9 Thought, hallucinations and schizophrenia

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Hallucinations are a hallmark symptom of schizophrenia. Although they can occur in the auditory, visual, olfactory, gustatory and somatosensory modalities, approximately 70% of individuals diagnosed with schizophrenia report hallucinations in the auditory modality (Andreasen and Flaum 1991). Auditory hallucinations can occur in the context of a wide range of psychiatric disorders, but their prevalence is highest in patients with schizophrenia (American Psychiatric Association 2000). The present chapter focuses on auditory hallucinations in schizophrenia. Research findings on hallucinatory experiences in other disorders and in healthy individuals have been recently synthesized elsewhere and will not be covered here (Jardri *et al.* 2013; Blom and Sommer 2012).

Cognition

Auditory hallucinations are defined as auditory perceptions that resemble a veridical perception but are experienced in the absence of a corresponding external stimulation. Different explanations have been proposed to account for the different phenomenological features of auditory hallucinations, each potentially representing a particular circuitry of brain structures and functions. The most recent model of auditory hallucinations in schizophrenia (Waters *et al.* 2012) postulates that auditory hallucinations arise from abnormal activation in brain networks involved in auditory processing (see Chapter 4), and disrupted interactions between these networks and cognitive processes that include deficits in signal detection and inhibition, top-down influences, and emotional processing. An overview of brain abnormalities associated with auditory hallucinations is provided later in this chapter.

The model proposed by Waters *et al.* (2012) focuses on the idea that auditory hallucinations are essentially perceptions induced by an interaction between information arising from neural activity and top-down activity. It is proposed that auditory hallucinations are formed at different stages, instantiated at different neuroanatomical locations: (i) abnormal signals in sensory regions; (ii) top-down cognitive deficits in self-/source monitoring,

signal detection and inhibitory control; (iii) and a contribution of emotions.

Abnormal signals in sensory regions

Salient auditory stimuli are thought to provide the basic signal for auditory hallucinations (the source). This is thought to arise from hyperactivation in functional networks involving the auditory cortex that generate aberrant auditory signals, possibly due to a deviant trigger of activations in language-related areas responsible for auditory hallucinations. Anomalous activations might be determined by environmental factors and/or internal (e.g. emotional) conditions. These anomalous neural activations may induce auditory signals that exceed the perceptual threshold, thereby causing unexpectedly salient sensory information. Specific forms of inner speech, or intrusive memories, may be particularly more likely to become an auditory hallucinations and may account for some of its verbal and phenomenological properties.

Top-down cognitive deficits in self-/source monitoring, signal detection and inhibitory control

Signal detection deficits increase the detection of ambiguous or salient signals and suppose an increased tendency to accept the salient signal as veridical. Deficient intentional inhibition cognitive mechanisms fail to suppress such information, which becomes functionally autonomous. This would contribute to the failure to control the onset and frequency of these salient auditory signals. Over time, expectations and hypervigilance over these experiences would increase the likelihood of them being repeated, increasing cognitive/perceptual biases and reducing the threshold to accepting the signal as veridical.

Contribution of emotions

The meaning of auditory hallucinations is determined by state and trait characteristics that influence how these experiences are interpreted. The presence of reduced insight, delusional beliefs, negative beliefs about the self and about the world, and negative emotion, can all combine to produce a complex and elaborate system of beliefs around the hallucination.

Emotion may play a particularly prominent role at all levels of hallucination formation (source, form, content, and meaning), and it may also provide the first traumatic insult in this ontogeny (Varese *et al.* 2012). The source of auditory hallucinations may be influenced by emotional content associated to trauma, and other intense negative emotions, increasing neural response and resulting in aberrant auditory signals. In addition,

auditory hallucinations may play a role in determining the content of the auditory signals, as emotional and personally salient material is preferentially processed over neutral information. At this level, as proposed by Waters *et al.* (2012), emotion may produce attentional biases toward negative information, hypervigilance, and negative schemas that may further reinforce the processing and recall of emotionally charged material. Over time, this can influence higher-order aspects such as the beliefs attributed to the voices (e.g. benevolence or malevolence).

In summary, auditory hallucinations are conceptualized as arising from interactions between hypersalient auditory sensory signals and top-down cognitive processing deficits involving error processing, cognitive control, and prior knowledge/experience, which may shape the form and content of the voices. Emotional processing plays a prominent role in this chain of events, with an impact at all levels of processing (e.g. an initial traumatic insult can create a vulnerability for experiencing auditory hallucinations, as well as determining the meaning attributed to the voices by influencing insight and belief systems). Finally, individual differences in the severity and localization of abnormal neural activity may determine the observed phenomenological variations, such that different combinations result in the many subtypes of auditory hallucinations (Jones 2010).

Neurobiology

Significant strides have been made in recent years in hallucination research, with the neuroscientific contribution to psychopathology being fuelled by brain imaging techniques such as magnetic resonance imaging (MRI). Brain imaging methods provided exciting opportunities such as imaging patients with schizophrenia while they were experiencing hallucinations inside the scanner (e.g. McGuire *et al.* 1993), and investigating more fine-grained features such as the neural correlates of the loudness or vividness of the voices (e.g. Vercammen *et al.* 2011).

Especially in the 1990s–2000s, neuroimaging techniques have been intensively applied with the aim to uncover the neural underpinning of hallucinations in schizophrenia. This section elaborates on the findings produced by these studies, covering structural and functional imaging studies of auditory hallucinations in schizophrenia. We show that, although early studies established the subsequently extensively replicated finding of auditory hallucinations being associated with differences in cortical areas responsible for auditory perception (i.e. primary and secondary auditory cortex, portrayed in Figure 9.1) and speech output (i.e. inferior frontal gyrus, anterior insular cortex; Allen *et al.* 2008), additional changes in a range of other cortical and subcortical regions have also been reported, with abnormalities currently being conceptualized as occurring at a network level.

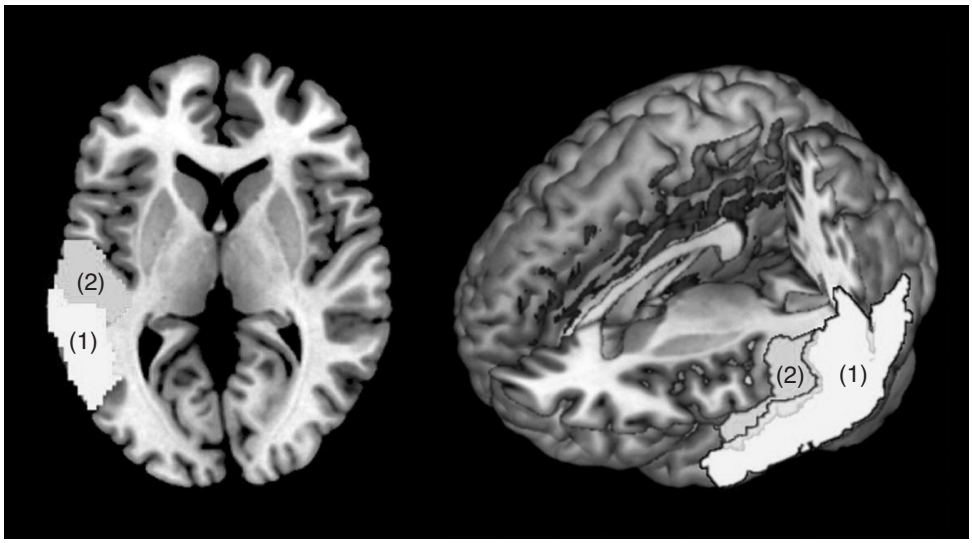

Figure 9.1 The most consistently reported areas of abnormalities in studies of auditory hallucinations in schizophrenia comprise the left superior temporal gyrus (1) and the left middle temporal gyrus (2). The images depict the anatomical landmarks of these regions on the axial (left), and rendered views (right). Images have been prepared with anatomically predefined masks using the WFU_PickAtlas Software in SPM8, overlaid on a standard brain template with MRICron

Structural MRI

In neurological diseases, hallucinations are commonly associated with evident anatomic lesions, typically located in the brain pathway of the sensory modality involved in the hallucination (Allen *et al.* 2008; Braun *et al.* 2003). In schizophrenia patients with hallucinations, no gross structural deficit can be distinctively observed at the individual level. Nevertheless, group-level analyses comparing patients with and without hallucinations, or correlation analyses between severity of hallucinations and brain structure, show subtle but robust variations in association with auditory hallucinations in this group. Of particular relevance are volume reductions in the superior (STG) and middle temporal gyri, predominantly on the left hemisphere, which have been repeatedly implicated in auditory hallucinations in schizophrenia across different imaging modalities.

Group-level analysis of structural brain images was initially performed with a region-of-interest approach. These early studies mainly reported volume reductions in the STG and increased lateral ventricles. More recently, voxel-based morphometry (VBM), a whole-brain, unbiased, semi-automated technique for characterizing regional cerebral differences in structural MRI (Ashburner and Friston 2000; Mechelli *et al.*, 2005) has been applied to investigate structural abnormalities associated with

auditory hallucinations at the whole-brain level. A recent meta-analysis was conducted on the nine studies available to date, which had used VBM to specifically examine gray-matter abnormalities in patients with schizophrenia (Modinos *et al.* 2013). The "severity" of auditory hallucinations was found to be associated with gray-matter reductions in the STG bilaterally, including Heschl's gyrus, which is primary auditory cortex (Figure 9.2, lower panel). Left superior temporal areas are known to be involved in speech perception, particularly in the comprehension of the phonological and semantic characteristics of speech. A subthreshold effect was also reported in the right STG, thought to be involved in auditory and language processing, particularly of the emotional and prosodic aspect of speech stimuli (Downar *et al.* 2000). These findings suggest that structural aberrations within neural systems involved at different levels of language processing are critical to auditory hallucinations in patients with schizophrenia. Aside from the meta-analytical results, single VBM studies have also documented significant effects of auditory hallucinations in non-sensory regions, including the insula, anterior cingulate, posterior cingulate, and inferior frontal gyrus, thalamus, cerebellum, and precuneus (Allen *et al.* 2008). These studies demonstrate that volumetric changes in regions within a wider network than that involved in speech and language processing are also associated with auditory hallucinations.

Functional MRI

Functional imaging procedures developed to examine neural correlates of auditory hallucinations can be conceptually classified into two main study categories. Firstly, cognitive "trait" studies are designed to investigate the neural bases of the susceptibility to hallucinate, independent of the subjects' experience during scanning, by comparing hallucinators and non-hallucinators during a specific functional MRI paradigm. Secondly, "state" studies are designed to directly measure brain activation associated with AH occurrence. "State" studies have widely implicated the recruitment of the secondary auditory cortex during AH, which has been recently supported by a coordinate-based meta-analysis of functional MRI studies in auditory hallucinations (Jardri *et al.* 2011). This meta-analysis included ten functional imaging studies investigating state activation during auditory hallucinations, and evidenced that hallucinators showed increased activation likelihoods in a distributed bilateral frontotemporal network, including Broca's area, anterior insula, precentral gyrus, frontal operculum, middle and STGs, inferior parietal lobule, hippocampus, and parahippocampal region (Figure 9.2, upper panel). These findings emphasize the involvement of a disrupted network of frontal language production and temporoparietal language perception areas in auditory hallucination occurrence. Jardri *et al.* (2011) argued that the results from their meta-analysis would support two main hypotheses: (i) aberrant activations within

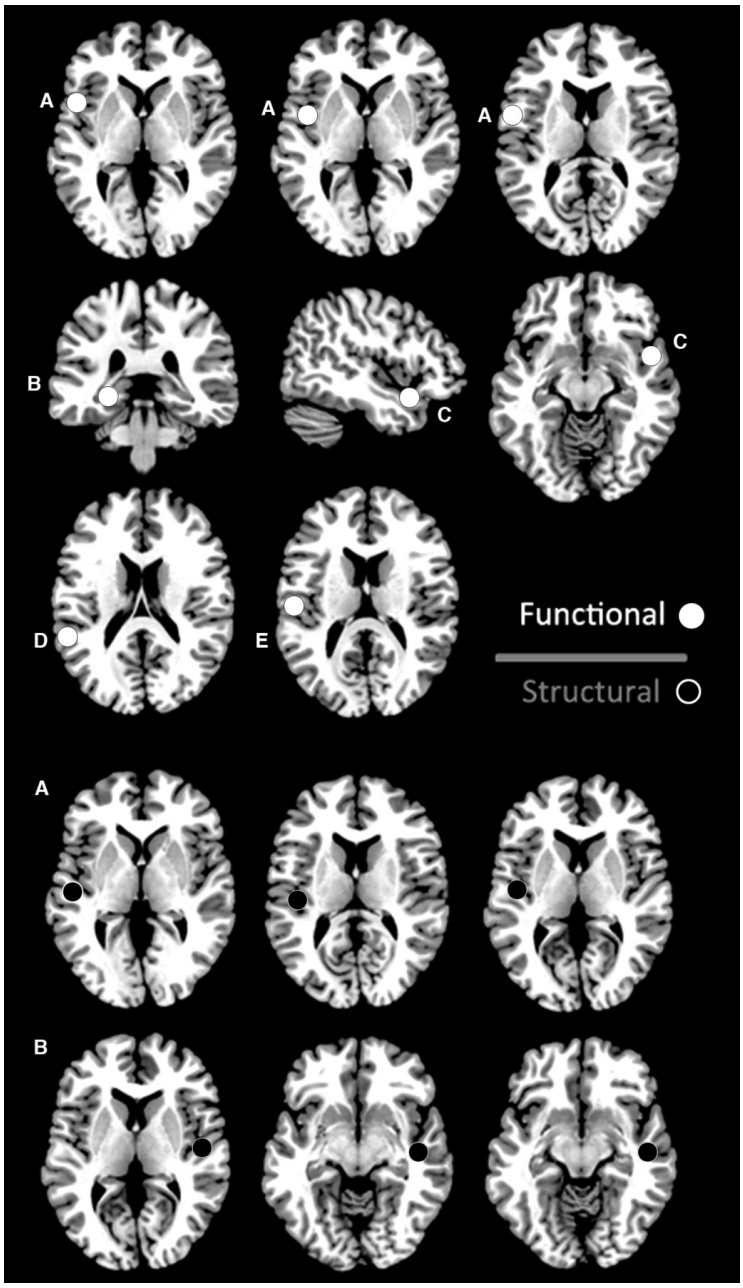

Figure 9.2 Areas of convergent findings in functional (white circles) and structural (black circles) studies of auditory hallucinations in schizophrenia. Coordinates, as reported in Jardri *et al.* (2011) and Modinos *et al.* (2012), are overlaid on a standard brain template using MRICron. Functional studies converged on five loci of activation (cluster A: left Broca's convolution, anterior insula, precentral gyrus; cluster B: hippocampus/parahippocampus; cluster C: anterior insula, frontal operculum; cluster D: left STG and MTG; cluster E: supramarginal gyrus), and structural studies in two loci (cluster A: left STG and MTG, and cluster B: right STG and MTG)

frontotemporal language areas during auditory hallucinations; and (ii) dysfunction of verbal memory systems which could lead to the occurrence of auditory hallucinations.

Further to the findings described above, neuroimaging studies in auditory hallucinations in schizophrenia have also examined abnormalities in white-matter structure and connectivity, gyrification (cortical folding), and neurochemistry, recently reviewed by Allen *et al.* (2012. In summary, the main findings to date are: (i) impaired white-matter connectivity between frontal and temporal brain regions, as measured with diffusion tensor imaging (which assesses the directionality of water diffusion within white matter fiber tracts, or fractional anisotropy); (ii) abnormal frontotemporal functional connectivity during task performance, and temporoparietal connectivity during resting state; (iii) subtle gyrification deviations; and (iv) neurochemical abnormalities (decreased N-acetyl-aspartate concentrations in hippocampus and thalamus; no significant effects on dopamine synthesis capacity have been reported).

In summary, abnormalities in the auditory cortex and language-related brain regions in patients with auditory hallucinations seem to be the most replicated finding across a range of imaging modalities. However, it should be noted that these areas also tend to be widely reported in schizophrenia regardless of specific symptoms (Honea *et al.* 2005). The main contributions with relative consistency across studies refer to decreases in gray-matter volume, while increases in brain activation during auditory hallucinations and in white-matter connectivity are commonly reported. More recent investigations have suggested aberrant neurochemical function and gyrification deviations. In order for this field to move forward, future studies should aim to address the number of methodological issues often associated with this body of work, mainly relating to sample sizes, choice of study design for functional MRI studies (state or trait studies), medication confounds, and the specificity of the findings to auditory hallucinations.

Etiology

Auditory hallucinations have a heritability of 0.43 (McGrath *et al.* 2009). Although no genes are known to code for complex clinical phenotypes, some allelic variants in certain genes may contribute to auditory hallucination formation (e.g. by exceeding the threshold for abnormal sensory processing). From the viewpoint of genetic studies, hallucinations are considered among the most reliable endophenotypes for genetic research in psychosis because they seem to be consistently associated with specific physiological (P50/P300) and neuroanatomical (left STG abnormalities) features (Allen *et al.* 2009).

Sanjuán *et al.* (2013) recently proposed an integrative etiological model of auditory hallucination, which differentiates between three etiopathogenic

pathways for auditory hallucination in psychosis: (i) vulnerability to hallucinate; (ii) vulnerability to abnormal emotional responding; and (iii) vulnerability to language disorder.

- The first pathway refers to an individual's general vulnerability to experience hallucinations, in any perceptual modality. Different genotypes might code for differences in the threshold for sensory gating, thereby inducing proneness to hallucinations in any sensory modality. This general vulnerability is proposed to be related to genes that modulate all perceptual input (in the glutamatergic, GABAergic, or cholinergic systems), through thalamocortical pathways.
- The second pathway refers to the vulnerability to produce an abnormal emotional response to stimuli. This would be partially regulated by genes related to serotoninergic and dopaminergic neurotransmission.
- The third pathway refers to the vulnerability to express abnormalities in language processing, which would increase the probability of hearing voices. This vulnerability could be the result of changes or abnormal expression in the *POXP2* gene (which is involved in central nervous system development), among others.

Besides the three pathways described above, genetic variants may also influence the vulnerability to hallucinations indirectly by predisposing the individual to expressing specific temperament and personality traits. For instance, it has been shown that some temperament and personality traits are important predisposing factors for hallucinations (Read *et al.* 2009), which are thought to result from complex gene–environment interactions (Ivorra *et al.* 2010). Many genes of small effects may thus be involved in these pathways predisposing the patient to experience hallucinations. On the other hand, cultural and environmental factors are vastly regarded to exert a clear influence on auditory hallucinations, particularly on the content and the social adjustments of the experiences (Johns *et al.* 2002a,b). In summary, the current view lies with an etiological model of auditory hallucinations, which integrates genetic and environmental factors in their origin.

At this point, the question arises of how would these vulnerabilities induce in the individual the neurobiological, cognitive, and ultimately behavioral expression that characterize what we call an auditory hallucination. The developmental neuroscience of hallucinations has been intensively researched in children and adolescents, since hallucinations are a hallmark symptom of early onset schizophrenia. This research has been centered on the neurodevelopmental theory of schizophrenia. As formulated by Weinberger (1987), this theory postulates increased risk associated with early abnormalities in brain development. This has been supported by evidence that harmful effects on fetal brain development (just prior to, or during, birth) in combination with subsequent brain changes later on in

adolescence can result in the onset of psychotic symptoms (Cannon *et al.* 2003). The notion is currently still held that early developmental deficits, such as famine (St Clair *et al.* 2005), lower birth weight and lower intelligence quotient (Polanczyk *et al.* 2010), may signal the starting point for risk pathways that may lead to any expression in between non-affective (mild) psychotic experiences and full-blown schizophrenia. The clinical or non-clinical result for each person is thus thought to depend on a complex combination of perinatal, genetic and environmental factors that have yet to be well understood.

In this context, developmental studies of psychotic children have shown marked abnormal brain trajectories. Childhood-onset schizophrenia (COS) is a rare, severe form of the disorder with more marked neurodevelopmental impairments (Rapoport *et al.* 2005), thought to be neurobiologically, diagnostically and physiologically continuous with the adult disorder (Nicolson *et al.* 1999; Addington *et al.* 2005). In COS, progressive decreases in cortical gray-matter volume in frontal (11%), parietal (8.5%), and temporal lobes (7%) have been reported, as well as a progressive increase in ventricular volume (Rapoport *et al.* 1999; Sporn *et al.* 2003). The imaging data overall portray a fourfold greater reduction in cortical volume than in scans of healthy adolescent subjects. This imaging evidence taken as a whole has led to the idea that schizophrenia is a progressive neurodevelopmental disorder, with an emphasis on neuroanatomical change as a result of excessive synaptic elimination, which produces aberrant neural connectivity. Although these data are extremely interesting, whether any of these aberrant progressive changes are specific to auditory hallucination still remains to be tested.

Treatment

Treatment for auditory hallucination typically consists of medication, psychoeducation, psychosocial interventions, psychotherapy and, in some refractory cases, transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT).

Sommer *et al.* (2012) noted that there had been no clinical trials aimed at comparing the efficacy of various antipsychotic drugs prescribed uniquely for hallucinations. They then used existing data from the European First-Episode Schizophrenia Trial (EUFEST) to assess the potential of five different antipsychotic agents to reduce the severity of hallucinations. The EUFEST study (Kahn *et al.* 2008) included 498 patients with first-episode psychosis, who were randomized to receive haloperidol, olanzapine, amisulpride, quetiapine, or ziprasidone. Among these patients, 362 presented auditory hallucinations at baseline. Severity of auditory hallucinations showed a mean reduction from "marked/severe" to "minimal/mild" after four weeks, at the decline continued with prolonged treatment to ratings of "absent/minimal" hallucinations after six months of

treatment. The proportion of patients with at least mild levels of hallucinations decreased strongly over time from 100% at baseline to 8% after 12 months of treatment. These results suggest that auditory hallucinations respond to anti-psychotic treatment in patients with psychosis, and that there is a marked reduction in auditory hallucination severity within the first four weeks.

In some cases, the drug of first choice is inefficient. It is then recommended to switch to another drug with a different receptor profile after a period of about two to four weeks. However, there will be patients who will not respond to a second anti-psychotic. In those cases, clozapine is considered the drug of choice. In fact, clozapine is nowadays still considered as having the most effective profile for patients with treatment-resistant auditory hallucinations (Kane *et al.* 1988). For patients with schizophrenia, it is recommended that, if successful, anti-psychotic treatment should be maintained in an unaltered dose for at least one year. In light of the evidence that the predisposition to auditory hallucination is in part genetically influenced, the vulnerability to experiencing auditory hallucinations may be lifelong, and in fact continuous maintenance treatment with the initial dose used for symptom remission has been associated with lowest relapse rates (Sommer *et al.* 2012).

There are cases in which clozapine also fails to reduce hallucinations. A number of treatment options may still be offered to these patients with refractory hallucinations, including psychotherapy, pharmacological augmentation, repetitive TMS (rTMS), and ECT. Cognitive behavioral therapy (CBT) can be applied as an augmentation to antipsychotic medication, thus not only in refractory cases. CBT aims at reducing the emotional distress associated with auditory hallucinations, and to develop new coping strategies. Overall, CBT has been found to provide beneficial effects, positive symptoms, negative symptoms, general functioning, mood, and social anxiety, with effect sizes ranging from 0.35 to 0.44, as reported by a recent meta-analysis (Wykes *et al.* 2008).

TMS involves the application of a strong pulse of electrical current, which sent through a coil placed over a person's skull, inducing a magnetic field pulse in a small brain area, depolarizing local neurones up to a depth of 2 cm. TMS is proposed as a non-invasive technique with only few side effects, and studies applying TMS for the treatment of auditory hallucinations have generally reported significant symptom reduction for TMS-treated groups compared with placebo groups (Aleman *et al.* 2007). TMS is currently being offered as treatment option to reduce the frequency and severity of auditory hallucinations in centers worldwide, combined with anti-psychotic treatment.

Finally, ECT may also be offered in some cases of treatment-resistant psychosis. ECT involves placing electrodes attached to the scalp by which an electrical current is passed to induce a generalized seizure; it is performed under general anesthesia and muscle relaxants are administered to prevent

body spasms. A number of neuropsychological deficits, mainly affecting memory, have been associated with the administration of ECT, although pretreatment functioning levels tend to be reached within the first months after treatment (Semkovska and McLoughlin 2010). Several studies have demonstrated clinical improvement after ECT in patients with schizophrenia, but a specific reduction in hallucination severity has not been demonstrated. The clinical improvement may thus be attributable to improving other symptoms (mood, motor retardation, agitation, and catatonia), rather than to core psychotic symptoms such as auditory hallucinations (Sommer *et al.* 2012).

Conclusions

From the point of view of cognitive science, the evidence to date suggests that auditory hallucinations arise from interactions between hypersalient auditory sensory signals and top-down cognitive processing deficits, which may shape the form and content of the voices. Emotional processing is thought to play an important role at all levels of processing. Finally, individual differences in neural activation may determine the observed variability in phenomenological presentations, resulting in the many subtypes of auditory hallucinations (Jones 2010).

Research into the neurobiological correlates of auditory hallucinations seems to converge in showing abnormalities in the auditory cortex and language-related brain regions in patients with auditory hallucinations. The most consistent findings across studies refer to decreases in gray-matter volume, while increases in brain activation during auditory hallucinations and in white-matter connectivity are commonly reported (Modinos *et al.* 2013; Allen *et al.* 2012, Jardri *et al.* 2011). In order for this field to move forward, future work should aim to overcome methodological issues such as reduced sample sizes, choice of study design for functional MRI studies (state or trait studies), medication confounds, and the specificity of the findings to auditory hallucination as a specific symptom.

In terms of the etiology of auditory hallucinations, the current etiological model integrates genetic and environmental factors in the origin of auditory hallucinations. How genetic and environmental vulnerabilities induce in the individual the neurobiological, cognitive, and ultimately the behavioral expression that characterizes auditory hallucinations is currently framed within the neurodevelopmental theory of schizophrenia. Thus, the notion is currently still held that early developmental insults may signal the starting point for risk pathways that may lead to any expression in between subclinical psychotic experiences and full-blown schizophrenia.

Finally, with regard to treatment options for auditory hallucinations in schizophrenia, there is vast evidence to suggest that auditory hallucinations respond to anti-psychotic treatment in patients with psychosis, and that

there is a marked reduction in severity of hallucinations within the first four weeks (Sommer *et al.* 2012). In cases in which the drug of first choice is inefficient, patients are changed to another drug with a different receptor profile within a period of about two weeks. Nevertheless, some patients do not respond to a second anti-psychotic either, and then clozapine is considered the drug of choice. For patients with schizophrenia, it is recommended that, if successful, anti-psychotic treatment should be maintained in an unaltered dose for at least one year, and continuous maintenance treatment with the initial dose used for symptom remission has been associated with lowest relapse rates. In addition to pharmacological options, other approaches such as CBT provides beneficial effects for positive symptoms, negative symptoms, general functioning, mood, and social anxiety (Wykes *et al.* 2008). Studies applying another approach, TMS, for the treatment of auditory hallucinations have generally reported significant symptom reduction for TMS-treated groups compared with placebo groups (Aleman *et al.* 2007). TMS is currently being offered as treatment option combined with anti-psychotics. Finally, ECT is offered in some cases of treatment-resistant psychosis, and although several studies have demonstrated clinical improvement after ECT in patients with schizophrenia, a specific reduction in hallucination severity has not been demonstrated.

In conclusion, the recent years have witnessed important progress in discerning the mechanisms underlying the emergence of hallucinatory experiences in patients with schizophrenia. This progress has been largely aided by the availability of advanced brain imaging acquisition and analysis techniques, together with rapid progress in genetic research. Challenges to be addressed in future research relate to the need to collect important clinical, environmental and genetic information on auditory hallucination, so that their contribution to the underlying deficits may be assessed. Another issue concerns the boundaries between auditory hallucination and other positive symptoms associated with schizophrenia such as delusions, so that shared and unique contributing processes may be identified. An additional challenge relates to the role of medications in neurobiological and cognitive measurements of auditory hallucination. Further research addressing these issues can lead to refined evidence-based models of the processes underlying hallucinations and ultimately provide an integrative understanding of these intriguing subjective phenomena.

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