be developed, and inconsistent data may be inadvertently overlooked.

Against this background, our search revealed evidence of only partial overlap in the cognitive mechanisms associated with hallucinated "voices" in psychotic and healthy individuals (see Fig. 23.1), including elevated rates of intrusive cognitions and poor executive control. These results suggest that, regardless of the presence or absence of psychosis, a similar neural network is involved in generating auditory hallucinations and "hearing voices" in psychotic and nonpsychotic populations, respectively, including both left temporal (speech-perception and voice-selective areas) and prefrontal (cognitive control and executive areas) cortices (Allen et al. 2008; Jardri et al. 2011). Consistent with this conclusion, Diederen et al. (2011) recently identified several common areas of activity – including bilateral inferior frontal cortex, the superior temporal gyri, the inferior parietal lobe, and the insula – during hallucinations in psychotic and nonpsychotic individuals. Although these results appear to implicate the same cortical network in both groups, the authors caution that similar patterns of brain activity could be triggered by different causal mechanisms that merge in a final common pathway. In this context the results of the current review may be particularly valuable since they suggest subtle but significant differences in language lateralization and cognitive processing in psychotic and nonpsychotic hallucinators and "voice hearers." For example, the observed difficulties binding external sources of information (e.g., voice and location) are typically linked to abnormal activity in the hippocampus and the parahippocampal cortex (Ranganath 2010), pointing to a particular role of the medial-temporal-lobe memory system in the hallucinations of psychosis (Badcock 2010; Waters et al. 2006). Several independent lines of research converge on a similar conclusion, including evidence

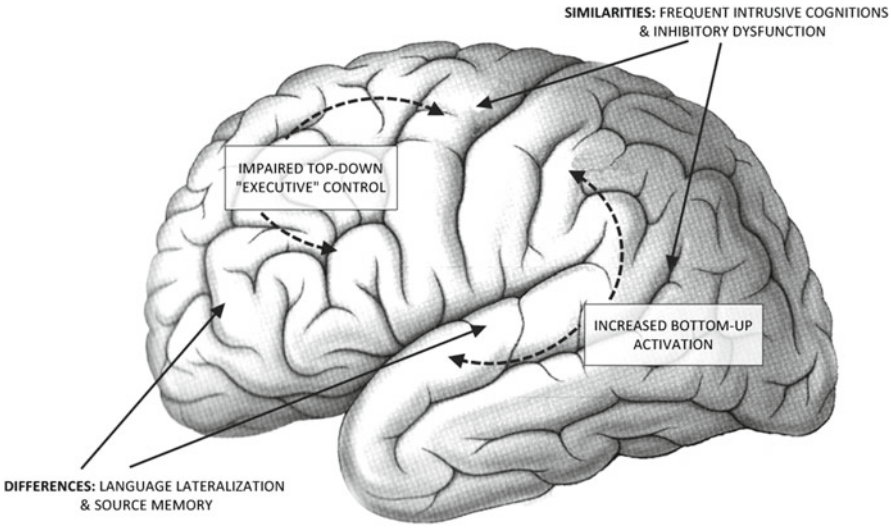

Fig. 23.1 Schematic illustration of similarities and differences in cognitive and neural processing in psychotic and healthy "voice hearers." Both groups share intrusive activations in separable auditory pathways and deficits in frontally mediated executive control. Reduced lateralization of word production and impaired spatial-source memory are only associated with auditory hallucinations in psychosis

of progressive deterioration in memory function (Frommann et al. 2011) and subtle signs of hippocampal pathology (Wood et al. 2010) associated with the onset of psychotic symptoms. Furthermore, significant deactivation of the parahippocampal gyrus occurs immediately prior to the onset of hallucinatory episodes (Diederen et al. 2010; Hoffman et al. 2008). Thus abnormal memory function may provide a critical "tipping point" or trigger in the genesis of auditory hallucinations.

On the basis of our findings, it is tempting to conclude that the similarities in voice features (e.g., attributions to real or familiar people) in psychotic and healthy individuals arise from dysfunctional activity in the same cognitive and neural substrates (e.g., intrusive representations from the human-voice area). We would like to take a more conservative standpoint, however, and suggest that a better model of the etiology of auditory hallucinations and "voice hearing" should combine evidence from both discontinuities and continuities models. However, this assumption must be empirically tested in future studies by examining psychotic and nonpsychotic subgroups that are closely matched phenomenologically. An important issue, when comparing clinical and nonclinical groups, with regard to auditory hallucinations and "hearing voices" is the extent to which the nonclinical subjects represent a "pure" nonclinical population. It is customary, therefore, to exclude individuals who have received a psychiatric diagnosis and/or medication for their "voices" (Sommer et al. 2010). This does not necessarily exclude individuals who consult a physician, but are not given a diagnosis. Thus, perhaps, a better criterion would be to exclude

all subjects who have ever "contacted a physician or psychologist" because of worries about their "voices." The argument is that it is not possible to get a diagnosis or have antipsychotic medication prescribed without "contacting" a physician (at least not legally), while the opposite is possible, i.e., contacting a physician without getting a diagnosis.

Our findings also highlight that research designs based solely on healthy "voice hearers" may be neither optimal nor sufficient for understanding hallucinations in clinical groups since they are likely to miss critical cognitive mechanisms, such as those linked to abnormal activity in the hippocampus and parahippocampal cortex in the medial temporal lobes. Conversely, many cognitive studies of psychosis compare patients with and without auditory hallucinations and conclude that only those cognitive processes *specific* to hallucinations are *relevant* to their etiology. Such conclusions may underestimate the importance of cognitive processes that underpin clusters of symptoms, including but not limited to auditory hallucinations. This point may be particularly salient when excluding other positive symptoms in the analysis since auditory hallucinations show high correlations phenomenologically (e.g., with delusions and conceptual disorganization), which should be expected to correlate with other cognitive domains and with brain activity in the same areas as for auditory hallucinations. Finally, wider recognition of the differences, as well as similarities, of "voice hearing" and auditory hallucinations in healthy and psychotic individuals, respectively, should encourage clinicians to conduct more detailed assessments of phenomenology and cognition in patients presenting with "voices" and develop more targeted (i.e., individualized) pharmacological and/or psychosocial interventions as necessary.

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Part IV
Treatment

Chapter 24
Classical Somatic Treatments: Pharmacotherapy and ECT

Iris E.C. Sommer and Jan Dirk Blom

24.1 Introduction

The treatment of hallucinations rests basically on psychoeducation, psychosocial interventions, psychotherapy, medication, and a number of additional somatic therapies. The present chapter will focus on medication and electroconvulsive treatment (ECT), whereas other types of treatment will be discussed elsewhere in this book. We will offer recommendations for the pharmacological and electroconvulsive treatment of hallucinations in psychotic disorders, Parkinson's disease, dementia, delirium, epilepsy, and sensory impairment, although the main focus will be on psychosis.

24.2 Assessing the Need for Treatment

Hallucinations occur in the context of many different disorders and syndromes. Therefore, the choice for a specific type of treatment does not only depend on the type of hallucination and its consequences for daily functioning, but also on the underlying disorder. If hallucinations occur in the context of epilepsy, for example, treatment should be focused on seizure control. In delirium, treatment should primarily be

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directed at improving somatic health. In patients who develop hallucinations in the course of progressive vision or hearing loss, it can be helpful to apply interventions aimed at restoring the loss of function at hand, such as a cataract operation or the providing of hearing aids (Tuerlings et al. 2009; Cope and Baguley 2009). Some individuals who hallucinate only sporadically may be merely concerned that their experiences are a sign of mental disease, without being troubled by the hallucinations themselves. For others, the burden of their hallucinations may not outweigh the side effects of treatment. As a consequence, pharmacological treatment may not be necessary in all cases at hand. In psychotic patients, however, comorbid delusions may be an important reason to advocate antipsychotic treatment, even when the patient himself is reluctant to consider this. Meanwhile, one should be transparent about possible side effects. All in all, the potential benefits of treatment should be weighed carefully against acute as well as long-term side effects, especially in cases of mild and/or transient types of hallucination.

24.3 Pharmacological Treatment of Hallucinations in Schizophrenia Spectrum Disorders

The only type of medication known for its potential to effectively reduce the frequency and severity of hallucinations in schizophrenia spectrum disorders is antipsychotic medication. An important benefit of this type of medication is that it can also diminish concurrent delusions. So far, no clinical trials have been published that compare the efficacy of various antipsychotic drugs for the sole and specific indication of hallucinations. Therefore, we used the data from the European First Episode Schizophrenia Trial (EUFEST) to assess the potential of five antipsychotic agents to reduce the severity of hallucinations. The EUFEST study (Kahn et al. 2008) assessed 498 patients with a first psychotic episode, who were randomized to receive either haloperidol, olanzapine, amisulpride, quetiapine, or ziprasidone in an open-label design. The reduction of the total symptoms was virtually the same in all groups, lying around 60% after 12 months of treatment, although some major differences were observed in the discontinuation rate (Kahn et al. 2008). We reanalyzed those data with item P3 (Severity of Hallucinations) of the Positive and Negative Syndrome Scale (PANSS, Kay et al. 1987) as the primary outcome measure.

In the PANSS interview, the severity of hallucinations is scored on a six-point Likert scale (i.e., None, Questionable, Mild, Moderate, Marked, Severe). All subjects with a score of 3 or higher at baseline were included ($N = 362$; 73% of the total sample). The number of subjects decreased over time, mostly due to treatment discontinuation. Latent growth curve (LGC) analyses (Muthén and Curran 1997) were performed to assess the change in hallucination item scores while including age (standardized), gender, and country as covariates. Even though 54% of the patients discontinued treatment within 12 months, unbiased parameter estimates were obtained under the assumption of missing at random. Out of these data, we extracted

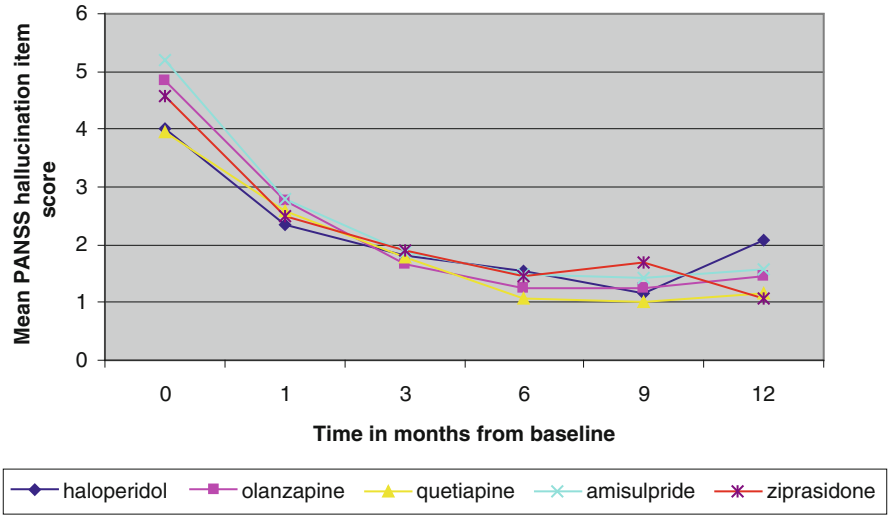

Fig. 24.1 Mean decrease in hallucination severity (item P3 of the PANSS) in first-episode patients with a nonaffective psychotic disorder after 1, 3, 6, 9, and 12 months on antipsychotic medication

a reduction of the severity of hallucinations from 4.4 on the PANSS item for hallucinations at baseline, indicating marked to severe hallucinations, to a mean value of 2.5, indicating mild to moderate hallucinations after 4 weeks. The severity of hallucinations continued to decline with prolonged treatment to mean values of around 1.5, reflecting the presence of questionable or mild hallucinations after 6 months of treatment (see Fig. 24.1 and Table 24.1). Likewise, the percentage of subjects with at least moderate levels of hallucinations decreased strongly over time from 100% at baseline to 8% after 12 months. These findings indicate that hallucinations in patients with a first episode of psychotic disorder respond fairly well to treatment, showing a sharp reduction in symptom severity occurring in the first month. After 1 year of pharmacotherapy, only 8% of the patients who continued their medication went on to experience hallucinations of moderate severity.

This result should be encouraging for patients suffering from hallucinations, and it might help them to decide in favor of pharmacotherapy. In parallel to the findings of the overall analysis of the EUFEST data, no differences in hallucination reduction between the five treatment groups were observed in those individuals who completed their treatment. Although these findings cannot be extrapolated to other antipsychotic drugs, they suggest that the most commonly prescribed antipsychotics are equally effective against hallucinations in patients with a first psychotic episode. However, the drop-out rates differed considerably among the five groups, with relatively high rates for the haloperidol group and relatively low rates for the amisulpride and olanzapine groups. This indicates that tolerability should be an important factor in the selection of an antipsychotic drug.

Table 24.1 Summary of augmentation strategies and their (mean) standardized differences (Taken from Sommer et al. 2011)

Augmentation strategy	Studies (N)	Subjects (N)	Hedges' g, 95% CI, and I^2 for PANSS/BPRS total	Hedges' g, 95% CI, and I^2 for positive subscores	Hedges' g, 95% CI, p and I^2 for negative subscores
Antiepileptics	7	189			
Lamotrigine	5	143	**0.53, 0.03–1.04, 60%**	0.38, −0.02–0.78, 39%	0.41, −0.13–0.94, 64%
Minus outlier	4	92	0.27, −0.10–0.65, 0%	0.15, −0.22–0.52, 0%	0.12, −0.25–0.49, 0%
Topiramate	3	89	0.75, −0.05–1.56, 69%	**0.63, 0.03–1.23, 47%**	0.66, −0.17–1.5, 71%
Minus outlier	2	57	0.38, −0.13–0.89, 0%	0.39, −0.24–1.01, 25%	
Antidepressants	4	129			
Citalopram	1	61	**0.81, 0.30–1.33**	0.28, −0.22–0.79	**0.81, 0.30–1.33**
Fluoxetine	1	33	No data	0.12, −0.55–0.79	0.19, −0.48–0.86
Mirtazapine	2	35	2.91, −2.69–8.51, 96%	0.04, −0.59–0.67, 0%	1.20, −0.25–2.66, 76%
Antipsychotics	10	548			
Amisulpride	1	20	0.13, −0.48–0.74	0.11, −0.50–0.72	0.21, −0.40–0.82
Aripiprazole	2	268	0.12, −0.12–0.36, 0%	0.22, −0.02–0.46, 0%	0.37, −0.19–0.93, 74%
Haloperidol	1	6	−0.15, −1.51–1.21	0.26, −1.11–1.62	−0.31, −1.68–1.06
Risperidone	5	226	0.18, −0.21–0.57, 53%	0.09, −0.24–0.74, 56%	0.22, −0.14–0.57, 43%
Sulpiride	1	28	**0.83, 0.07–1.59**	**0.77, 0.02–1.52**	**0.76, 0.01–1.51**
Glutamatergics	7	137			
CX516	1	18	**1.35, 0.32–2.38**	0.20, −0.74–1.14	**1.43, 0.38–2.46**
D-cycloserine	1	11	No data	No data	−0.76, −1.59–0.08
D-serine	1	20	No data	0.40, −0.45–1.24	0.33, −0.52–1.17
Glycine	3	68	−0.16, −0.62–0.30, 0%	−0.36, −1.19–0.46, 67%	−0.14, −0.60–0.32, 0%
Sarcosine	1	20	−0.21, −1.06–0.63	−0.07, −0.91–0.77	−0.07, −0.91–0.77

Significant effects are indicated in bold

As regards their side effects, antipsychotics can be divided roughly into those predominantly inducing weight increase and sedation (i.e., quetiapine, olanzapine, and clozapine) and those frequently associated with dystonia, parkinsonism, and akathisia (i.e., all other antipsychotic drugs). The guidelines issued for treatment in schizophrenia by the Patient Outcomes Research Team (PORT) do not recommend olanzapine or clozapine as drugs of first choice because of the severe weight gain they may induce (Buchanan et al. 2010). Sedation should never be a treatment goal in and of itself, although it may sometimes be welcomed as a side effect in agitated or aggressive patients (Lambert et al. 2008). Severe side effects, such as acute dystonia and epileptic seizures, tend to occur chiefly in association with steep dose increases and relatively high dosages (Ciranni et al. 2009; Hedges et al. 2003). As a consequence, dose increases should always be monitored carefully, especially when the clinical situation calls for a dramatic upward change (Chengappa 2004).

If remission is not obtained with the aid of the drug of first choice, a relatively quick switch is warranted (Buckley and Correll 2008). The exact moment at which this switch can be made is still under discussion (Derks et al. 2010), but contrary to the traditional view, there is cumulating evidence that antipsychotic drugs require only little time (i.e., on the order of hours rather than days or weeks) to manifest their potential (Agid et al. 2008). If true, this would imply that a switch can be considered after a relatively short period of time (i.e., after 2 or 3 weeks). A second antipsychotic is usually chosen from among a group of drugs with a different receptor profile, although any direct evidence to support this strategy is scarce (Buchanan et al. 2010). Expert guidelines issued in 2003 recommended risperidone as a "preferred second-choice drug" (Kane et al. 2003), but the 2008 guidelines did not include this recommendation any longer. For those patients who even fail to respond to a second antipsychotic agent, clozapine is considered the drug of choice. The landmark trial by Kane et al. (1998) demonstrated a superior efficacy of clozapine for this subgroup of medication-resistant patients in comparison with any other antipsychotic agents, a finding that has since been replicated consistently (Chakos et al. 2001; Lewis et al. 2006; McEvoy 2006). In order to optimize clozapine therapy, various studies have evaluated the relationship between blood levels and therapeutic response. Blood levels above 350–450 μg/mL are associated with superior treatment results (reviewed by Schulte 2003), not only for intractable hallucinations but also for intractable negative symptoms, disorganized behavior, and thought disorder (Chakos et al. 2001; Lewis et al. 2006; McEvoy 2006). However, despite those unique qualities, clozapine has failed to gain the status of a drug of first or second choice. This is due to its rare, but potentially severe side effects. One of these side effects is leukocytopenia, or even agranulocytosis, i.e., the cessation of the production of white blood cells, which can lead to treatment-resistant infections and even death (Atkin et al. 1996). For this reason, blood is sampled weekly in patients starting on clozapine therapy to count the white blood cells and sampled at larger intervals during the complete course of treatment. In case of a severe decrease in leukocyte numbers, the treatment can be interrupted, which usually leads to a complete recovery of the white cell count (Esposito et al. 2005). As most patients using clozapine have psychotic symptoms that are resistant to other drugs, it is advisable

to restart clozapine treatment after the leukocytopenia has subsided. Dunk et al. (2006) restarted clozapine after neutropenia in 53 patients and reported that 55% of them did not have another blood dyscrasia. For the remaining group, addition of lithium (which has the potential to induce leukocytosis) may be an option. Alternatively, granulocyte colony–stimulating factor can be prescribed as comedication (Whiskey and Taylor 2007). Another severe side effect of clozapine is heart disease, presenting in the form of pericarditis, myocarditis, or even cardiomyopathy. If clozapine-induced heart disease occurs, it usually does so within the first 15 days of treatment (Kamphuis et al. 2010). These effects are not always reversible after the cessation of clozapine therapy and can occasionally be fatal (Layland et al. 2009). Because of them, and because of clozapine's reputation as a "last resort," clinicians tend to show a certain hesitancy to prescribe it. However, careful monitoring can effectively reduce the risk of side effects, and here again, the cons should be carefully weighed against the pros (Agid et al. 2007).

24.3.1 Maintenance Treatment

When successful, antipsychotic medication should be prescribed in an unaltered dose for a duration of at least 1 year (Buchanan et al. 2010). However, this does not imply that the treatment should be discontinued as soon as the year is over. As the propensity to hallucinate would seem to depend in large part on our genetic makeup, the vulnerability for developing symptoms such as these can be expected to remain in force. In times of distress, either mentally or physically, the risk of a new psychotic episode may be high in unmedicated patients. Therefore, as long as the side effects are tolerable, it is preferable not to discontinue the medication that has led to the initial improvement, not even after a prolonged psychosis-free episode.

To prevent relapses, either of two strategies can be followed: continuous maintenance treatment with antipsychotic medication or intermittent treatment, to be started as soon as any signs of potential relapse are detected. In a double-blind randomized study, maintenance treatment was found to be more effective than targeted intermittent treatment in preventing relapses, even in stable first-episode patients after their first year of maintenance treatment (Gaebel et al. 2011). As regards continuous maintenance treatment, there has been considerable discussion regarding the optimal dose to be prescribed. In an elegant study, Wang et al. (2010) randomized 404 patients diagnosed with schizophrenia-in-remission to three conditions: (1) initial optimal therapeutic dose continued throughout the study, (2) initial optimal therapeutic dose continued for 4 weeks and then reduced to 50%, and (3) initial optimal therapeutic dose continued for 6 months and then reduced to 50%. After 1 year, the relapse rates were 9.4% for group 1, 30.5% for group 2, and 19.5% for group 3. These findings indicate that a dose reduction of 50% may increase the risk for psychosis two- or threefold. Whether a dose reduction of *less* than 50% is as effective as continuation of the initial dose remains as yet unclear (Uchida et al. 2011). All in all, current evidence suggests that maintenance treatment with the initial optimal dose is the safest way to go.

24.3.2 Depot Medication

As psychotic relapses are most frequently associated with nonadherence to antipsychotic treatment (Morken et al. 2008), long-acting injectables (or depots) constitute a valuable alternative for oral medication. Studies comparing short-acting oral and long-acting injectable antipsychotics found the latter to be superior in terms of relapse prevention and improvement of social functioning (Emsley et al. 2008). This superiority is largely due to improved adherence. If patients forget or refuse to take their oral medication, it may take their caretakers weeks or even months to notice an exacerbation, whereas nonadherence to injectables is instantly noticeable. In clinical practice, however, the prescription of depot medication has declined since the introduction of second-generation antipsychotics. Although 40–60% of all patients suffering from psychosis are partially or totally nonadherent to their antipsychotic medication, less than 30% are now treated with long-acting injectables (Patel et al. 2009). Possible reasons for this decline include prejudices against injectables, as well as the erroneous assumption that one's own patient group shows better adherence than those treated by others (Patel et al. 2009). However, there is actually little reason to refrain from prescribing depot medication for patients with psychosis (Heres et al. 2010). On the contrary, its advantages deserve to be explained to all patients in need of maintenance treatment.

24.3.3 Poor Response to Antipsychotic Medication

Although clozapine is considered the most efficient antipsychotic agent for refractory patients, as many as 40–70% of them achieve only a poor or partial response, even with adequate blood levels of clozapine (Kane et al. 1998). Treatment of these patients has remained a persistent public health problem, as they tend to suffer severely from their symptoms and often have a significantly reduced quality of life (McGlashan et al. 1988). For these ultra-resistant patients, several treatment strategies are available, including psychotherapy (see Chap. 26), pharmacological augmentation, repetitive transcranial magnetic stimulation (see Chap. 25), and electroconvulsive therapy. In clinical practice, clozapine is often augmented with lithium, sodium valproate, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), risperidone, haloperidol, or aripiprazole. A recent meta-analysis quantitatively summarized all randomized controlled trials (RCTs) involving the pharmacological augmentation of clozapine (Sommer et al. 2011). That review included 29 RCTs reporting on 15 different augmentation strategies prescribed to 1,066 patients in total. Improvement of total symptom severity – in comparison with placebo – was found for lamotrigine, sulpiride, citalopram, and the glutamatergic agonist CX516. However, the superiority of lamotrigine turned out to depend on the inclusion of a single outlier, whereas the claim to superiority of sulpiride, citalopram, and CX516 was based on single RCTs. Significantly better efficacy on positive symptom severity was found for topiramate and sulpiride, although here it must be noted that the

results for topiramate became nonsignificant after outlier exclusion, while those for sulpiride were based on a single RCT. Citalopram, sulpiride, and CX516 showed better efficacy for negative symptoms than placebo, all based on single studies. We must conclude, therefore, that pharmacological augmentation strategies in clozapine therapy are not (yet) supported by much convincing evidence from the literature.

24.4 Electroconvulsive Treatment for Hallucinations in Schizophrenia

In clinical practice, another augmentation strategy for the treatment of intractable hallucinations occurring in the context of psychosis is electroconvulsive treatment (ECT). Introduced as a treatment method with highly promising results during the 1930s, and subsequently discarded during the 1970s, it continues to be the most stigmatized therapeutic in psychiatry, although for a limited number of indications (notably catatonia and psychotic depression) it can be extremely helpful and potentially lifesaving (Payne and Prudic 2009).

During ECT, an electrical current is passed briefly through the brain via electrodes attached to the scalp, so as to induce a generalized seizure. The individual receiving treatment is under general anesthesia and given muscle relaxants to prevent body spasms. The ECT electrodes can either be placed on both sides of the head (bilateral placement) or on one side of the head alone (unilateral placement). Unilateral placement is usually over the nondominant half of the brain, with the aim of reducing any cognitive side effects. However, bilateral electrode placement tends to yield a faster improvement (Kellner et al. 2010) and may be preferable in urgent situations such as severe catatonia. The amount of current required to induce a seizure (called the seizure threshold) can vary largely among individuals and may increase during the course of treatment (Van Waarde et al. 2009). Cognitive impairments, especially memory problems, can occur immediately after the administration of ECT as well as afterward. However, pretreatment functioning levels tend to be reached within the first months following treatment (Semkovska and McLoughlin 2010).

Although ECT has been used in clinical practice since the 1930s, there is still no generally accepted hypothesis explaining its mechanism of action. In rat models, ECT (contrary to antidepressants, for example) can induce mossy fiber sprouting (Lamont et al. 2001), and there is growing evidence that it impacts brain-derived neurotropic factors capable of inducing neuroproliferation (Grønli et al. 2009). It is most frequently used as a treatment method for severe, medication-resistant depression, and it is also used for the treatment of mania and catatonia. There is no consistency whether persistent psychosis in patients diagnosed with schizophrenia should also be considered a valid indication for ECT. Recently, the National Institute of Clinical Excellence (NICE) concluded that “the current state of the evidence does not allow the general use of ECT in the management of schizophrenia to be recommended” (Young et al. 2010). Thus, despite 80 years of

practice, only little systematic evidence for the efficacy of ECT in psychosis is available. However, various naturalistic studies have assessed the outcome of patients with medication-resistant schizophrenia receiving a combination of ECT and antipsychotic medication. König and Glatter-Götz (1990) reported "stable remission" in 9 out of 12 patients receiving ECT. Likewise, Kupchik et al. (2000) reported on 36 patients treated with ECT and clozapine and found that 67% showed "satisfactory clinical recovery." Finally, Hustig and Onilov (2009) described a naturalistic follow-up of 27 patients receiving ECT and antipsychotic medication and found that 63% improved at least two points on the Clinical Global Impression Scale (CGI, Guy 1976). After 1 year, 37% of the initial sample had consolidated this improvement. Understandably, few studies have assessed the effects of ECT in a double-blind, sham-controlled design. In 2005, Tayran and Adams published a systematic meta-analysis of double-blind randomized studies comparing ECT and antipsychotic medication to sham and medication. They included 10 RCTs with a total of 392 patients. The relative risk for clinical improvement was 0.78 in favor of real ECT.

It should be noted that none of the above-mentioned studies provided any details on the reaction of hallucinations to ECT. As a consequence, the reported clinical improvement in all those studies is not necessarily attributable to a reduction in the frequency or severity of hallucinations. In fact, we were unable to retrieve a single study demonstrating a specific relief of hallucinations in medication-resistant psychosis thanks to ECT. As a consequence, we must conclude that ECT as an augmentation to antipsychotic medication is capable of improving the clinical status of some patients with medication-resistant psychosis, although its effects on hallucinations per se are as yet unclear and might well be low.

24.5 Treatment of Hallucinations in Parkinson's Disease and Related Disorders

Hallucinations and other psychotic symptoms are quite common in patients with Parkinson's disease (PD), with reported lifetime prevalence rates of up to 80% (Forsaa et al. 2010). In Lewy body dementia, a condition closely associated with PD, these numbers are even higher, especially for visual hallucinations. Cross-sectional studies show that visual hallucinations occur in approximately one-third of PD patients, whereas up to three-quarters of all PD patients develop them during a 20-year period (Fénelon and Alves 2010). Auditory hallucinations are present in up to 20% (Fénelon and Alves 2010). Prospective longitudinal cohort studies suggest that hallucinations tend to persist and worsen in individual patients and that their prevalence increases over time (Fénelon and Alves 2010). Those hallucinations can have substantial psychosocial effects and historically constitute the main reason for the placement of patients in nursing homes (Diederich et al. 2009).

Our understanding of the pathophysiology of psychosis in PD and Lewy body dementia has expanded dramatically over the past 15 years, from an initial interpretation of symptoms as dopaminergic drug adverse effects to the current view of a complex interplay of extrinsic and disease-related factors. These include central dopaminergic overactivity and an imbalance of dopaminergic and cholinergic neurotransmission, dysfunction of the visual pathways (including specific PD-associated retinopathy and functional alterations of the extrastriate visual pathways), alterations of brainstem sleep-wake and dream regulation, and impaired attentional focus (Diederich et al. 2009). The most important extrinsic factor, however, is still the antiparkinson medication. While hallucinations can be triggered by amantadine and anticholinergics, they are more commonly experienced after changes in dopaminergic medication. Within the latter category, dopamine agonists have a greater potential to induce hallucinations than L-dopa (Poewe 2008).

The treatment of hallucinations in PD involves patient-initiated coping strategies, a reduction of antiparkinson medication, augmentation with atypical neuroleptics, and, potentially, augmentation with cholinesterase inhibitors. When the reduction of anti-PD medication to the lowest tolerated dose does not improve hallucinosis, further interventions may be warranted. Various atypical antipsychotic agents (i.e., clozapine, olanzapine, quetiapine) are used to decrease the severity and frequency of hallucinations in PD and Lewy body dementia. While the use of clozapine requires monitoring of the leukocyte count (see above), olanzapine tends to lead to an aggravation of the motor symptoms (Zahodne and Fernandez 2008). Studies of ziprasidone and aripiprazole use are limited to open-label trials and case reports and highly variable in outcome; while either drug may be effective in some patients, both are associated with various adverse effects (Zahodne and Fernandez 2008). While two randomized controlled trials could not demonstrate the efficacy of quetiapine, it is a common first-line treatment method for psychosis in the context of PD because of its tolerability, ease of use, and demonstrated utility in numerous open-label reports (Zahodne and Fernandez 2008). A small, double-blind RCT with a mean dose of 58 mg quetiapine showed a significantly larger reduction of the severity of hallucinations (Fernandez et al. 2009). Eng and Welty (2010) conducted a review of the literature, thus including 13 studies on antipsychotic treatment for PD patients, all involving clozapine and quetiapine. They concluded that patients with PD might well benefit from long-term clozapine therapy, whereas the results of the quetiapine studies were conflicting. However, when quetiapine and clozapine were compared head-to-head, no statistically significant differences in effectiveness were found.

The group of cholinesterase inhibitors currently represents the most promising pharmacological alternative to antipsychotics. Various open-label studies and one double-blind, placebo-controlled trial among 188 hallucinating PD patients are in support of the efficacy of rivastigmine (Burn et al. 2006). The cholinesterase inhibitor tacrine, however, has hardly been tested because of its hepatic toxicity, and controlled trials with donepezil have not yielded any significant reduction of psychotic symptoms due, perhaps, to methodological limitations (Burn et al. 2006). Thus, while the use of cholinesterase inhibitors, especially rivastigmine, appears to be a

promising treatment method for hallucinations in PD, evidence-based studies support only the use of a single atypical antipsychotic drug, namely clozapine (Eng and Welty 2010).

24.6 Treatment of Hallucinations in Dementia

In Alzheimer's disease (AD), the occurrence of psychosis in 30–50% of the cases has serious consequences for both patients and caregivers (Spalletta et al. 2010), especially since the optimal type of treatment is still elusive. Interventions that optimize environmental and interpersonal factors can be helpful and should be attempted in all cases, although their overall effectiveness and applicability are not entirely clear. Cholinesterase inhibitors such as donepezil may have a beneficial effect on hallucinations while showing a relatively mild side effect profile (Wynn and Cummings 2004). In a similar vein, memantine has been shown to be more effective than placebo treatment without causing any disturbing side effects (Wilcock et al. 2008).

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study included 421 AD outpatients with psychosis and agitated and/or aggressive behavior. The patients were randomized to obtain masked, flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. As regards the effects of those drugs upon the psychotic symptoms, risperidone appeared to be superior to the other two and placebo (Sultzer et al. 2008). Although antipsychotic medication can have a positive effect on hallucinations in dementia, several reports issue warnings against the excess risk of morbidity and even death associated with its use in older patients (Kalapatapu and Schimming 2009). As a consequence, it is strongly advised not to consider antipsychotic drugs as the first choice for treatment of psychotic symptoms in dementia. Extrapyramidal symptoms and arrhythmias due to QTc prolongation are well-known complications of the use of conventional antipsychotic agents, while cerebrovascular events appear to occur more frequently in association with atypical as well as conventional antipsychotics in comparison with placebo treatment (Kalapatapu and Schimming 2009). Nevertheless, a trial of these agents may be indicated when the severity of symptoms is extreme or when the symptoms fail to respond to other types of medication or to nonpharmacological interventions.

24.7 Treatment of Hallucinations in Delirium

Delirium is an acute neuropsychiatric syndrome, by definition due to organic disease, which is characterized by psychotic symptoms such as hallucinations and delusions in the presence of decreased attention, fluctuating consciousness,

and other cognitive dysfunctions. It is very common in patients admitted to intensive care units, with a reported cross-sectional incidence of 32% (Salluh et al. 2010) and a marked association with poor prognosis and increased mortality (Kuehn 2010). The only causal treatment of delirium is the improvement of somatic health. Sometimes this can be accomplished by relatively simple means, for example, by restoring the volume of the blood plasma in dehydration or by treating a urinary tract infection. However, delirium frequently affects severely ill patients suffering from multiple somatic conditions such as cardiac failure complicated by asthma cardiale and diabetes, a combination which can be very hard to treat.

In such cases, the symptomatic treatment of hallucinations and other symptoms of delirium should commence with measures aimed at improving the patient's circadian rhythm and orientation. Symptomatic pharmacological treatment should preferably consist of haloperidol or olanzapine, as recommended by the latest NICE guidelines (Young et al. 2010). This type of treatment should be started at the lowest clinically effective dose and titrated cautiously. Although benzodiazepines are widely applied for the treatment of delirium, they are recommended only for delirium tremens (i.e., alcohol abstinence delirium). Two recent randomized controlled trials yielded good results for quetiapine in comparison with placebo (Devlin et al. 2010; Tahir et al. 2010), but so far no head-to-head comparisons with haloperidol or olanzapine have been published. Cholinesterase inhibitors are not recommendable, as demonstrated by an RCT with rivastigmine in delirious patients admitted to an intensive care unit. That trial was terminated at an early stage because of a significantly higher mortality and an increased duration of delirium in comparison with the control group (Van Eijk et al. 2010).

24.8 Treatment of Hallucinations in Epilepsy

The reported cross-sectional incidence of hallucinations and other psychotic symptoms in epilepsy is 3.3%, and in temporal lobe epilepsy, as high as 14% (Torta and Keller 1999). Those symptoms can occur shortly before, during, or after an epileptic seizure, and even independently of any motor seizures. Ictal hallucinosis is considered relatively rare. Postictal hallucinosis comprises some 25% of the hallucinatory episodes in epileptic patients. As post- and interictal psychotic episodes resemble those in patients diagnosed with schizophrenia, they are also designated as "schizophrenia-like psychoses of epilepsy."

The treatment of ictal as well as post- and interictal hallucinations should primarily consist of minimizing any medication capable of mediating these symptoms. Various antiepileptic drugs, such as phenobarbital, zonisamide, levetiracetam, and gabapentin, are known for their potential to induce hallucinations (Alper et al. 2002). In such cases, dose reduction or a switch to another antiepileptic drug may lead to a relatively quick cessation of the hallucinations. When antiepileptic drugs

cannot be reduced or traded, or when such interventions are unsuccessful, antipsychotic medication is the next therapeutic step. Clozapine and chlorpromazine should be avoided, if possible, because of their epileptogenic properties. Molindone is the antipsychotic with the lowest epileptogenicity, making it very useful in epileptic patients (Alper et al. 2002). However, antipsychotics such as quetiapine, risperidone, and haloperidol also tend to be tolerated well. In all cases, the initial dose should be lower than in patients with hallucinations due to psychosis (Tadokoro et al. 2007).

24.9 Treatment of Hallucinations in Sensory Impairment

Visually impaired patients may experience complex visual hallucinations, a condition known as the Charles Bonnet syndrome (see Chap. 6). Likewise, individuals with progressive hearing loss may develop auditory hallucinations consisting of music (see Chap. 11), voices (see Chaps. 9 and 10), or other sounds. It is believed that such hallucinations are actually release phenomena due to a deafferentation of the visual or auditory association areas of the cerebral cortex, a process capable of yielding so-called phantom percepts (Menon et al. 2003). Cognitive defects and social isolation may act as additional risk factors. Release hallucinations generally affect the elderly, women more frequently than men. Patients who comprehend their unrealistic nature tend to be affected less severely by them, although they may still be distressed by the fear of imminent insanity. Reassurance and an explanation that the visions or auditory percepts do not imply any kind of mental illness may have a powerful therapeutic effect (Menon et al. 2003). Further therapeutic measures are not always necessary because release hallucinations may cease either spontaneously or upon the termination of social isolation. If warranted and possible, the treatment of first choice is the restoration of sight or hearing, for example, by carrying out a cataract operation, cleaning the meatus externus, or applying hearing aids (Tuerlings et al. 2009). In addition, one may consider the optimization of visual or auditory stimuli. When interventions such as these are unsuccessful, pharmacological treatment may be considered, although the pros do not always outweigh the cons of side effects. Both antipsychotic and antiepileptic drugs have been reported to be effective in case reports and open-label case series. There are currently no randomized trials on the efficacy of those types of medication in patients with release hallucinations. If pharmacological treatment is considered necessary, quetiapine may be a good choice (David and Fernandez 2000) as it is usually tolerated well in elderly populations (Rossom et al. 2010). However, as the dopamine receptor density tends to diminish in old age, initial doses should be very low and they should be increased only gradually. Pharmacological treatment in release hallucinations should preferably be carried out during a limited period of time (i.e., 2 or 3 months) and then tapered off when they are not effective in order to avoid unnecessary and potentially harmful side effects.

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Chapter 25
Experimental Somatic Treatments: Transcranial Magnetic Stimulation in the Treatment of Auditory Verbal Hallucinations – A Meta-Analysis and Review

Christina W. Slotema and Z. Jeff Daskalakis

25.1 Introduction

Transcranial magnetic stimulation (TMS) is a technique in which a strong pulse of electrical current is sent through a coil (see Figs. 25.1 and 25.2). When the coil is placed over a person's skull, this induces a magnetic field pulse in a small brain area, depolarizing local neurons up to a depth of 2 cm. Barker and colleagues developed the first modern TMS device (Barker et al. 1985, 1990). TMS can be used as a brain mapping tool, as a tool to measure cortical excitability, as a probe of neuronal networks, and as a modulator of brain function. It is thought that it can induce longer-lasting effects as a result of long-term potentiation or depression at the neuronal level (Siebner and Rothwell 2003). TMS is non-invasive, has few side effects, and is a relatively safe technique. In the past, epileptic seizures have occurred during repetitive TMS, as it has been applied at high frequency, during a longer time, or at a high threshold. However, since Wassermann developed specific safety guidelines in 1998, seizures have become extremely rare (Wassermann 1998). Side effects such

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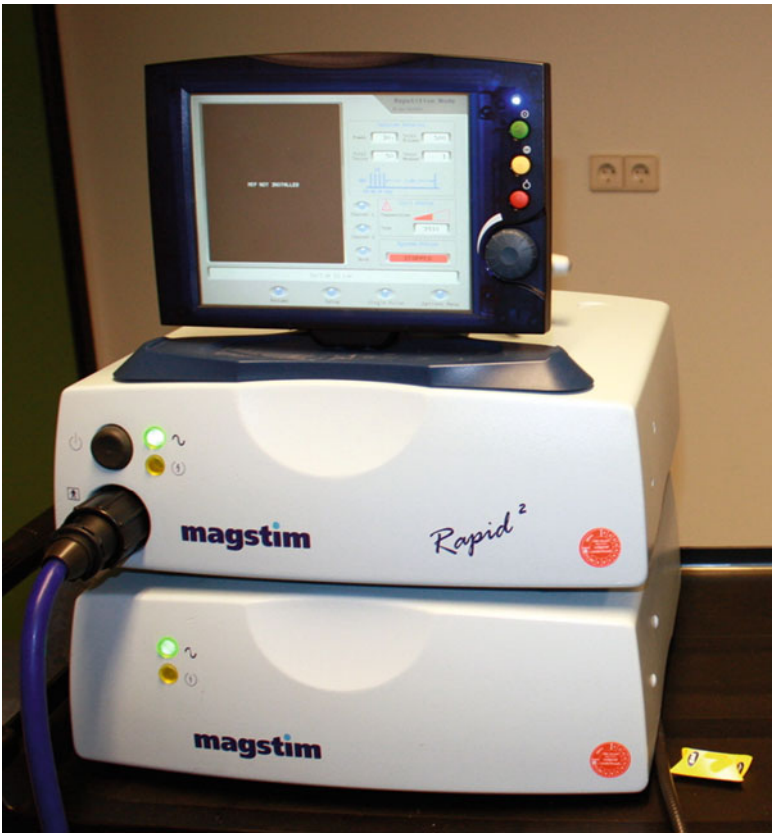

Fig. 25.1 Transcranial magnetic stimulation device

as headache, local discomfort due to direct stimulation of the facial musculature, and transient changes in the auditory threshold have been described, and in order to prevent the latter, earplugs are recommended during TMS treatment.

George et al. (1995) were the first to investigate the effects of rTMS for depression. This was followed by several other studies, and resulted in approval of rTMS by the Food and Drug Administration in October 2008 as a treatment option for depression.

In 1999, Hoffman et al. (1999) started to explore rTMS for the treatment of auditory verbal hallucinations (AVH). They directed the coil at the left temporoparietal cortex (see Fig. 25.3) overlying Brodmann's area 40 (Homan et al. 1987), which is critical to speech perception (Benson et al. 2001). Thus, they were able to ameliorate medication-resistant AVH. Since then, more studies on this subject have

Fig. 25.2 Two types of figure-of-eight coils of the transcranial magnetic stimulation device

been published in the literature. The results of these studies have been summarized in four meta-analyses, which all conclude that rTMS has a moderate to good effect on AVH, with effect sizes ranging from 0.51 to 1.04 (Aleman et al. 2007; Freitas et al. 2009; Slotema et al. 2010; Tranulis et al. 2008). As the number of publications is still increasing, this chapter provides an up-to-date review and a new meta-analysis.

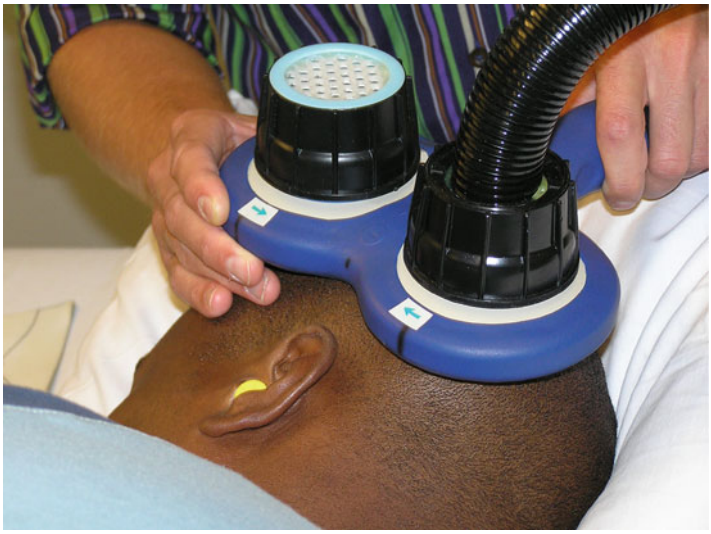

Fig. 25.3 Repetitive transcranial magnetic stimulation is applied to the left temporoparietal cortex

25.2 Methods

25.2.1 Study Selection

The methods for the present meta-analysis were adopted from Slotema et al. (2010). A literature search was performed in PubMed (1990 through January 2011), Ovid Medline (1990 through January 2011), Embase Psychiatry (1997 through January 2011), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and PsycINFO (1990 through January 2011), using the search terms transcranial magnetic stimulation, TMS, repetitive TMS, auditory hallucination, and psychosis.

Criteria for inclusion were:

1. Treatment with rTMS.
2. Symptom severity of AVH was used as an outcome measure.
3. The study was performed in a parallel, double-blind, randomized controlled design using a placebo condition. (We chose for parallel designs only because patients usually do not remain completely blinded in crossover studies, which may influence the results.)
4. The data provided sufficiently exact data to compute Hedges's *g* (sample size, means, and standard deviations or exact *t*, *F*, or *p* values for rTMS main effect for change scores).

5. More than three patients were included per study.
6. Articles were written in English.

When various articles described overlapping samples, only the article with the largest sample size was included.

25.2.2 Data Extraction

The following data were acquired: number of treated patients, mean and standard deviation of the outcome measure at baseline and at the end of treatment (or exact F, t, or p value), study design, and treatment parameters (localization of treatment, frequency, intensity, number of stimuli per session, and number of treatment sessions). When a publication contained insufficient or incomplete data, the authors were contacted and invited to send additional data so that their study could be included in the meta-analysis. All meta-analyses were checked for cross-references.

25.2.3 Effect Size Calculation

Effect sizes were calculated for the mean differences (sham treatment versus rTMS) of the pretreatment-posttreatment change in rating scales. In a random effects model, the mean gain for each study was computed using Comprehensive Meta-Analysis Version 2.0. First, the individual effect sizes for each study were computed; after which, meta-analytic methods were applied to obtain a combined, weighted effect size (Hedges's g). The means of separate studies were weighed according to the sample sizes. A homogeneity statistic, I^2 (Higgins et al. 2003), was used to test whether the studies shared a common population effect size. An I^2 statistic (i.e. 30% or higher) indicated heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. If heterogeneity was high, a moderator analysis was performed wherever possible to investigate the potential influence of moderating factors. Sub-analyses were performed to investigate different treatment conditions, such as localization, frequency, number of stimuli, number of treatment sessions, and total number of stimuli. These parameters were correlated with Hedges's g using Pearson's correlations in SPSS18 (Statistical Package for Social Sciences version 18).

In studies comparing three treatment conditions, the two actual treatments were compared separately with the sham condition. We also computed a fail-safe number because effect sizes can be unreliable due to the omission of studies in which rTMS was not effective (Rosenthal 1979). This fail-safe number is an estimation of the number of missing studies that is needed to change the results of the meta-analysis to non-significant. Side effects and dropouts are presented according to rTMS localization.

25.3 Results

Ten studies were included, with a total number of 308 patients. One hundred and eighty-two of them received real rTMS, while 126 were included in the sham condition. Twenty studies did not fulfil the criteria for inclusion due to a crossover design ($n=5$), overlap with other studies ($n=4$), insufficient data ($n=3$), the use of rTMS as maintenance therapy ($n=3$), the absence of a sham condition ($n=3$), or the absence of 'severity of AVH' as an outcome measure ($n=2$).

Repetitive TMS was directed at the left temporoparietal cortex (i.e. T3P3 in terms of electroencephalogram electrode placements) in 137 patients, at the right temporoparietal cortex (T4P4) in 12 patients, at the left *and* right temporoparietal cortex in 14 patients, and at miscellaneous locations (using fMRI guidance) in 20 patients. Details of the rTMS paradigms are presented in Table 25.1. Most studies applied low-frequency rTMS at 1 Hz and at intensities below the motor threshold.

In three studies, a different localization was used. Lee et al. (2005) chose the right temporoparietal cortex (T4P4) as their focus of treatment. Only one study examined the effects of bilateral rTMS, directed at the left temporoparietal cortex (T3P3) during one half of each session, whereas during the second half, stimulation was switched to the right temporoparietal region (Vercammen et al. 2009). Recent functional magnetic resonance imaging (fMRI) studies indicate that the left temporoparietal cortex is not a general focus of activation during the experience of AVH (Sommer et al. 2008), but rather the right temporoparietal area. Based on these findings, a randomized controlled trial was performed in which rTMS was directed at the focus of maximal hallucinatory activity as assessed with the aid of individual fMRI scans (Slotema et al. 2011).

Table 25.1 rTMS parameters used in the treatment of auditory verbal hallucinations

Study	Location	Frequency (Hz)	MT (%)	Number of stimuli	Number of sessions
De Jesus et al. (2011)	T3P3	1	80	1,200 (day 1 480, day 2 960)	20
Slotema et al. (2011)	T3P3	1	90	1,200	15
Slotema et al. (2011)	fMRI-guided	1	90	1,200	15
Vercammen et al. (2009)	T3P3	1	90	1,200	12
Vercammen et al. (2009)	T3P3 and T4P4	1	90	1,200	12
Rosa et al. (2007)	T3P3	1	90	960	10
Brunelin et al. (2006)	T3P3	1	90	1,000	10
Chibbaro et al. (2005)	T3P3	1	90	900	4
Fitzgerald et al. (2006)	T3P3	1	90	900	10
Hoffman et al. (2005)	T3P3	1	90	900	10
Lee et al. (2005)	T3P3	1	100	1,600	10
Lee et al. (2005)	T4P4	1	100	1600	10
Saba et al. (2006)	T3P3	1	80	300	10

Hz Hertz, *MT* motor threshold, *T3P3* left temporoparietal cortex, *fMRI* functional magnetic resonance imaging, *T4P4* right temporoparietal cortex

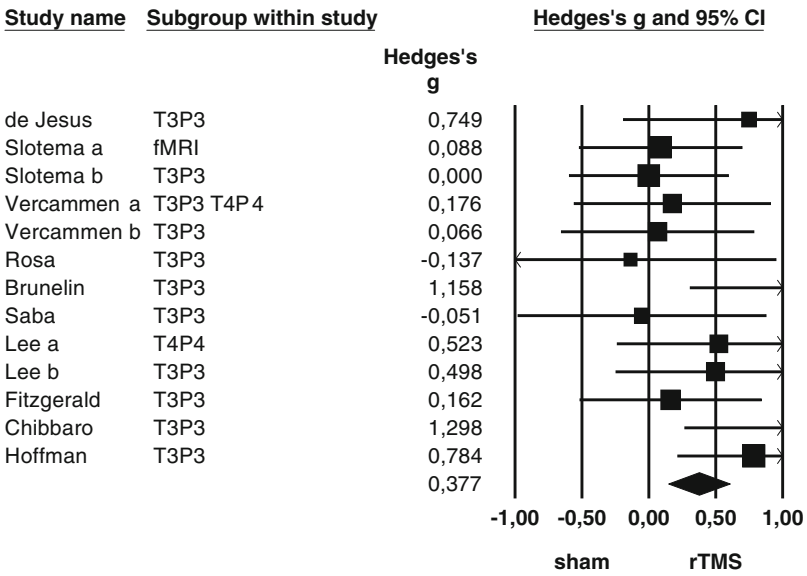

Fig. 25.4 Results of a meta-analysis of rTMS studies involving the treatment of auditory verbal hallucinations

Table 25.2 Reasons for dropout

	T3P3 (%)	fMRI-guided (%)	Sham (%)
Side effects	5 (3.6)	1 (5)	1 (0.7)
Worsening of psychosis	1 (0.7)	1 (5)	3 (2.2)
Other/unknown	1 (0.7)	0	2 (1.6)
Total	7/137 (5.1)	2/20 (10)	6/126 (4.8)

T3P3 left temporoparietal cortex, *fMRI* functional magnetic resonance imaging

The results of the present meta-analysis are presented in Fig. 25.4. Analysis showed that real rTMS is better than sham treatment, the mean weighted effect size being 0.38 (Hedges's g, $p=0.001$). Heterogeneity was moderately low ($I^2=17.9$, $p=0.26$). The fail-safe number was 372 studies.

Only the effects of rTMS directed at the left temporoparietal cortex turned out to be superior to those of sham treatment (Hedges's $g=0.431$, $p=0.005$), with a moderate heterogeneity ($I^2=31.8$, $p=0.15$). A correlation analysis of the effect sizes and the rTMS parameters 'motor threshold', 'number of stimuli', 'number of treatment sessions', and 'total number of stimuli' did not indicate that any of the paradigms used were superior to the others.

The dropouts and side effects are presented in Tables 25.2 and 25.3. It should be noted that these are listed per treatment condition, as a minority of the studies did not include any descriptions of the side effects and/or dropouts per treatment

Table 25.3 Side effects of rTMS treatment occurring in at least 1% of the participants per indication

	T3P3 (%)	fMRI-guided (%)	T3P3 and T4P4 (%)	Sham (%)
Headache	15 (10.9)	3 (15)	4 (33.3)	3 (2.1)
Dizziness	4 (3)	0	0	2 (1.6)
Facial muscular twitching	0	7 (35)	0	1 (0.8)
Scalp discomfort	0	1 (5)	0	0
Cervical pain	0	1 (5)	0	0
Tingling sensation in arm	0	0	1 (8.3)	0
Other	6 (4.4)	1 (5)	0	0
Total	25/137 (18.2)	13/20 (65)	5/14 (35.7)	6/126 (4.8)

T3P3 left temporoparietal cortex, *fMRI* functional magnetic resonance imaging, *T4P4* right temporoparietal cortex

condition. An equal percentage of patients dropped out of the real and sham TMS treatment groups (5.7% and 4.8%, respectively). Side effects were mentioned more frequently in the real TMS group (25.1% versus 4.8% in the sham condition).

25.4 Discussion

The aim of this chapter is to present an up-to-date meta-analysis of the results of rTMS in the treatment of AVH. A significant but moderate effect of and 0.43 respectively 0.38 was found for all included studies *and* for low-frequency rTMS directed at the left temporoparietal cortex alone. The magnitude of the effect sizes per study did not correlate with specific levels of the TMS treatment parameters such as frequency, intensity, or location.

These findings are in concordance with the results of four previous meta-analyses (i.e. Aleman et al. 2007; Freitas et al. 2009; Slotema et al. 2010; Tranulis et al. 2008). However, a note of caution may be in place here. When new treatment strategies are introduced, the initial reports tend to feature relatively small sample sizes and to provide favourable results, while small studies with negative findings do not tend to be published (Emerson et al. 2010). In the course of time, sample sizes tend to increase, and negative findings tend to become published as well. Such trends have led effect sizes to decrease per year of publication (Munafo and Flint 2010). As rTMS is a relatively young treatment method, future studies may show less favourable results. We indeed found a trend towards larger studies being published in recent years, yielding negative results. We therefore take into account that the initially reported positive effects may well disappear when more studies with larger patient samples will be published, but the present state of the evidence allows us to recommend low-frequency rTMS for AVH, especially when the relatively mild side-effect profile and the lack of other treatment options are taken into account.

Only few studies examined the effects of low-frequency rTMS targeted at other brain regions than the left temporoparietal cortex. A reduction in the severity of AVH

after rTMS directed at the right temporoparietal cortex (Lee et al. 2005) could not be replicated by others (Jandl et al. 2006; Loo et al. 2009). Repetitive TMS directed at the left and right temporoparietal cortex (Vercammen et al. 2009) and rTMS directed at foci with maximal hallucinatory activity, as indicated by fMRI findings (Slotema et al. 2011), were not superior to sham treatment. Stimulation of the left temporoparietal cortex and the adjacent supramarginal gyrus, Broca's area, the left primary auditory cortex, and their contralateral homologues revealed only a greater improvement of AVH when the treatment was focused at the left temporoparietal cortex and the adjacent supramarginal gyrus (Hoffman et al. 2007). Furthermore, the effects of rTMS applied to either Broca's area or the left superior temporal gyrus were equal to those of sham treatment (Schönfeldt-Lecuona et al. 2004). It is possible that the facial musculature overlying the skull prevents rTMS from reaching Broca's area, as the electromagnetic pulse reaches a depth of no more than 2 cm (Hoffman et al. 2007). No firm conclusions can be drawn due to the small number of studies, but there is currently no evidence to suggest that locations other than the left temporoparietal cortex are suitable options for the treatment of AVH with rTMS.

In the majority of studies, rTMS was applied with a frequency of 1 Hz. But also, high-frequency rTMS has been studied as a treatment option for AVH (Montagne-Larmurier et al. 2009), yielding a strong clinical response when a frequency of 20 Hz was used. However, the patient population under study was small (11 participants), and no control condition was included, which precludes any firm conclusions regarding this type of treatment. A recent study from the Utrecht group assessed 20-Hz stimulation and 1-Hz stimulation in a double-blind, head-to-head comparison and found no differences between the two treatment arms (De Weijer et al. 2011). In a randomized controlled trial, the effects of low-frequency rTMS preceded by 5 min of 6-Hz rTMS was compared with low-frequency rTMS alone, and again no differences could be revealed between the two conditions (Slotema et al. submitted).

Two case reports described relief from chronic, intractable auditory hallucinations after bilateral and continuous theta-burst TMS (i.e. in a frequency of approximately 50 Hz), respectively (Eberle et al. 2010; Poulet et al. 2009). However, before any large sham-controlled RCTs become available, we cannot recommend high-frequency or theta-burst stimulations for the treatment of AVH.

The effects of rTMS for AVH using a motor threshold higher than 100% are unknown. However, so far, an increase in the number of stimuli and in the number of sessions has never resulted in a significantly stronger reduction of the severity of AVH (Slotema et al. 2011; Vercammen et al. 2009).

The majority of studies have been performed with the aid of a figure-of-eight coil (see Fig. 25.1). H-coils, on the other hand, are designed to maximize the electrical field in deep brain tissues by their ability to summate separate fields projected into the skull from several points around its periphery (Zangen et al. 2005). In an open-label study, eight patients were treated with deep-brain TMS using an H-coil, which resulted in a significant reduction of the severity of AVH (Rosenberg et al. 2011). However, this study also failed to employ a control group. As a consequence, its results need to be replicated in randomized, placebo-controlled, double-blind studies before any firm conclusions can be drawn from them.

25.5 Conclusion

The present meta-analysis of studies using rTMS for the treatment of auditory verbal hallucinations shows mildly favourable results. All of the included studies used low-frequency rTMS, and the majority of them directed the electromagnetic pulse at the left temporoparietal cortex. A significant yet moderate effect was found, which was significantly lower than the results of previous meta-analyses. This would seem to be primarily due to the publication of various new studies with larger samples and negative findings. We therefore take into account that this mildly favourable effect may well disappear when more studies with larger patient samples will get published. So far, no double-blind, randomized controlled trials have been performed applying other rTMS paradigms (using high-frequency rTMS, for example, or a higher motor threshold, or an H-coil) which may have the potential to yield an efficacy superior to that of low-frequency stimulation.

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Chapter 26
Cognitive-Behavioral Therapy

Mark van der Gaag

26.1 Appraisal Is the Foundation of the Cognitive Model of Hallucinations

Medication is the treatment of choice for many types of hallucination, but a lack of results – due to noncompliance and the persistence of residual symptoms, for example – has led researchers to develop various ancillary treatment forms (Pantelis and Barnes 1996). Two decades ago, psychological research focused primarily on coping strategies. But although many patients do apply self-developed coping strategies, they tend to lose confidence in their efficacy over time, while patients with a long history of voice hearing do not always appear to select the most effective coping strategies (Carter et al. 1996; Farhall et al. 2007).

Cognitive-behavioral therapy (CBT) advocates a wholly different approach. In the context of the traditional medical model, which also infused the coping model, the primary variable to be treated is the symptom of disease (e.g., "hallucination") rather than the patient's depression, anxiety, or dysfunctional behavior, which are all considered *secondary* to the hallucinations at hand and only amenable to treatment when the hallucinations themselves are being treated. The cognitive model differs from more conservative variants of the medical model in that its primary goal is not the eradication of the primary symptoms per se but the reduction of distress and dysfunctional behavior. After all, symptoms only become "real" symptoms (as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and other psychiatric classifications) when they cause distress and/or dysfunctional behavior. However, within the context of the cognitive model, it is not so much the symptom itself that is held responsible for causing any distress or dysfunctional behavior but the patient's appraisal of that symptom (Birchwood and Trower 2006b).

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Auditory hallucinations, for example, do not always occur in the context of disease (see Chap. 28). Actually, most people who hear voices lead perfectly normal lives and do not tend to seek any kind of treatment for them. Only when voices are appraised in a catastrophical way they are bound to cause depression, anxiety, social isolation, and so on (Honig et al. 1998; Lawrence et al. 2010). Those who are indifferent to their hallucinations, and live their lives the way they did before, will seldom become psychiatric patients. Those who do become patients are those who appraise their voices in a malevolent way and endow the latter with so much power that they develop a passive and submissive attitude (Mawson et al. 2010). For that reason, CBT for auditory hallucinations focuses on the ways in which voices are being appraised, and aims at a reduction of distress and dysfunctional behavior, even if the hallucinations themselves continue to be experienced.

26.2 Psychological Models for Hallucinosis

In recent years, various psychological models for hallucinations have been developed. Some of the earlier models were based on evidence – obtained from a number of highly intriguing studies – that the mediation of verbal auditory hallucinations may depend on subvocal speech. That finding set the stage for the subsequent neuroimaging of speech-related versus hallucination-related activity in the brain, the investigation of psychological processes underlying speech and hallucinations, and the investigation of the content, appraisal, and metacognitive aspects of auditory hallucinations. All those research avenues yielded valuable new data, but an integration into a unitary model has not yet been achieved, and to date many of the phenomena under study have remained unexplained. All in all, the psychological model of hallucinosis is still tentative and "under construction." And yet it boasts sufficient clinically relevant data to justify the application of cognitive-behavioral interventions, the efficacy and effectiveness of which are small to medium-sized, but stable (NICE 2009).

26.2.1 The Origin of Verbal Auditory Hallucinations

26.2.1.1 Inner Speech and Self-Monitoring Failure

A study of "tension in the throat" showed that automatic speech (or "inner speech") may well underlie the mediation of verbal auditory hallucinations (Gould 1948). Gould used an electromyograph with leads on the lower lip and chin to examine 100 patients diagnosed with schizophrenia. In that study, a hallucinating subgroup of 48 patients showed an increased tension in the muscles of the lip and chin in 83% of

the cases, whereas the nonhallucinating group showed such tension in only 10% of the cases. The author therefore concluded that verbal auditory hallucinations are associated with an involuntary intensification of the psychomotor mechanisms of speech. Another study found similar changes in activity in the tongue and the chin, as well as changes in the patients' breathing amplitude, but no changes in the tension of their arm musculature (McGuigan 1966).

In the years following this pioneering work, many small intervention studies were carried out. Most of them were multiple-baseline studies comparing multiple-treatment conditions with multiple returns to baseline within series of hallucinating patients (Corrigan and Storzbach 1993). Those studies yielded some evidence for the effectiveness of systematic desensitization, operant conditioning (using reward and punishment), the voluntary use of the vocal cords (through humming and gargling), social conversation (which appeared to be incompatible with ongoing hallucinatory experiences), and the manipulation of auditory input by means of earplugs or loud music (see also Chaps. 11 and 28). Favorable short-term effects were recorded for all those interventions, but randomized controlled trials (RCTs) of sufficient power were never performed.

The concept of inner speech continues to play an important role in the cognitive-behavioral model of hallucinations, even though it fails to explain the occurrence of voices in the second or third person or the simultaneous occurrence of multiple voices. To account for the latter phenomena, the model now proposes that hallucinations may arise when the self-monitoring of inner speech is failing. The hearing of external voices and the awareness of one's own verbal thoughts both depend on activity in Wernicke's speech perception area. Wernicke's area "knows" the difference between the two because a corollary discharge feed-forward mechanism "tells" it that thoughts are on their way (Ford and Mathalon 2005). When Broca's speech production area "translates" a thought into a train of words and then sends them off to Wernicke's area, a collateral message is sent to that monitor to allow for its identification as "inner speech." When that monitor fails to inform Wernicke's area, the latter will "conclude" that the words must have an external origin (see also Chap. 21).

26.2.1.2 Intrusions from Traumatic Memories

And yet not all types of auditory hallucination appear to be associated with inner speech. Some individuals experience voices that are clearly related to earlier traumatic experiences. Such voices tend to constitute reexperienced verbal messages, conveyed priorly by people involved in the traumatic situation (Jones 2010). They can perhaps be conceptualized best as intrusions of traumatic memories (or "reperceptive hallucinations"). In contrast, voices attributed to inner speech tend to be involved with the planning and execution of one's present actions. They usually tell the percipients what to do next or threaten him with aversive consequences when he refuses to obey (Jones 2010).

26.2.2 Psychological Processes

26.2.2.1 Source Monitoring

Heilbrun found that 12 psychiatric patients with a history of hallucinations turned out to be insufficiently capable of identifying the words, meaning, and grammatical style of their own spoken sentences following a 1-week lapse of time, as compared to eight nonhallucinating psychiatric patients. Incidentally, the two groups did not differ with regard to their ability to remember verbal material, the stability of their opinions, or the level of their communication skills (Heilbrun 1980). A meta-analysis of 23 studies carried out over the past 30 years confirmed that individuals diagnosed with schizophrenia who are prone to hallucinations tend to attribute self-generated thoughts and utterances to other people (Waters and Badcock 2010). That cognitive bias tends to increase when their attention is directed to the self, and/or when strong emotions are aroused. It has been suggested that this source-monitoring bias may also be a source of verbal auditory hallucinations. However, a drawback of this model is that it does not explain why voices are actually *heard*. It would seem to explain experiences of thought insertion or "indirect Gedankenlautwerden" rather than the occurrence of hallucinations. The bias itself appears to be endophenotypical, as it has also been found during prodromal states and episodes of remission, as well as in siblings of patients diagnosed with schizophrenia (Brunelin et al. 2007).

26.2.2.2 Appraisal

Because verbal auditory hallucinations may differ from the percipient's "inner voice" and the utterances often convey specific themes that are coherent over time (Nayani and David 1996), voice hearers easily appraise them as coming from a different person or agent. When the voices are also appraised as omnipotent or omniscient and the percipient becomes convinced that they have malevolent intentions, anxiety is bound to set in. Once anxious, voice hearers often start to deal with the voices by making promises to them and by obeying their orders and commands (Birchwood and Chadwick 1997). The association between such appraisals and the severity of verbal auditory hallucinations has been repeatedly confirmed (Mawson et al. 2010). And yet changing those appraisals does not always lead to a reduction of the severity of the hallucinations at hand. In order to attain that goal, interpersonal aspects and self-esteem need to be addressed as well (Mawson et al. 2010).

26.2.2.3 Interpersonal Aspects

The relational aspects of hallucinations were noticed many years ago. In hospitalized patients, for example, who may experience extreme hallucinations, therapists found it hard to relate to the patient at all (Erickson and Gustafson 1968). The average

therapist is available for no more than an hour per week, whereas in such cases, the voices may be present 24×7. Many patients do not feel free to discuss their voices because they appear to be listening – and speaking – all the time. That relational inequality was examined for the first time by Gilbert and Birchwood (2001), who demonstrated that the presence of powerful voices tends to correlate positively with subordinate behavior (including flight-or-fight reactions) and depression. They also found that the concomitant tendency to consider oneself as low-ranking in a hierarchy does not only characterize the relationship with the voices, but all of the patients' social relationships (Birchwood et al. 2000; Gilbert et al. 2001). Moreover, their research showed that this perceived low-ranking position is not due to depression, distress, or the power with which the voices are endowed. Nor do the voices themselves lead to depression, or the appraisal of power to the occurrence of voices. Instead, the authors found that the distorted perception of one's own social rank and power leads up to the appraisal that the voices are powerful, and also to distress and depression (Birchwood et al. 2004).

Self-criticizing thoughts occurring in the context of depression appear to have a role similar to that of voices in psychosis: they serve to punish the patient. In either case, the patients' own attempts to stop them tend to be futile. Gilbert (2009) developed a therapy based on the two-chair technique borrowed from Gestalt therapy, and combined it with evolutionary thoughts on the "soothing system" of social mammals. In young mammals, the "threat system" needs to be inactivated by a caring parent to allow for a normal development. Only when sufficiently caressed and comforted will the young mammal feel capable of exploring the world. By repeatedly experiencing safety and soothing, that feeling can be internalized, and the adult thus treated is able to sooth himself to overcome any inappropriate anxieties and feelings of threat. In patients who experience hallucinations, the threat system tends to be permanently active due to the presence of threatening voices. Gilbert's method consists of introducing the patient to thinking about what a caring and soothing voice might say. Thus, the patient may gradually learn to rely on the trustworthy, soothing "voices" and to escape the terror caused by the threatening ones (Gilbert 2009).

Two other interpersonal aspects are shame and stigmatization. Shame for being psychotic, and attempts to hide from others that one may in fact be different (or that one is using medication, etc.) tend to lead to a heightened self-awareness and social phobia anticipating the possible rejection by others (Birchwood et al. 2007).

26.2.2.4 Self-esteem and Depression

Low self-esteem plays a pivotal role in the continuation of hallucinatory experiences. Patients with low self-esteem also tend to be more severely depressed and to experience verbal auditory hallucinations with a higher degree of severity and associated distress (Smith et al. 2006). Beliefs about the omnipotence and malevolent intentions of voices, as well as low self-esteem, contribute independently to feelings of depression in patients experiencing persistent verbal auditory hallucinations (Fannon et al. 2009). Fannon et al. also conclude that low self-esteem is crucial to

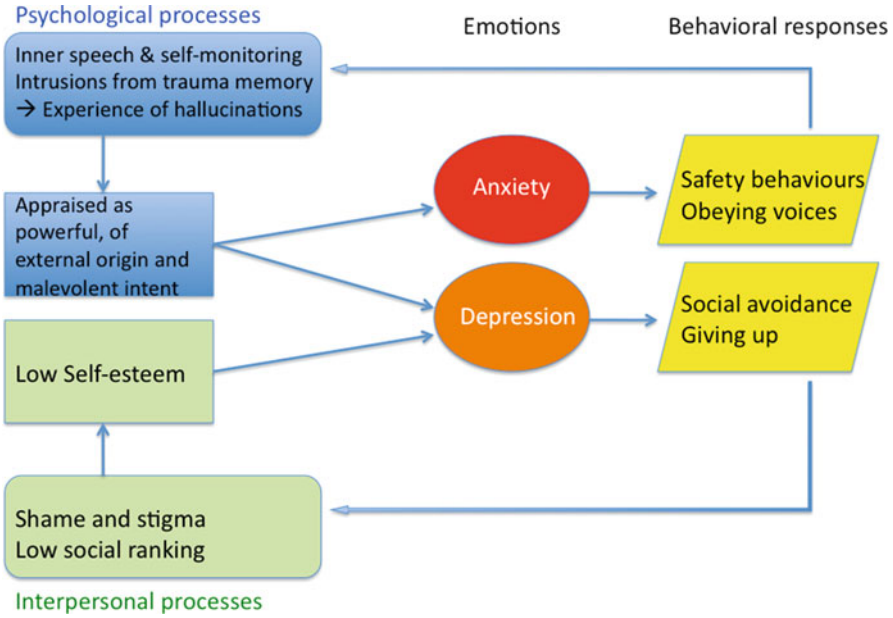

Fig. 26.1 The psychological model of verbal auditory hallucinations

our understanding of any affective disturbances that may occur in voice hearers and that therapeutic interventions therefore need to address the way the voices *and* the self are being appraised.

26.2.3 Conclusions Based on the Psychological Model

Although the psychological model of auditory hallucinations (see Fig. 26.1) is far from complete and leaves many aspects of their mediation unexplained, it has certainly aided to increase our insights into these phenomena. First of all, we have learned that the propensity to hear voices is distributed continuously in the general population (Van Os et al. 2010). Secondly, we now have two basic explanatory models at our disposal (the inner speech model and the self-monitoring model), whereas a third model (i.e., the reperception model) suits those cases where intrusive traumatic memories are reexperienced in the form of hallucinations. In the third place, we now know that hallucinations tend to lead to distress when they are being appraised as powerful, as having an external source, and as having malevolent intentions, whereas low self-esteem contributes independently to the severity of verbal auditory hallucinations and of depression. In the fourth place, we now know that anxiety tends to lead to submissiveness to the voices, as well as to a tendency to obey and appease them, while depression often entails feelings of defeat and surrender. Fifth, we have learned that feelings of shame and stigmatization may entail severe

anxiety, a social phobia-like self-awareness, and attempts to avoid exposure to other people and their judgments. Sixth and finally, we have learned that those behavioral responses tend to lead to a consolidation of the appraisals and to the inability to experience any emotionally corrective experiences.

26.3 Cognitive-Behavioral Therapy

CBT targets the ways in which events are being appraised. It puts the appraisals in perspective through a collaborative approach in which other possible explanations for the events in question are considered together with the patient and in which any concomitant feelings and behavioral reactions are extrapolated when they are considered valid. To find out which type of appraisal may suit an event best, the patient is challenged to carry out behavioral experiments and to experience the adequacy or inadequacy of different approaches. The cognitive aspect of CBT involves the guided discovery of alternative explanations and alternative reactions. The behavioral part involves the testing of alternative ways to deal with particular situations and attempts to change one's feelings about them. The discovery that catastrophes fail to occur, e.g., that resisting the voices' commands does not lead to any kind of punishment, is a powerful way to diminish distress.

26.3.1 Education and Normalization

In addition, CBT for hallucinations has various normalizing and educational aspects. Many patients already feel better when they hear that each and every year, about 2% of the population start to experience hallucinations, and that at any given moment some 4% of the population are experiencing them (Van Os et al. 2010). It is also highly educational to tell patients that most of those people are not bothered very much by their voices, that they continue to live the way they did before, and that people with severely threatening voices can learn to ignore them and to continue with the things that make their lives worth living and meaningful.

When patients express the wish to learn something about their voices and the way they are mediated, it may be helpful to tell them about the sensitization of the dopamine system which gives rise to intrusions and hallucinations, but also makes them jump to conclusions, and renders them overly confident about those conclusions. One may also consider explaining that voices have a certain tendency to make people anxious or angry, i.e., that they "thrive" or "feed" on anxious and angry feelings. Patients may well have noticed that strong emotions make the voices louder and more persistent. Therefore, they tend to acknowledge that it is good advice to try to stay calm whatever the circumstances and to imagine that a "game" is being played where the one who shows any strong emotions will lose.

26.3.2 Challenging the Way Voices Are Appraised

Appraisals that tend to aggravate the severity of hallucinatory experiences are those that exaggerate their power, characterize them as omnipotent and omniscient, place their source in the external world, endow them with malevolent intentions, and make believe that they can actually do harm.

26.3.2.1 Power

Threatening voices and command hallucinations can pose a danger to the patient and his environment. Many patients are bent on resisting any dangerous and aggressive commands they may hear and on trying to appease their voices without letting themselves be lured into dangerous or aggressive behavior. But not all patients are able to resist their voices. The risk that they will comply with command hallucinations can be reduced by changing the patients' beliefs about the voices' power (Birchwood and Trower 2006a; Trower et al. 2004). Trower and colleagues tested the effectiveness of cognitive therapy in command hallucinations by randomizing 38 patients who had recently complied with their voices' commands and had suffered the consequences. The control condition was treatment-as-usual, and the patients were followed up after 6 and 12 months. In the cognitive therapy group, the authors found large and significant reductions in compliant behavior, with an effect size of 1.1. Improvements were also recorded in the patient group (but not in the control group) as regards the power attributed to the voices, the perceived need to comply, and the levels of concomitant distress and depression. No changes in the frequency, loudness, and content of the voices were recorded. The differences were still significant after 12 months of follow-up.

Beliefs about omniscience and omnipotence can be challenged with the aid of behavioral experiments. "Are those omniscient voices able to predict the headlines of tomorrow's newspaper?" "Do they possess knowledge that you do not already possess yourself?" "Is it possible to verify their knowledge?" Answers to questions such as these can be very revealing. The same method is applicable to beliefs about the voices' alleged omnipotence. Sometimes a shortcut can be taken by telling the patient that you yourself, as a therapist, have dealt with dozens of threatening voices, and that they are all mouth but no trousers. An alternative, and perhaps more elegant, way is to encourage the patient to look for examples of what happened when he refused to do what the voices commanded him to. He may then become aware that he has in fact experienced many occasions in which his refusal to obey failed to have any consequences.

Another elegant way is to draw the voices. Being unable to act, they do not have any arms or legs. Being only capable of seeing what the patient sees, they probably have no eyes of their own. Being reluctant to listen to the patient's pleas, they may well have no ears either. One ends up with the cartoon of a smiley, having nothing but a mouth that is solely capable of repeating the same old stuff over and over again.

26.3.2.2 External Hallucinations Versus Intrusions

A problem with external voices is that they do not consist of any actual sounds. If so, anyone would be able to hear them, which is obviously not the case. When the patient believes that he has a natural radio receiver inside his head – which is of course highly improbable – then one might suggest that it should be possible to disrupt the radio waves received by his brain. A cap made of aluminum foil (also known as a cage of Faraday) is sometimes used by physicists to create an anechoic space. Such a device prevents electrical fields to enter from the outside and vice versa, thus reducing the power of high-frequency radiation with 120 dB. Elaborating on that line of thought, myriad behavioral experiments can be thought of to test the patient's hypotheses and to challenge his beliefs about the alleged radio receiver.

26.3.2.3 Identity, Goals, and Meaning

Voices are there for a reason. What do they want to accomplish? Do they want to punish the patient? And if so, why? To destroy the patient? And do they have any reason to want this?

26.3.3 Challenging the Content of Voices

Voices can say many different things. Some of them constantly humiliate the patient by telling him that he is a loser, that nobody cares for him, that he is incompetent, or that he would be better off dead. Is all that true? Did the patient never gain anything? Has there never been anyone who cared for him? By exploring the voices' contents, many of the classical CBT questions can be put forth: Is it true what the voices say? And if it is true, is that something to worry about? And if it is something to worry about, is there a way to cope with it and preserve one's quality of life?

26.3.4 Changing the Patient's Attitude Toward His Voices and His Safety Behaviors

When it is possible to raise some doubt, it is time to encourage various behavioral changes. The patient might consider to limit the time spent with his voices, to pick up the routines of daily life, and to regain important social roles that lend meaning and fulfillment to his life. Also, safety behaviors must be broken down in order to accomplish the experience that any anticipated disastrous consequences fail to happen.

26.3.5 The Effects of CBT for Hallucinations

The effect sizes of CBT for voices are varying. The first report of CBT in psychosis was published some 60 years ago (Beck 1952). Structural research into the efficacy of CBT for this condition started about two decades ago in the UK, and in 2003, the results of meta-analyses entailed a recommendation for CBT in the psychosis guidelines of the National Institute of Clinical Excellence and in those of many other countries. In meta-analyses of trials with general CBT for psychotic symptoms in general, the effect sizes vary from small to medium-sized (NICE 2009), whereas trials with CBT for command hallucinations and other specific targets tend to show larger effect sizes (Trower et al. 2004). As the number of RCTs in those meta-analyses is large and the findings are robust, CBT for hallucinations is now accepted as an evidence-based treatment for hallucinations as well as for psychosis in general.

26.4 New Developments

CBT has always focused on the contents of thoughts and on thinking styles. Recently, the focus has shifted to issues such as interpersonal relations, loss and trauma, self-esteem, acceptance, metacognitive processes, and cognitive biases. There is a growing trend to work with schemas, emotion regulation, interpersonal relationships, and a more accepting relationship with one's thoughts and one's self.

26.4.1 Competitive Memory Training

Competitive memory training (COMET) is based on the notion that a therapy is successful when it succeeds to change the hierarchy of relevant neural networks and the order in which they are activated (Brewin 2006). In depression, it is quite easy to activate depressing thoughts and memories (i.e., mood-induced memories), to ruminate on them, and to induce feelings of defeat and entrapment. A successful treatment reinforces the neural networks that are incompatible with so-called negative networks. When instead "positive" networks are activated over and over again, they may well move up in the hierarchy of networks and come to surpass the negative ones. COMET teaches to reexperience personal memories that are incompatible with the dominant voices' messages. For instance, when the voices go on about a person's alleged incompetence, then the advice is to reexperience a memory of earlier competent behavior (e.g., scoring a winning goal) and to practice reexperiencing that memory five times a day. During the second stage of treatment, the positive and negative networks are activated in tandem. While reenjoying the winning goal, the patient is requested to "turn off" the audience's imagined cheering and to imagine the voices telling him again that he is a loser while he continues to enjoy the feelings of joy and pride associated with the winning goal. Most patients are able to accomplish

that within a single session, and many of them report to then be able to tolerate the voices without being overcome by depressive feelings. During the third stage of treatment, patients are taught to distance themselves from the voices by "zooming out" – by turning the voices' volume down or by "watching" them from the last row in a theater with an attitude and posture that expresses boredom. COMET is a transdiagnostic technique that has proved to be effective for such varying conditions as eating disorders, panic disorder, and personality disorders. Applied to hallucinations, COMET primarily reduces depression. That effect is accomplished by the reduction of power attribution, the improvement of self-esteem, the acceptance of the voices, as well as a less submissive attitude (Van der Gaag et al. 2010).

26.4.2 Metacognitive Training

Metacognitive training (MCT) is based on scientific evidence regarding cognitive biases in psychosis and designed to teach patients to be aware of those biases and to prudently work around them (Moritz and Woodward 2007). The biases involved are working toward conclusions, attribution biases, problems with theory of mind, and biases against disconfirmatory evidence. The training consists of two blocks of eight sessions each, in which different issues are addressed in parallel. A small – and unfortunately underpowered – study found small to medium-sized effect sizes that were statistically nonsignificant but favored MCT above staying on a waiting list (Aghotor et al. 2010).

26.4.3 Mindfulness Training

Detached mindfulness has multiple components, requiring the activation of metacognitive knowledge, metacognitive monitoring and control, the suspension of conceptual processing, attentional flexibility, and a decentered relationship with one's own thoughts (Wells 2005). Those cognitive skills can be of aid to put hallucinations in perspective. The field is only just developing, and there are a small number of case studies as well as a single – underpowered – controlled feasibility study that found nonsignificant changes favoring the mindfulness condition over staying on a waiting list (Chadwick et al. 2009).

26.4.4 Compassionate Mind Training

Compassionate mind training (CMT) targets shame and self-criticism, as well as the ensuing submissiveness and negative affect. With the aid of the two-chair technique, a criticizing voice (or "inner bully") is interviewed, and the criticisms are compared

with the patient's personal needs and distresses. The patient is then encouraged to reply to himself with warmth and compassion rather than with criticism. Case series reports are promising (Mayhew and Gilbert 2008), and an RCT is underway.

26.5 Concluding Remarks

Cognitive-behavioral therapy has a well-established track record that proves its efficacy, effectiveness, and cost-effectiveness for verbal auditory hallucinations. The effect sizes are small to medium-sized and in need of further improvement. The work that is currently going on is aimed at the further development of the cognitive model of hallucinations, which will hopefully allow for more targeted interventions to be developed and tested. Recently, a number of techniques have been developed that do not primarily focus on the content of thoughts and thinking styles but rather on emotional processing and the acceptance of persistent symptoms by finding a decentered perspective that gives room for recommitting to valuable personal goals and social roles in the community.

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Chapter 27
Groundwork for the Treatment of Voices: Introducing the *Coping-With-Voices Protocol*

Willemijn A. van Gastel and Kirstin Daalman

27.1 Introduction

Kenny is 35 years old. He has been hearing voices since he enrolled in university. He has endured three psychotic episodes, which prevented him from successfully finishing his education. For 3 years, he has been working as a library assistant, but last autumn he was fired. Due to a lack of concentration, he tends to make many mistakes, and as part of his negative syndrome, he frequently oversleeps. He suffers from derogatory voices and has a delusional system in which he imagines himself to be a target of various secret organizations. His physician advised him to seek specialized treatment for those symptoms and referred him to our Voices Clinic. While his medication was being optimized, he also started with the Coping-With-Voices Protocol.

This chapter introduces the Coping-With-Voices Protocol as a first aid for patients who experience distressing voices. Each step in the program is designed to yield a quick reduction of distress through simple and practical interventions. The Coping-With-Voices Protocol aims for immediate effectiveness, right from the very first session, and requires no extensive prior training of the healthcare practitioner or the patient. The method was developed at the Voices Clinic of the University Medical Center Utrecht. It can be applied by family physicians as well as professionals working in psychiatric hospitals or any other type of mental health service and proceeds from various existing approaches such as psycho-education, stimulating daily activities, and (the shaping of) adaptive coping mechanisms (for an overview, see Farhall 2010). It shares some of the elements characteristic of cognitive-behavioral therapy (CBT) and Hallucinations-focused Integrative Therapy (HIT) (see Jenner 2010 for an overview). Its principal aim is the exploration – in close collaboration with the patient – of those occasions on which the voices are most disturbing and of ways in

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which they can be dealt with. By assessing the efficacy of the coping mechanisms already applied, the most successful ones can be selected for further elaboration, while the unsuccessful or even harmful ones can be replaced by new and better ones. The first step of the Coping-With-Voices Protocol is to provide psycho-education for the hearing of voices, and – if applicable – for psychosis.

At our Voices Clinic, the Coping-With-Voices Protocol is offered as an initial treatment step to all voice hearers in order to lower the threshold for any further treatments that may be necessary and to establish a therapeutic alliance that is solid enough to allow for more demanding types of therapy. The treatment program offers the patient some basic knowledge about voices and psychosis, while the healthcare professionals involved are allowed to gain some insight into the unique and often complex world of the patient's voices and delusions. As the therapy also aims to optimize the patient's motivation for further treatment, quick results are of crucial importance. Other advantages of this treatment method are its low level of abstraction and its applicability to patients suffering from poor insight, concentration problems, or a lack of motivation.

While medication is usually prescribed to decrease the frequency and severity of voices, the Coping-With-Voices Protocol aims to help the patient cope with the impact that the voices may have on his daily life. As with CBT, the patient's active participation is mandatory. In contrast, however, the Coping-With-Voices Protocol does not require the patient to change his ideas about the voices, thus making it more easily applicable. In some cases, the therapy itself may suffice to bring the distress down to an acceptable level. For example, patients who only experience voices under exceptionally strenuous or stressful circumstances may learn to avoid those circumstances and to stop the voices effectively once they set in. More persistent types of hallucinations, however, require more extensive CBT or pharmacotherapy.

The Coping-With-Voices Protocol comprises psycho-education, mapping of the voices, coping techniques, stimulating healthy living, stimulating a positive outlook, and the prevention of relapse. In what follows, each of those issues will be explained in detail and illustrated with the aid of case vignettes.

27.2 Psycho-Education

Psycho-education basically involves the explanation of the results of scientific studies about auditory verbal hallucinations. Some of those studies report on the benefits of psycho-education for psychotic patients. Although an increase in insight through psycho-education appears to correlate with an increase of depression and a worsening of daily functioning (Trauer and Sacks 2000), the majority of therapists nonetheless consider it an effective treatment method. A review of studies reporting on psycho-education for patients diagnosed with schizophrenia by Lawrence et al. (2006) concludes that brief and preferentially groupwise treatment reduces positive as well as negative symptoms. A recent randomized controlled trial in an at-risk population suggests that types of psycho-education that aim at a

normalization of symptoms aid to reduce the level of distress and to prevent any catastrophical delusional explanations (Rietdijk et al. 2010). Such a normalizing approach may well be the key element of the beneficial effects of psycho-education. In our clinic, we always emphasize that the hearing of voices does not necessarily imply losing control or developing a severe psychiatric disorder. Some examples of the topics we discuss are the following.

27.2.1 Who Hears Voices?

Voices are probably best known as a symptom of schizophrenia and other psychotic disorders. However, they are also experienced in the context of personality disorders (e.g., borderline personality disorder (see Chap. 10) and schizotypal personality disorder) and neurological disorders (e.g., the auditory variant of the Charles Bonnet syndrome, epilepsy, and tinnitus), as well as by otherwise healthy individuals. Approximately 15–20% of the general population hear voices at least once in their lives (Tien 1991). The majority of them are not bothered by those voices and therefore never seek any kind of help or treatment for them.

27.2.2 Brain Activity

With the aid of functional magnetic resonance imaging (fMRI), our research group demonstrated that the right cerebral hemisphere shows an increase in activity during verbal-auditory hallucinatory experiences, as opposed to the predominantly left-sided activity co-occurring with speech (Sommer et al. 2008; Diederen et al. 2010; see also Chap. 9). It may well be that, due to a lack of right-hemispheric inhibition, the homologues of Broca's and Wernicke's areas do not recognize the activity as coming from within the brain itself and thus misinterpret it as an externally generated voice (for an explanation of this default-corollary-discharge mechanism, see Chap. 21). Moreover, voices were found to be preceded by a change of activity in the parahippocampal gyrus, which would seem to imply that memories are involved in their mediation (Diederen et al. 2010).

27.2.3 Treatment Options

Broadly speaking, two kinds of treatment can be distinguished: the elimination or reduction of the voices themselves and the elimination or reduction of the ensuing distress. For the first purpose, antipsychotic medication can be prescribed, whereas for the second purpose, CBT or the Coping-With-Voices Protocol can be offered.

The hearing of voices is often accompanied by delusional ideas and formal thought disorders. Although such accompanying symptoms tend to be less recognized by patients, they may exert an even greater impact upon their social functioning. Therefore, we also provide information about those symptoms – illustrated with clear examples – to help patients to recognize them and find out how they apply to their own situation. Patients often wonder how it is possible that they hear voices while nobody in their vicinity is speaking. Knowing the answer about their endogenous origin can give them a sense of enormous relief. Those who foster idiosyncratic – and especially delusional – ideas about their origin may be convinced that they come from the neighbors or the police, from devils, criminals, and so on. In such cases, it may be difficult to discard the patients' own ideas. By providing them with our neurological explanation, an alternative and less threatening possibility is offered. The following case vignette describes how this may work out in actual practice.

For years, Kenny believed to be the only one who could overhear secret messages meant for the CIA. During psycho-education, he learned that the hearing of voices is a lot more common than he thought and that they often summon associations with secret agencies. He found himself trying to convince a fellow patient that she could not possibly hear her deceased uncle and was then told by her that she did not see why the CIA would be so interested in him. Although this did not immediately change his conviction, merely being provided with such an alternative explanation made him less certain about his own ideas.

27.3 The Mapping of Voices

To gain insight into the specific situations and moments of the day in which the voices are present, patients are asked to fill out a registration form (see Table 27.1) where they can indicate date and time and the activity or situation preceding or accompanying the voices. In addition, they are requested to rate the degree of ensuing distress (on a scale of 0–10). Patients often find this difficult and alarming because they now have to actively focus on those frightening experiences rather than ignoring them as much as possible. Moreover, chances are that they have had prior negative experiences when discussing the voices with others and therefore ceased to do so. Voices frequently prohibit the patient to talk about them. As a consequence, this treatment phase can be very difficult. However, it is also one of

Table 27.1 Mapping-of-voices registration form

Day and time	Location	Content of voice	Distress
Wednesday 5:30 p.m.	Supermarket	"They are looking for you, go home and hide."	I felt frightened, and went home
Thursday 1 p.m.	Library	"It's quiet, it's quiet, it's quiet, it's quiet."	Only a little bothered in the beginning, but able to ignore later on
Friday 9 p.m.	Birthday party of father	Various voices at once, making me feel insecure	Went upstairs for a while, voices calmed down only a little

the most important phases of the Coping-With-Voices Protocol because of its potential to identify strategies that can be used during the actual treatment phase that is to follow.

Kenny discovered that he was more bothered by the voices in crowded places and especially when he was sad and distressed. He noticed that they had less impact on him when he was at the library. They were also less prominent when he heard the sound of the traffic rushing by. The traffic noises appeared to drown out the voices, making them almost inaudible.

As voices tend to be more upsetting in the early morning and the late afternoon, at those moments coping techniques can be extra helpful.

27.4 Coping Techniques

Another important element of the Coping-With-Voices Protocol is the exploration of different techniques that can provide relief from the voices and associated distress. Those techniques can be physiological, cognitive, or behavioral in nature (Farhall et al. 2007). Although they are widely applicable, their effectiveness varies in individual cases. It is therefore helpful to assess each strategy individually with each patient. People who have already developed their own coping strategies – sometimes even unknowingly – tend to use only a limited number of them and can be quite oblivious to alternatives. By extending their repertoire, and thereby giving them a chance to try out different coping techniques, they have the opportunity to pick those that work best for them.

Patients participating in the Coping-With-Voices Protocol receive a list of coping techniques (see Table 27.2) and are asked which ones they have already adopted and which of those were successful. There may well be strategies on that list that they never tried before but may nonetheless prove helpful. Although the use of coping strategies has been studied extensively (e.g., Farhall 2010), it remains unclear to which degree they can contribute to the improvement of symptoms (Hayashi et al. 2001; Sayer et al. 2000; Nayani and David, 1996; Wiersma et al. 2001). Still, coping strategies continue to be an important aspect of most psychosis therapies.

The list we use in our Voices Clinic proceeds from information provided by our patients and from the literature (see the reference list at the bottom of this chapter).

After patients have experimented with all the coping strategies, they are requested to list their own "top five." This top five is then printed onto a small card for them to keep in their wallet as a reminder. Obviously, the strategies cannot be applied 24/7, but it may be comforting to have a few options at hand when the voices are most distressing.

By mapping his voices, Kenny learned that visiting the library and hearing the sound of traffic could bring him considerable relief. He now visits the library when the voices are particularly distressing. As sitting along the highway is not his favorite pastime, he recorded the sound of cars passing by and plays it on his headphones

Table 27.2 List of coping strategies

1.	Talking to others
2.	Sleeping
3.	Thinking about something else
4.	Reading (out loud)
5.	Using earplugs (right, left, or in both ears)
6.	Listening to music (with or without headphones)
7.	Listening to a certain type of music
8.	Singing
9.	Humming
10.	Whistling
11.	Listening to the radio
12.	Watching television
13.	Adjusting body position
14.	Relaxing
15.	Indulging in a hobby
16.	Holding water in the mouth or opening the mouth wide
17.	Chewing gum
18.	Physical activity (i.e., strolling, running, cycling)
19.	Talking back to the voices, negotiating with them
20.	Ignoring the voices
21.	Talking out loud (i.e., naming objects in the environment)
	Patients are always asked for their own unique coping strategies: "Are there any other things that you have tried, and that are not on the list?"
22.	…
23.	…
24.	…

when he needs to. Kenny also discovered that visiting the library worked out best in the morning, whereas in the evening the sound of traffic was more helpful. In addition, he found out that singing sometimes helped against the voices. This was new to him, and he was thrilled to use this strategy at home when he was alone.

27.5 Healthy Living

For patients who are bothered or distressed by their voices, it is important to have enough daytime activities and distractions to shift their focus of attention. Even for those with severe negative symptoms, minor changes in their daily routine may improve their mood and render them less vulnerable to their voices.

On good days, Kenny strolls around the city, making small talk with the people he meets. He has been taking the same route for years, so he has become acquainted with quite a few of them. On days such as these, he may well be hearing voices,

but chatting helps him to ignore them. During the winter, however, he is liable to depression. One morning, when taking a stroll, a neighbor called out to him, "Awful weather, isn't it?" upon which the voices immediately claimed that the man had called him awful and that he was an awful person. The voices went on to comment on his dirty clothes and on the way he walked and suggested that he looked shabby. Kenny got very upset and tried to reach home as soon as possible. During the weeks that followed, he hardly left his home at all, which made him feel even worse. His therapist went over various aspects of healthy living with him.

27.5.1 Sleep

When Kenny became more psychotic he started to sleep during the daytime. As a consequence, he developed nighttime insomnia. With psycho-education on the beneficial effects of daylight on mood, and the influence of melatonin on sleep, he eventually became motivated to readjust his sleeping pattern.

27.5.2 Daily Activities

Kenny was asked how he spent his days and whether he enjoyed it. He had to admit that most of the time he was watching movies to avoid going out. Because of his mood, he had forgotten about the things that used to bring him joy, and so he had to think back: What did he use to like? He remembered enjoying soccer in high school and was advised to give that another try. With the help of his therapist, he contacted a nearby soccer club and now goes to practice once a week. The therapist also advised him to try out some new activities. As a result, he joined his cousin in a chess club.

27.5.3 Social Contacts

Having a social life is important for everyone. But it is particularly important for voice hearers because talking has the capacity to eliminate the hearing of voices by activating the same brain areas that are involved in their mediation. An actual conversation is therefore capable of stopping verbal-auditory hallucinatory activity in some patients. Moreover, talking with others helps us to stay in touch with reality and to correct delusional beliefs at an early stage. When listening to voices on one's own, chances are higher that one starts to believe them.

Kenny realized that he benefitted from his social contacts at the library and was pleased with the new ones at the soccer club and the chess club.

27.5.4 Physical Exercise and Eating Habits

Due to the release of endorphins, physical exercise is an effective way to improve one's mood. It also has a positive effect upon body weight, which can be a critical issue when using antipsychotic medication. The best way to lose weight, however, is to follow a healthy diet.

27.5.5 Cannabis

The use of cannabis and the risk of psychotic symptoms have consistently been found to be associated (for a review, see Moore et al. 2007). The use of cannabis is associated with higher symptom severity, an increase in the number of relapse episodes, and a worse outcome (for a review, see Linszen et al. 2004). Two of the psychoactive compounds of cannabis have been found capable of affecting psychotic symptoms, one being cannabidiol, the other, tetrahydrocannabinol (THC). Cannabidiol is thought to have some short-term beneficial effects upon anxiety and stress (Zuardi et al. 2006; Morgan and Curran 2008) but this advantage is outweighed by the increased risk for psychosis due to the other compound, THC (DiForti et al. 2009). In individuals who hear voices, quitting on cannabis can lead to a reduction of psychotic symptoms and to a considerable improvement of one's mental health in the long run.

Prior to his first psychotic episode, Kenny had never used any cannabis. However, during his stay in the hospital, the other patients had advised him to try it to alleviate his anxiety. Unfortunately, it took him some time to realize that the short-term benefits did not outweigh the long-term adverse effects. Psycho-education on this issue helped him to reduce his cannabis use.

27.6 Focusing on the Positive Aspects of Life

Patients who visit our Voices Clinic often suffer from a depressed mood due to the negative content of their voices. This can have a negative effect on their self-esteem. Unfortunately, it also works the other way around: having a low mood and self-esteem can make a person more vulnerable to the hearing of voices. To break this vicious cycle, patients can be stimulated to focus their attention on more positive aspects of life. This can be done, for example, with the aid of a diary, in which they write down three positive things about themselves that happened during the day.

Three positive things that Kenny wrote down are:

I did my groceries this morning.
My neighbor told me I looked happy.
I went for a drink with my best friend.

Table 27.3 Kenny's warning protocol

Name: Kenny

Which signals can predict a relapse in your case?

- *I can't sleep well, I wake up several times during the night, and I lie awake. I tend to stay at home and don't answer the phone. I get irritated quite easily, and become more paranoid.*

What are proper actions for you to undertake?

- *Talk about the voices with my father*
- *Keep taking my pills*
- *Play games on my computer*

What are the things that you shouldn't do?

- *Stop taking my pills*
- *Unplug my telephone and my doorbell*
- *Watch thrillers*

What should the people around you preferentially do?

- *Keep in touch with me, although not too much*
- *Ask whether I would like to talk about it, rather than just ask questions out of the blue*
- *Listen to what I have to say about my voices without immediately telling me that they are not real and that I am merely imagining them*

What shouldn't they do?

- *Call up on me various times a day*
- *Give me their advice or opinion all the time*
- *Urge me to come along to parties, shopping malls, or other crowded places*

27.7 Relapse Prevention

For those who are at risk for novel psychotic episodes, it is important to learn to recognize any symptoms and signals that may precede them and to take precautions to avert them. Patients in our clinic are therefore requested to write down which warning signals they (or their families or friends) are aware of and which actions should be undertaken once they occur. An example of the ensuing warning protocol can be found in Table 27.3.

27.8 Conclusion

In this chapter, we provided patients who hear voices an introduction to the Coping-With-Voices Protocol, a treatment method for patients who hear voices developed at the Voices Clinic of the University Medical Center Utrecht. The therapy's principal focus lies on the improvement of coping techniques, and each of its constituent parts aims to quickly and simply reduce the distress caused by the voices. The Coping-With-Voices Protocol can be applied by nurses, physicians, and psychologists, although it works best when the same professional can also offer further treatment (in the form of medication, cognitive-behavioral therapy, or both), thus benefitting from the working alliance established during this first treatment step.

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Chapter 28
The Hearing Voices Movement

Sandra Escher and Marius Romme

28.1 Introduction

The Hearing Voices Movement is an international movement directed at creating opportunities for voice hearers to exchange experiences and knowledge about the hearing of voices. This is mostly done in groups of voice hearers where the participants can feel safe and respected and where their experiences are accepted rather than criticized. The participants also explore the personal backgrounds of their voices and learn coping strategies from each other.

The movement's initial development was sparked by Ms. Patsy Hage, who in 1987 had successfully convinced her psychiatrist (M.R.) that her voices were real, in the sense that she could really hear them. She wanted to learn to cope with those voices because she felt overwhelmed, powerless, and very afraid of them. Medication had not helped her sufficiently, and she had become more and more isolated because of all the things that the voices forbade her to do. She had also become suicidal, which was the reason for me (M.R.) to bring her into contact with another voice hearer, with the purpose of relieving her isolation and of being able to find out exactly how real the voices were to her. The two of them enjoyed talking about their experiences, which was a rather strange experience for me, sitting there and listening to all the things they had to say to each other. To my surprise, they comprehended each other perfectly well. We repeated this procedure a few times with other voice hearers, but at the time, neither Patsy nor any of the others knew how to cope with their voices or how to reduce the anxiety they provoked. This gave us

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Fig. 28.1 Logo of the Dutch *Stichting Weerklank* ("Resonance Foundation")

(S.E. and M.R.) the idea to set out and search for people who had learned to successfully cope with experiences such as these. We found a Dutch national TV show willing to spend an episode on the voices experienced by Patsy, and they allowed me to invite people who were able to cope with their voices to comment. At the time, none of us were able to foresee the far-reaching consequences of this single broadcasting. Following the show, 700 people contacted the studio's special team of telephone counselors, with 500 of them saying that they themselves were familiar with the hearing of voices. We were overwhelmed by the sheer number of respondents and sent them a questionnaire with 30 questions, which were selected together with Patsy Hage, who went on to advise us and to explain the relevance of the remarks people had made during their telephone calls.

That same year, we organized the first Hearing Voices Congress in Utrecht, the Netherlands (see also Romme and Escher 1989). Prior to as well as during the congress, we learned from our personal contacts with voice hearers that they wished for their experiences to be accepted as actually perceived voices with a nonself quality. During the congress, we founded Resonance (*Stichting Weerklank* in Dutch), an organization for voice hearers and people who support them (Fig. 28.1).

The above mentioned questionnaire was eventually sent out to 450 voice hearers, 254 of whom replied, and 186 of whom answered sufficiently comprehensively to allow for a detailed analysis (the remaining 68 tended to send extensive letters). From the results of that analysis (see Romme et al. 1992), we learned that some 66% of the voice hearers under study could not cope with their voices, whereas 34% could.

In 1988, together with the chair of Resonance (Ans Streefland, a voice hearer who had never been a psychiatric patient, being able to cope well with her voices), we helped to establish the Hearing Voices Network in the UK. Soon thereafter, similar

Fig. 28.2 Logo of Intervoice

networks followed in Finland, Italy, Austria, Portugal, Sweden, Wales, Scotland, Switzerland, Germany, Japan, Norway, Spain, Denmark, Ireland, Brazil, and Greece. Ron Coleman from Scotland introduced the movement to Palestine, New Zealand, and Australia. The USA and Canada followed somewhat later. Currently, the UK boasts the highest number of self-help groups, around 180 in total, followed by Finland with 24 groups (which is quite large a number considering the relatively small population). Since 1996, the training and education of the voice hearers and professionals participating in those groups has been in the hands of Intervoice, an international organization which runs an informative website (www.intervoiceonline.org) and organizes annual meetings for its members (Fig. 28.2).

28.2 Basic Principles of the Hearing Voices Movement

The basic principles of the Hearing Voices Movement can be summarized as follows:

- The hearing of voices is not *in itself* a sign of mental illness.
- The hearing of voices is experienced by many people who lack any symptoms that would warrant a psychiatric diagnosis.
- The hearing of voices is often related to prior social-emotional problems in the percipient's life history.
- The hearing of voices can cause serious distress, although it is an experience that one can learn to cope with, and become able to change one's relationship with.

The first principle, which states that voices do not necessarily constitute a sign of mental illness, is based on our numerous meetings with voice hearers who had not become psychiatric patients and had never needed any kind of help for them. Those people were able to cope well with their voices, and to live their own lives, functioning well socially. It is also based on the second principle, about the occurrence of voices in the general population, which was later confirmed by various large-scale epidemiological surveys (Tien 1991; Eaton et al. 1991; Van Os et al. 2001). The third principle, which links the hearing of voices to prior life events, was based on a study of our own (i.e., Romme et al. 1992) in which we found that some 70% of the respondents to the above mentioned questionnaire related their voices to earlier

traumatic experiences. That number was later confirmed by various additional studies (i.e., Romme and Escher 1993; Romme 1996; Escher 2005; Escher and Romme 2010; Romme et al. 2009). The 1993 study compared six voice hearers with a psychiatric diagnosis with six who had no diagnosis. They were all interviewed in depth about their experiences and life histories. In the study by Romme (1996), 33 voice hearers who had become patients were compared with 15 others who had not and who had been able to cope well with their voices. It indicated that the experiences of both groups were similar with regard to the phenomenological characteristics of the auditory hallucinations at hand, but that the patients tended to be afraid of their voices whereas the nonpatients did not. It also showed that both groups tended to relate their voices to earlier traumatic experiences. The Escher studies (2002, 2004, 2005), which describe a 3-year follow-up of 80 children who hear voices, show that no less than 80% of the young participants relate the hearing of voices to traumatic experiences. The fourth basic principle, about the distress that voices may cause and the possibilities to learn to cope with them, followed from our meetings with voice hearers who had succeeded to recover as well as from our own study of 50 recovered voice hearers (Romme et al. 2009).

28.3 Voices as a Problem of Living

As noted above, epidemiological studies indicate that the hearing of voices, in and of itself, is not a symptom of disease (Tien 1991; Eaton et al. 1991; Van Os et al. 2001). The phenomenon has been reported in 2–4% of the general population (with some studies yielding substantially higher estimates), while even more people (i.e., 8%) foster peculiar convictions, also known as delusions, without being "ill" in any way. Our own research has corroborated those findings (Romme and Escher 1989, 1993; Romme 1996). Over a third of the 350 voice hearers we interviewed with the Maastricht hearing voices interview (Escher et al. 2000) in the Netherlands had never been in contact with psychiatric services (Romme and Escher 1989; Romme et al. 1992; Romme 1996; Escher 2005). Most of them were able to cope well with their voices, and many of them even described them as life enhancing. Moreover, people who were able to cope well with their voices and those who were not showed marked differences in the way they related to their voices and the kinds of strategies they employed to manage them. Those who coped well tended to use active strategies such as setting limits and selective listening, but they also welcomed positive voices, especially those which gave them good advise (Romme 1989, 2000; Romme et al. 1992).

Meeting people such as these stimulated our interest in the hearing of voices itself. Hence, we designed a study (Romme 1996; Romme and Escher 2000) to compare voice hearers who had become patients with those who had not, and focused on three groups: one consisting of people diagnosed with schizophrenia ($n = 18$), one with dissociative disorder ($n = 15$), and one without any psychiatric diagnosis ($n = 15$). The patients were all recruited from our Maastricht-based outpatient clinic, and the

healthy voice hearers were volunteers we had met at congresses and other opportunities. All 48 participants were screened for pathology with the aid of the Composite International Diagnostic Interview (CIDI, Robins et al. 1988) and the Dissociative Experience Scale (DES, Bernstein and Putnam 1986). The results showed that the experiences among the three groups did not differ significantly. In all cases, the voices heard had the phenomenological characteristics of genuine auditory hallucinations. Nor were there any differences as regards the perceived location of the voices, i.e., inside or outside the head. The most significant difference we found was that the patients were all afraid of the voices they heard, whereas none of the healthy voice hearers were. We also found a reported relationship with traumatic experiences in 70% of the cases in the schizophrenia group, in a full 100% of the cases in the dissociative disorder group, and in only 53% of the nonpathological group. Due to a lack of statistical significance, however, they could not be used to differentiate between the three groups.

We also found that the long-term developmental processes of psychological adjustment, which typically precede the onset of the hearing of voices, tend to be governed by memories of "undigested" emotional events connected with key relationships (Romme et al. 2009). The types of trauma reported include sexual abuse, physical abuse, being bullied for longer periods of time, and emotional neglect (in the sense of being educated in a setting where the voice hearer was discouraged to express his emotions and/or criticized for longer periods of time). Our study among children identified similar traumatic experiences, but even more often a divorce, a bereavement phase, a love affair, or a pregnancy (Escher 2005).

28.4 Self-help Groups

Many people who hear voices, regardless of whether they are able to cope with them or not, feel an urgent need to gain a personal understanding of their experiences and to discuss them with others without being designated as "mad." The failure to do so in the presence of mental health professionals can be highly frustrating. Many service users report that their voices tend to be viewed quite exclusively as symptoms of a psychiatric disease and that they are discouraged to talk about them. This would still seem to be the case today, although we admit that we are aware of various notable exceptions. Instead, the Hearing Voices Movement advocates the following approach based on the recent work of Lucy Johnstone (2011):

- Voices can be considered part of a normal range of experiences.
- Voice hearers need to take responsibility for their own recovery.
- It is important for them to actively engage with the voices.
- It is important for them to rely on their own understanding of the voices.
- They should work with the unresolved trauma.
- If feasible, they should rely on self-help groups and workbooks.
- It is important to change people's relationship with their voices.

Fig. 28.3 Attendants of a Hearing-Voices Congress in Sweden, 2003. Photograph by Sandra Escher

Most importantly, however, we learned from our most recent study (Romme et al. 2009) that recovery is not a matter of the effectiveness of psychopharmacological agents but a personal process that is inextricably bound up with the nature of the experience at hand (see also Boyle 1990). As a corollary, we are convinced that the primary challenge for voice hearers is to meet people who are willing to accept that their voices constitute genuine experiences which are neither some strange product of their imagination nor a sign of mental disease or madness, and which can be viewed as reflecting something that has actually occurred to them in the past. The primary challenge for professionals is to accept that voices can be meaningful, in the sense that they may constitute a link with the voice hearer's prior life experiences. In our opinion, voices often represent an abuser, at least in those cases where the voice hearer has been the victim of sexual or physical abuse, while the age of the "person heard" may indicate the age at which the trauma was actually experienced. Our whole approach starts from the dictum that those vital links should not be eradicated with the aid of pharmaceuticals but explored with the aid of psychological therapy and self-help methods (see also Dillon and Longden 2011). The instruments we consider of crucial importance to that process are the groups of voice hearers which are now slowly spreading around the world (Fig. 28.3).

And yet most mental health professionals have not been trained to discuss their patients' voices with them. Instead, they are trained to treat the diseases supposedly

underlying them, preferably with the aid of medication. A problem with that approach is that it fails to take into account the possibility that people are often perfectly capable to develop initiatives of their own and that those initiatives are equally capable to bring recovery within their reach. It also tends to alienate people from their experiences and to promote their social isolation. As Ron Coleman (2009) remarked, "They take my experience, mould it, and give it back unrecognisable."

The first self-help groups proved what we had been suspecting for quite some time, namely, that the traditional medical approach is far of the mark when it comes to the treatment of voices. The groups turned out to be extremely helpful in making people realize that they were not the only ones who were hearing voices, that it was possible to find acceptance for them, and that they were not in fact isolated. The participants were able to discuss their voices freely with each other, benefiting from each other's experiences, and exchanging and exploring numerous coping strategies. Their participation in the groups also stirred up their emotions, which were often so overwhelming that they could hardly be coped with. Soon, we realized that that seemed to be the core problem to be dealt with, the apparent inability to handle such powerful emotions. That was what the voices had been talking about all the time. Learning to cope with one's voices meant learning to cope with one's most difficult emotions. The fact that people wanted to learn to cope with their voices made them aware that that could only be done by reclaiming their own power. They felt that they had been rendered powerless by their voices – as well as by the mental health professionals who had tried to suppress their voices – and that they needed to regain their power if they ever wanted to recover.

28.5 The Need for a New Paradigm

As remarked by Ms. Jacqui Dillon, the coordinator of the Hearing Voices Network in the UK, "A starting point for me was creating a new paradigm for myself that honoured my resilience and capacity to heal." (Romme et al. 2009, p. 188). As it turned out, the need for such a new paradigm was shared by voice hearers and professionals alike. For voice hearers, that need springs naturally from their need to regain control over their lives. As regards professionals, the situation would appear to be slightly more complicated. In the first place, perhaps, because professionals tend to come into contact only with those voice hearers who have been rendered powerless by their voices. As a consequence, it may be difficult for them to believe that the hearing of voices deserves to be conceptualized and appreciated in a way that departs radically from the traditional medical model, and to grasp that prescribing medication may not be exclusively beneficial. Secondly, mental health professionals – not unlike other human beings – have a certain tendency to hold on to the models and assumptions that are familiar to them. Even when confronted with overwhelming proof, for example, of the lack of scientific validity of the schizophrenia concept (Blom 2003), they may be reluctant to abandon their familiar paradigms and choose to keep on working within the confines of the old ones.

Nevertheless, there are various advantages lying in store for those professionals who are brave enough to challenge their familiar assumptions about the hearing of voices. As summarized by Hoffman (2011), they – and we – should:

- Talk about "hearing voices," while the term "auditory hallucination" in therapy makes the thorny path into a good patient-therapist relationship even thornier, because the term hallucination does not make allowance for the fact that voice hearers actually do hear voices.
- Accept the reality of the experience. The development of a sound working relationship becomes easier with the staff member's simple explanation that he or she does not doubt that the voice hearer actually hears voices, and by pointing out that he or she knows quite a lot about people who hear voices.
- Accept the possibility of hearing voices as nonpathologic. In closing one's eyes to the fact that there are many people who have found ways to live with their voices without being "disturbed" or "ill," and who may not even want to lose this ability, professionals lose sight of a chance to observe how people can decide which voices they want to listen to and when, to mention some of the techniques mastered by those people.

28.6 The Need for Role Models

A final issue that we would like to discuss is the need for role models. From childhood onward, we all seek out role models that can help us make important decisions in life and shape our identity. In the book *Living With Voices* (Romme et al. 2009), one can find the stories of 50 voice hearers who managed to learn to cope with their voices and to recover from the patient roles many of them had played for up to 18 years. They are role models with whom many voice hearers can identify and which might inspire professionals in their daily practice. Voice hearers capable of viewing their own position from a certain distance, and of combining their individual experiences with general scientific data, may well be in a position to bridge the gap between mental health workers' daily practices and that which their professional education has taught them to believe. Some of the people we would like to recommend for that purpose are Peter Bullimore, Ron Coleman, Jacqui Dillon, Rufus May, and Rachel Weddingham in the UK; Olga Runciman and Johnny Sparvang in Denmark; Liz Bodil and Ami Rohnitz in Sweden; Flore Brummans en Frans de Graaf in the Netherlands; Debra Lampshire in New Zealand; and Marleen Janssen in Australia.

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ERRATUM

Chapter 3
Consciousness, Memory, and Hallucinations

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Due to errors in copyediting, text was omitted from the published version of the Conclusion. The Conclusion is reproduced in full below. The publisher regrets the error.

3.5 Conclusions

Normal perception, dreaming, and hallucinations are equivalent because even normal perception in wakefulness is fundamentally a state of hallucinations, one however that is constrained by external physical reality. Although Kant (1781) was not the first idealist, he can be credited with first recognizing idealism as the appropriate philosophical framework for understanding the nature of the perceived world and its phenomena and, at the same time, recognizing the embeddedness of the phenomenal world in a shared physical world that lies beyond subjective experience. The adaptive state of wakefulness depends on sensory information about changes taking place in the physical world, but we do not see, hear, feel, or smell physical reality itself. Instead, physical reality constrains the internal and fundamentally subjective process of conscious experience.

Activation of thalamic relay cells during arousal is normally balanced by sensory-specific and attention-specific inhibitory input from neurons in the reticular thalamic nucleus. The reticular thalamic nucleus, in turn, is under cholinergic control by the mesencephalic reticular formation and basal forebrain nuclei. In patients

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diagnosed with schizophrenia, deficient nicotinic activation of reticular thalamic neurons during arousal may lead to a loss of specific inhibition and an excess of random activity in specific thalamic nuclei. This would mask sensory input to the thalamus and weaken its impact on thalamocortical self-organization, resulting in impaired γ response synchronization to sensory stimulation. Thalamic relay cells could be recruited into "large functional states", involved in conscious experience, without regard for the actual pattern of sensory input. Inhibition of the reticular thalamic nucleus and disinhibition in specific thalamic nuclei may also result from dopaminergic hyperactivity, as found in schizophrenia, or exogenous NMDA receptor antagonists, such as phencyclidine (Behrendt and Young 2004).

Patterns of resonant thalamocortical activity, representing sensory information in egocentric or action-centered frameworks or in semantic terms, provide the dynamic substrate from which the hippocampus rapidly constructs allocentric environmental representations that serve mnemonic functions and self-localization. The CA3 autoassociation network, forming unitary activity patterns at θ intervals, integrates information about objects and their spatial context into allocentric representations of the environment. Unitary conscious experiences, referring to *discrete* epochs of conscious experience (VanRullen and Koch 2003), may be an emergent property of unitary activity patterns formed through attractor dynamics in CA3 (Behrendt 2010). Regarding the stream of consciousness as a sequence of higher-order symbols that characterize unique states in CA3 formed through attractor dynamics agrees not only with Kant's idealism but also Chalmers' (1996) argument that consciousness is imbued with nonphysical properties (and therefore cannot make a difference to the trajectory of behavior). Hallucinations may not differ from normal conscious perception in terms of their intricate relationship with episodic memory formation and recall.

Increased excitability in CA3 (due to NMDA receptor hypofunction or GABAergic interneuron dysfunction) may cause hallucinations in patients diagnosed with schizophrenia through the formation of parasitic attractors. Alternatively, pathophysiological processes that predispose to the formation of large-scale patterns of thalamocortical activity that are underconstrained by peripheral sensory input could be responsible for hallucinations. Ultimately, much of the thalamocortical system, processing external sensory input, interacts with hippocampal region CA3 in producing view-dependent allocentric representations that manifest as discrete epochs of conscious experience (including hallucinatory experience). The precise locus of pathophysiology may be reflected in the type or phenomenology of hallucinations. The presence of visual hallucinations, alongside auditory hallucinations, in patients diagnosed with disorganized schizophrenia may indicate pathologically increased hippocampal activity, due to GABAergic hypofunction, whereas hallucinations occurring exclusively in the auditory modality in patients diagnosed with paranoid schizophrenia may indicate externally underconstrained thalamocortical activation that, due to abnormal reticular thalamic nucleus function, remains excessively sensitive to attentional influences reflecting psychosocial or personality factors.

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