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Review

The hallucinating brain: A review of structural and functional neuroimaging studies of hallucinations

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Abstract

Hallucinations remains one of the most intriguing phenomena in psychopathology. In the past two decades the advent of neuroimaging techniques have allowed researchers to investigate what is happening in the brain of those who experience hallucinations. In this article we review both structural and functional neuroimaging studies of patients with auditory and visual hallucinations as well as a small number of studies that have assessed cognitive processes associated with hallucinations in healthy volunteers. The current literature suggests that in addition to secondary (and occasionally primary) sensory cortices, dysfunction in prefrontal premotor, cingulate, subcortical and cerebellar regions also seem to contribute to hallucinatory experiences. Based on the findings of these studies we tentatively propose a neurocognitive model in which both bottom-up and top-down processes interact to produce these erroneous percepts. Finally, directions for future work are discussed.

Keywords: Hallucinations; Auditory; Visual; Schizophrenia; Neuroimaging; Functional magnetic resonance imaging (fMRI); Positron emission tomography (PET); Auditory cortex and language

Contents

1. Introduction

In many ancient cultures the experience of auditory verbal hallucinations (AVH) or 'hearing voices' was considered a message from the gods or other spiritual entities (Jaynes, 1976). Today, however, AVH are often

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regarded as an abnormal experience and a sign of mental illness. They are a cardinal feature of schizophrenia and other psychotic disorders and are one of the main diagnostic criteria for the illness (Diagnostic and Statistical Manual IV; 1994). Hallucinations can be defined as any perceptual experience in the absence of external stimuli and must be sufficiently compelling to be considered a true perception. They may involve any of the senses, although auditory and visual hallucinations are most common in psychiatric and organic disorders. Much of the research into this intriguing phenomenon has addressed the question 'what is happening in the brain that hears voices when nobody is speaking?' The advent of neuroimaging techniques in the last two decades has allowed us to at least begin to formulate answers to this question. Techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been widely used. Studies have also been directed at investigating the structural correlates of hallucinations, i.e. whether volume reductions of certain brain areas are associated with hallucinations.

Weiss and Heckers (1999) published the first systematic review of the hallucination neuroimaging literature. This influential review covered literature relating to both visual and auditory hallucinations derived from structural and functional imaging studies. However, in the intervening 8 years the field has progressed and an update of the literature is timely. For example, diffusion tensor imaging (DTI) and increasingly sophisticated analytical techniques have allowed us to examine connections between neural regions in patients with hallucinations (Hubl et al., 2004; Shergill et al., 2007). Later studies have also identified a more distributed network of regions including non-sensory areas in addition to the sensory area implicated in earlier studies. This has allowed researchers to address the questions of bottom-up and top-down processes involved with hallucinations as well as the issue of lateralization.

In this review we will systematically cover PET and fMRI studies examining brain structure, function and connectivity in patients experiencing hallucinations. Studies conducted in healthy samples using tasks designed to assess cognitive mechanisms associated with hallucinations have also been included. The vast majority of the studies included in this review report on patients with schizophrenia or schizophreniform disorders simply because most studies are conducted in this group. Finally, a neuroanatomical model of AVH will be presented and directions for future work discussed.

2. Methods

The papers reviewed have been drawn from comprehensive MEDLINE, EMBASE and PsycINFO searches of the English language literature. All articles reporting data on the neural substrates of hallucinations using PET and MRI and DTI techniques were included. To qualify for inclusion, studies must be an original work appearing in a peer—reviewed journal. In total 54 published articles reporting PET structural and functional MRI and DTI studies of the neural substrate of hallucination were found spanning a period from 1990 to 2007.

3. Brain structure and hallucinations

Structural neuroimaging, using computerised tomography (CT) or magnetic resonance imaging (MRI), is often used clinically to rule out a focal lesion such as a tumour or a stroke. Braun et al. (2003) reviewed a large number of case studies of post lesion hallucinations in the visual, auditory and somatic modalities. The authors report that the lesion is almost always located in the brain pathway of the sensory modality of the hallucination and suggest that compensatory over-activation of the nearby brain tissue as causative in hallucinosis. It is suggested that the lesioned tissue must have contained a predominance of inhibitory over excitatory neuron for the sensory modality in question. These inhibitory neurons would normally be responsible for 'gauging down' brain circuits containing complex sensory representations. One recent study by Lin et al. (2006) not included in the review by Braun et al. (2003) reports on Alzheimer's disease patients with and without visual hallucinations. Patients with visual hallucinations had more occipital periventricular white matter hyperintensities than patients without visual hallucinations whilst occipital deep white matter hyperintensities were not seen in either group (Lin et al., 2006). The authors concludes that structural lesions in geniculocalcarine regions and preserved subcortical connections are involved in the genesis of visual hallucinations in Alzheimer's disease.

In psychiatric groups; however, no gross brain abnormalities can be seen on scans at the individual level. Despite this, a large body of structural imaging literature has been published reporting on studies of patients with schizophrenia (for a review see (Shenton et al., 2001). A number of these studies have specifically addressed structural abnormalities associated with AVH in schizophrenia. Two methodological approaches are normally used. Brain scans are averaged across groups of subjects with and without hallucinations to investigate subtle abnormalities at the group level. Alternatively, correlational analyses between biological indices and symptom severity (i.e. severity of AVH) can be performed. The results of these studies are summarised in Table 1.

Weiss and Heckers (1999) summarised the results of studies published up to 1999. Two of these studies involved patients with Alzheimer's disease (Forstl et al., 1993; Howanitz et al., 1995), one study is of elderly people with idiopathic visual hallucinations (Shedlack et al., 1994) and one study includes patients with schizophrenia (Barta et al., 1990). The patients with schizophrenia were characterised by volume reductions of the superior temporal gyrus (STG) in addition to larger ventricles. In particular, hallucination severity was inversely correlated with left STG volume.

Table 1
Summary and characteristics of structural neuroimaging studies

Author	Sample size and characteristics	Method	Regions of grey/white matter alterations in patients.
Barta et al. (1990)	15 Patients with schizophrenia 15 Healthy volunteers	MRI	↓ Volume of the left superior temporal gyrus associated with severity of hallucinations
Cullberg and Nyback (1992)	33 Patients with schizophrenia	CT	Association between the width of 3rd ventricle and occurrence of AVH
Forstl et al. (1993)	17 Alzheimer's disease patients with/without hallucinations 33 Healthy volunteers	CT	↑ Ventricles in patients with hallucinations
Shedlack et al. (1994)	5 Geriatric patients with visual hallucinations 12 Healthy volunteers	MRI	↑Hyperintensities in posterior periventricular regions
Howanitz et al. (1995)	20 Alzheimer's disease patients with psychosis 12 Alzheimer's disease patients with psychosis	MRI	↑ Overall cerebral atrophy and enlarged ventricles in patients with AVH compared to patients without AVH
DeLisi et al. (1994)	85 Patients with 1st episode schizophrenia 40 Healthy volunteers	MRI (ROI)	No difference in STG or PT volume in hallucinator subgroup vs. controls
Flaum et al. (1995)	166 Schizophrenia spectrum disorders patients	MRI (ROI)	Hallucinations predicted ↓ in left STG volume
Cowell et al. (1996)	91 Schizophrenia patients 114 Healthy volunteers	MRI (ROI)	No association between Schneiderian symptom subtype and grey matter volumes
Havermans et al. (1999)	15 Schizophrenia patients with AVH 15 Schizophrenia patients without AVH 17 Healthy volunteers	MRI (ROI)	No group differences for left STG volume and Other temporal lobe structures.
Levitan et al. (1999)	30 Schizophrenia patients with history of AVH	MRI (ROI)	AVH severity associated with ↓ anterior STG volume
Rajarethinam et al. (2000)	20 Patients with schizophrenia 20 Healthy volunteers	MRI (ROI)	Anterior and posterior STG volumes associated with severity of hallucinations
Shapleske et al. (2002)	41 Schizophrenia patients with AVH 31 Schizophrenia patients without AVH 32 Healthy volunteers	MRI (VBM)	↓ Grey matter volumes in the left insula and Adjacent temporal lobe in patients with AVH compared to patients without AVH
Onitsuka et al. (2004)	23 Patients with schizophrenia 28 Healthy volunteers	MRI (ROI)	Severity of hallucinations associated with ↓ grey matter volumes in left S/MTG
Gaser et al. (2004)	85 Patients with schizophrenia	MRI (DBM)	Severity of AVH associated with ↓ volume of Heschl's gyrus (primary auditory cortex), left super marginal gyrus, middle/inferior right frontal gyrus
Sumich et al. (2005)	25 1st episode schizophrenia patients	MRI(VBM)	↓ In left Herschl's gyrus associated with AVH and delusions
Shin et al. (2005)	17 1st episode patients with AVH 8 1st episode patients without AVH	MRI(VBM)	Hallucinators ↑ temporal white/grey matter, frontal grey matter compared to nonhallucinators
Neckelmann et al. (2006)	12 Schizophrenia patients 12 Healthy controls	MRI(VBM)	Severity of hallucinations associated with ↓ grey matter volume in left STG (transverse), left thalamus, left and right cerebellum
Lin et al. (2006)	5 Alzheimer's disease patients with VH 5 Alzheimer's disease patients without VH	MRI	↑ Occipital periventricular white matter hyperintensities in patients with VH

AVH = auditory verbal hallucinations, VH = visual hallucinations, CT = computerised tomography, MRI = magnetic resonance imaging, VBM = voxel based morphometry, ROI = region of interest, DBM = deformation based morphometry.

Another study in schizophrenia patients (Cullberg and Nyback, 1992), not mentioned in the Weiss and Heckers (1999) review, reported a correlation between persistent auditory hallucinations and the width of the third ventricle. A limitation is that all these studies included small numbers of patients (less than 20), making it difficult to establish any firm conclusion. However, taking into account of the auditory association cortex abnormalities in schizophrenia and the visual pathway abnormalities in idiopathic visual hallucinations, Weiss and Heckers (1999) cautiously suggest that abnormalities in the production of hallucinations may be sensory modality-specific.

Other studies have reported a relationship between auditory hallucinations and the STG (Flaum et al., 1995) replicating the finding of Barta et al. (1990) of an inverse correlation between STG volume and AVH in patients with schizophrenia. A more recent study by Onitsuka et al. (2004) also reported that increased severity of AVH is correlated with reduced left anterior STG and middle temporal gyrus (MTG) grey matter volumes.

Five other MRI studies concerning regional abnormalities in brain structure related to hallucinations are also of interest. Using a more sophisticated analytical technique (voxel based morphometry; VBM) that allows for whole brain analysis, these studies have reported structural alteration in non-sensory regions in addition to the auditory cortex. Shapleske et al. (2002) used a computational morphometric technique to analyze whole brain grey and white matter in 41 hallucinating, 31 non-hallucinating patients and 32 age and gender matched controls. When patients with and without AVH were compared reduced grey matter tissue was seen in the left insula and adjacent temporal pole in hallucinators. Neckelmann et al. (2006) also used voxel-based morphometry methods (capable of analysing whole brain grey matter), to study grey matter volume differences between patients with schizophrenia and healthy controls. Areas of grey matter volume reduction that correlated with hallucinations were found in the left superior temporal gyrus, in addition to thalamus and cerebellum. This was a very small study; however, including only 12 patients. Gaser et al. (2004) studied 85 patients with schizophrenia, of which 29 experienced hallucinations. They found severity of hallucinations to be correlated with volume loss in the left transverse temporal gyrus of Heschl (i.e. primary auditory cortex) and left (inferior) supramarginal gyrus, as well as the right dorsolateral prefrontal cortex. The authors suggest that the volume reduction in left hemisphere auditory and speech perception areas may lead to a failure to inhibit and correctly attribute internal speech, as proposed in the verbal self-monitoring hypothesis (Frith and Done, 1988). In addition, 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). That is, impairments in this network could erase the volitional signature of subjective perceptual awareness arising 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) and these are the densest of all the interhemispheric pathways (McGuire et al., 1991). Impairment of one region may thus lead to hyperactivation of the homotopic region. Because the authors applied a novel automated whole-brain morphometric technique in a large group of patients using high-resolution scans, this study might have been more sensitive than previous studies. Furthermore, their method assesses differences at the voxel level over the entire brain and minimises user bias. Sumich et al. (2005) assessed positive and negative symptomology in 25 first episode patients and its relationship with grey matter volumes in the temporal lobe. The study used linear regression to establish associations between symptom dimensions and stereological measurements of Heshl's gyrus and the planum temporale. The authors report that a volume decrease in the left Heshl's gyrus was associated with hallucinations whereas increased volumes in the left planum temporale were associated with delusions.

Contrary to most other studies, Shin et al. (2005) reported *increased* grey and white matter volumes 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 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. One other study also reports increased total brain volumes in patients with AVH compared to patients without (Rossell et al., 2001). Such findings may be consistent with theories of increased connectivity between cerebral regions in hallucinating patients or may reflect methodological shortcomings, (e.g. small samples, poor definition of hallucination status).

Despite the apparent alteration in STG volume reported in patients with AVH, Stephane et al. (2001) cautioned that 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). However, although the results of earlier structural MRI studies are equivocal, later works using more sophisticated analysis techniques suggest that AVH are associated with reduced grey matter volumes in the temporal lobe. Eight studies report decreased grey matter volume in the left temporal lobe associated with hallucinations while three failed to find an association. One study found an increase in frontal and temporal grey and white matter and another four report ventricular and periventricular alterations. Overall, grey matter reductions in the left STG including the primary auditory cortex are most

consistently reported. This is 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). Reduced grey matter volumes in non-sensory regions have been reported in four studies. Volume reductions in the prefrontal and cerebellar corticies may be associated with impairments in the monitoring or awareness and volition of internal speech.

4. Brain activity during hallucinations

Functional imaging studies of hallucinations are concerned with changes in blood flow and metabolism associated with the occurrence of hallucinations. Two types of studies can be distinguished. First, several studies have attempted to directly measure brain activity occurring during the experience of hallucinations. These are generally referred to as 'activity studies' (Table 2). A number of these studies have also presented patients with an auditory stimulation task (involving sounds or speech) while they were experiencing hallucinations. Second, studies compare patients with and without hallucinations on cognitive tasks presumed to measure cognitive processes underlying the disposition to hallucinate. These have been referred to as 'cognitive studies' (Table 3). An advantage of these functional studies is they use whole brain analytical approaches and almost all have identified altered function in regions outside the sensory corticies. We will discuss evidence from both types of studies, with an emphasis on schizophrenia patients, as most have been concerned with this group. However, we will also pay attention to imaging studies of visual hallucinations in neurological conditions.

4.1. Activity studies

Some heuristic information comes from PET studies that measured regional cerebral blood flow during a resting state and then correlated this with clinical features. Liddle et al. (1992) were the first to directly investigate the association between symptoms and brain activity in patients with schizophrenia. They showed that different symptom clusters (psychomotor poverty, disorganisation and reality distortion) were associated with different patterns of cerebral blood flow in a group of 30 patients. In particular, reality distortions (hallucinations and delusions) were correlated with resting state perfusion in the medial temporal lobe. In a similar study, Gur et al. (1995) observed a positive correlation between the presence of positive symptoms (hallucinations and delusions) and superior temporal lobe metabolism in a group of 42 drug-free schizophrenia patients. More recently, Lahti et al. (2006) studied two cohorts of drug-free schizophrenia patients using PET. Positive symptoms correlated positively with resting activation in the anterior cingulate cortex and negatively with the hippocampus/parahippocampus.

A limitation of these studies is that no direct relationship between brain activity and the occurrence of hallucinations during scanning was investigated. A small group of studies have addressed this issue directly comparing brain activity between patients when they are experiencing hallucinations and when they are not. In general, patients in these studies were symptomatic and using antipsychotic medication at the time of scanning. McGuire et al. (1993) scanned 13 patients using PET during an episode of their illness in which they regularly experienced AVH). They were scanned again on a second occasion, when the hallucinations were absent. Compared to the second measurement, hallucination-related activity was observed in language-related areas, especially Broca's area (involved in speech production). To a lesser extent, activity was also found in the anterior cingulate (involved in attentional processes), and in the left temporal cortex (involved in auditory perception and memory processes). Suzuki et al. (1993) observed an increase in regional blood flow in the left temporal lobe (auditory association cortex) in five hallucinating patients. Silbersweig et al. (1995) report activation of subcortical structures (bilateral thalamus, right putamen and caudate), bilateral parahippocampal gyrus, right anterior cingulate and left orbitofrontal cortex in five patients during auditory hallucinations). It is of interest to note activation of brain regions involved in the experience and regulation of emotion in this study (parahippocampal gyri, cingulate, orbitofrontal cortex). The authors suggest that activity in deep brain structures might generate or modulate hallucinations, whereas cortical activity may affect the specific perceptual content of the hallucinations. One of the patients studied by Silbersweig et al. (1995) also hallucinated in the visual modality. For these hallucinations, activation was observed in visual areas (lingual, fusiform and occipital gyri) and in the superior and middle temporal cortex. In the first extensive study of brain activation during visual hallucinations Ffytche et al. (1998) also observed activity in extrastriate visual cortex (ventral occipital lobe). The study included 8 patients with Charles Bonnet syndrome who experienced complex visual hallucinations of colour, faces, textures and objects. Besides activation of the visual cortex, the authors observed that the content of the hallucinations reflected the functional specialisations of the activated regions. Thus, in patients who hallucinated in colour, activity was found in the colour centre, V4, whereas in the only patient who hallucinated in black and white, the activity was outside this region. A recent functional study of visual hallucinations by De Haan et al. (2007) used fMRI to examine the neuroanatomical correlates of visual hallucinations in patients with left visual field defect who had suffered bilateral occipital infarction. Bilateral activation was observed during visual stimulation in the calcarine fissure and the same activation was found medially in the left and right occipital cortex adjacent to the infarcted areas. Holroyd and Wooten (2006) used fMRI to examine visual cortex function in Parkinson's disease patients who did and

Table 2
Summary and characteristics of activity studies of patients with hallucinations

Author	No. of subjects in group and design	Method	Activation pattern associated with hallucinations
McGuire et al. (1993)	12 Patients with schizophrenia and AVH (scans were compared when patients were symptomatic and remitted)	SPET	↑ Broca's area. ↑ L. anterior cingulate ↑ L. temporal lobe.
Suzuki et al. (1993)	5 Patients with schizophrenia and AVH (scans were compared when patients were symptomatic and remitted)	PET	↑L. Superior temporal gyrus ↑ Anterior cingulate gyrus
Woodruff et al. (1995)	1 Patient with schizophrenia and AVH (scans were compared when patients were symptomatic and remitted)	fMRI	↑ Superior and middle temporal gyrus
Silbersweig et al. (1995)	5 Patients with schizophrenia with current AVH (scans were compared for periods when AVH were present and absent)	PET	↑ Hippocampus ↑ Parahippocampal gyrus ↑L/R thalamus ↑R. ventral striatum ↑R. anterior cingulate
Ffytche et al. (1998)	8 Patients with Charles Bonnet syndrome (visual hallucinations) 5 Healthy volunteers	fMRI	↑ Ventral extrastriate visual cortex
Szechtman et al. (1998)	8 Healthy volunteers hallucinating under hypnosis 6 Healthy volunteers not hallucinating under hypnosis	PET	↑ Anterior cingulate
Kasai et al. (1999)	1 88 Year old woman experiencing musical hallucinations	SPET	↑ R. superior/inferior temporal gyrus during musical hallucinations
Lennox et al. (1999)	1 Patient with schizophrenia and AVH	fMRI	↑ R. middle temporal lobe
Dierks et al. (1999)	3 Patients with schizophrenia and AVH (scans were compared for periods when AVH were present and absent)	fMRI	↑ L. posterior superior temporal gyrus ↑ L. anterior superior temporal gyrus ↑ L. middle temporal gyrus ↑ hippocampus/ amygdala ↑ Broca's area
Shergill et al. (2000a)	6 Patients with schizophrenia and AVH (scans were compared for periods when AVH were present and absent)	fMRI	↑ Inferior frontal gyrus ↑ Anterior cingulate ↑ L/R temporal cortex ↑ R. thalamus ↑ Inferior colliculus ↑ L parahippocampal/hippocampal gyrus
Lennox et al. (2000)	8 Patients with schizophrenia and AVH (scans were compared for periods when AVH were present and absent)	fMRI	↑ R/L superior temporal gyrus ↑L inferior parietal gyrus ↑L middle frontal gyrus
Shergill et al. (2001)	1 Patient with schizophrenia and auditory/ tactile hallucinations	fMRI	↑ Somatosensory cortex, thalamus, parietal cortex during tactile hallucinations ↑ R. temporal cortex during auditory hallucinations
Bentaleb et al. (2002)	1 Patient with schizophrenia and AVH 1 Healthy volunteer	fMRI	↑L primary auditory cortex ↑L middle temporal gyrus
Izumi et al. (2002)	1 Patient with AVH and musical hallucinations	SPET	↑ Bilateral lower frontal area and basal ganglia during musical hallucinations. ↑ left lower temporal area, right lower frontal areas and left basal ganglia during verbal hallucinations
Van de Ven et al. (2005)	6 Patients with schizophrenia and AVH (ICA used to establish activation associated with AVH)	fMRI	↑ Primary auditory cortex (Heschl's gyrus) in 3 patients
Mori et al. (2006)	1 Patient with Alzheimer's Disease and auditory hallucinations	SPET	↑ L temporal lobe and L angular gyrus
Holroyd and Wooten (2006)	Parkinson's Disease patients with and without VH	fMRI	↑ Activation in visual association cortex and ↓ in primary visual cortex
De Haan et al. (2007)	1 Patient with bilateral occipital infarction and VH using visual stimulation	fMRI	↑ Bilateral occipital cortex adjacent to the infarcted area

SPET = single photon emission tomography, PET = positron emission tomography, fMRI = functional magnetic resonance imaging.

Table 3
Summary of cognitive activation, asymmetry and connectivity studies in patients with hallucinations

Author	No. of subjects in group and design	Method	Activation Pattern associated with hallucinations/ patients with AVH
Howard et al. (1995)	1 Patient with Lewy body dementia and visual hallucinations using external visual stimuli.	fMRI	↓ Visual cortex response during hallucinations
David et al. (1996)	1 Patient with schizophrenia and AVHs using external auditory and visual stimuli	fMRI	↓ Superior temporal gyrus (STG) activation to auditory stimuli during AVH.
McGuire et al. (1996a)	6 Schizophrenia patients with AVH, 6 Without AVH, 6 Healthy volunteers using Inner speech/Auditory verbal imagery task.	PET	↓ Left middle temporal gyrus (MTG) & supplementary motor area (SMA) for auditory verbal imagery task.
McGuire et al. (1996b)	6 Healthy controls using an overt verbal self-monitoring task	PET	Monitoring of self-generated speech associated with bilateral temporal activations.
Woodruff et al. (1997)	8 Patients with schizophrenia and trait AVH 7 Trait hallucinators 8 Healthy volunteers using an auditory perception of speech.	fMRI	No difference in temporal cortical activation between trait positive and trait negative patients. Comparison of patients when experiencing severe hallucinations and when hallucinations were mild revealed reduced Responsivity of the R MTG to external speech.
Shergill et al. (2000b)	8 Patients with schizophrenia and AVH 6 Healthy volunteers using inner speech/auditory verbal imagery task.	fMRI	↓ Posterior cerebellum, hippocampal complex, bilateral lenticular nucleus, right thalamus, MTG & STG during auditory verbal imagery
Shergill et al. (2003)	8 Patients with schizophrenia and AVH 8 Healthy volunteers using a parametric inner speech generation task.	fMRI	↓ R.STG, right parahippocampal gyrus, right cerebellum during increased rate of speech generation
Copolov et al. (2003)	8 Patients with schizophrenia and AVH 7 Patients without AVH 8 Healthy volunteers Perception of externally generated speech.	PET	↑ Bilateral auditory cortex, left limbic regions, R medial prefrontal and R. prefrontal cortex
Fu et al. (2006)	13 Healthy volunteers using an overt verbal self-monitoring task	fMRI	Correct attributions self-distorted speech associated ↑ temporal lobe activation than misattributions.
Aleman et al. (2005)	6 Healthy volunteers using a metrical stress evaluation task.	fMRI	Posterior part of the L STS/STG activated during imagery condition.
Plaze et al. (2006)	15 Patients with schizophrenia and AVH sentence listening task.	fMRI	Severity of AVH correlated with reduced activation in LSTG.
Allen et al. (2007)	10 Patients with schizophrenia and AVH 10 Patients without AVH 11 Healthy volunteers source monitoring of pre-recorded speech.	fMRI	↓ In anterior cingulate in ↑ RSTG activation associated with misattribution of self speech in patients with AVHs compared to control groups
Asymmetry & Connectivity			
Shapleske et al. (2001)	44 Patients with schizophrenia and AVH 30 Patients without AVH 32 Healthy volunteers	sMRI (ROI)	No group differences in planum temporale, sylvian fissure (SF). ↑ leftward asymmetry of SF correlated with severity of AVH.
Lawrie et al. (2002)	8 Patients with schizophrenia 10 Healthy volunteers Covert sentence completion task	fMRI	Correlation coefficients between L temporal cortex and LDLPFC prefrontal cortex were significantly lower in the schizophrenic group and negatively correlated with the severity of AVH
Hubl et al. (2004)	13 Patients with schizophrenia and AVH 13 Patients without AVH	MRI (DTI)	↑ White matter directionality in the lateral parts of the temporoparietal section of the arcuate fasciculus and in parts of the anterior corpus callosum compared with control groups

Table 3 (*continued*)

Author	No. of subjects in group and design	Method	Activation Pattern associated with hallucinations/ patients with AVH
	13 Healthy controls		
Weiss et al. (2006)	7 Patients with schizophrenia (5 antipsychotic naïve)	fMRI	↓ Leftward lateralization in IFG associated with severity of hallucinations
	Verbal fluency Task		
Mechelli et al. (2007)	10 Patients with schizophrenia and AVH 10 Patients without AVH	fMRI (DCM)	↓ Effective connectivity between left STG and anterior cingulate in patients with AVH compared to control groups.
	11 Healthy volunteers source monitoring of pre-recorded speech.		
Shergill et al. (2007)	33 Patients with schizophrenia	MRI (DTI)	↓ FA in patients with schiz in regions corresponding to bilateral superior longitudinal fasciculi and genu of corpus collosum. AVH associated with ↑ FA in longitudinal fasciculi and anterior cingulum.
	4 Healthy controls		
Stephane et al. (2006)	8 Patients with schizophrenia and AVH 10 Patients without AVH 12 Healthy volunteers Reading single word	PET	↑ Activity in Wernicke's area in all patients during reading. Patients with AVH showed reversed laterality index of SMA

PET = positron emission tomography, fMRI = functional magnetic resonance imaging DTI = diffusion tensor imaging. DCM = dynamic causal modelling. FA = fractional anisotropy.

did not experience visual hallucinations. Patients with visual hallucinations demonstrated increased activation in the visual association cortex and deficits in the primary visual cortex, suggesting that visual hallucinations are associated with an abnormality of visual-cortex function in this Parkinson's patients.

One PET study of particular interest was reported by Szechtman et al. (1998). The study is unusual in that it compared brain activation in highly hypnotisable volunteers during different experimental conditions: hearing, imagining and hallucinating. Eight of these volunteers were able to hallucinate under hypnosis (these were termed hallucinators), whereas six lacked this ability (control group). A region in the right anterior cingulate cortex was activated in the group of hallucinators when they heard an auditory stimulus and when they hallucinated hearing it, but not when they merely imagined hearing it. The same experimental conditions did not yield such activation in the control group. The investigators suggest that the anterior cingulate activation 'tags' an auditory event as originating from the external world. Thus, in hallucinations, such activation may reflect a mismatch between externally directed attention and internally generated events. They propose that the involvement of rostral anterior cingulate cortex (which has been implicated in modulating affect) may imply that the attention of hallucinators is more affect-laden than that of non-hallucinators, and speculate that when attention is more affect-laden, self-generation of the expected auditory event is more likely to occur. A major problem; however, is that no anterior cingulate activation was observed in the hearing versus baseline condition for the non-hallucinators. If anterior cingulate activation tags an auditory event as originating from the external world, one would expect such activation also in the control group.

With the widespread availability of fMRI that came about in the late 1990s a number of studies attempted to replicate earlier PET findings in patients with hallucinations. Lennox et al. (1999) used fMRI to image a male patient with schizophrenia experiencing intermittent AVH. Hallucinations occurred for approximately 26 s in which time the patient heard a voice, followed by a comparable period in which hallucinations were absent. The patient indicated with a key press when he heard the voice, which enabled a within-subject comparison between hallucinatory periods and hallucination-free periods. The results revealed strong activity in the right MTG during hallucinations. Using a similar method Dierks et al. (1999) scanned three patients with fMRI. Besides recording brain activity during hallucination periods, they also measured brain activity in response to acoustic stimulation (speech in one condition and a tone in another condition). They observed hallucination-related activity in Broca's area, the temporal gyri and in the primary auditory cortex (Heschl's gyrus). A striking observation of this study was that the highest correlation of the fMRI signal time course with acoustic stimulation was observed in the transverse gyrus of Heschl, at the same location as the focus of activation during hallucinations. Because inner speech in healthy people is not associated with activity in the primary auditory cortex (Aleman et al., 2005; McGuire et al., 1996a), it is possible that the abnormal occurrence of activity in primary cortex observed in patients interacts with inner speech to produce an experience that has the quality of a real external sound.

This may lead hallucinating patients to infer a non-self perceptual source (Dierks et al., 1999; Frith, 1999). A case study of a patient with schizophrenia who experienced continuous auditory-verbal hallucinations, that disappeared when she listened to loud external speech, also implicated the primary auditory cortex (Bentaleb et al., 2002). The authors report activation of left primary auditory cortex in addition to right temporal cortex when the hallucination condition was compared to a condition in which external speech was presented. However, activation of the primary sensory cortex during hallucinations has not been consistently replicated. Lennox et al. (2000) studied 4 patients with schizophrenia who experienced episodes of hallucination whilst in the scanner, which were compared with periods of rest in the same individuals. Group analysis demonstrated shared areas of activation in right and left superior temporal gyri, left inferior parietal cortex and left middle frontal gyrus but not the primary auditory cortex.

Most of the above studies relied on a button press method to indicate when hallucinations were being experienced. This may confound the associated activation, which may reflect the patient monitoring for hallucinations, preparing to press and then making a motor response. Moreover studies using fMRI may be further complicated by the effects of acoustic scanner noise on activation in the auditory cortex. Shergill et al. (2000a) used a novel fMRI method that involved a random sampling approach to overcome these limitations). This entailed collecting a large number of single fMRI volumes at unpredictable intervals while patients with schizophrenia were intermittently hallucinating. Immediately after each acquisition, patients report whether they had been hallucinating when they first heard the noise of that volume being acquired. Neural activity was then compared for the volumes when patients were and were not experiencing hallucinations. The results revealed a distributed network of cortical and subcortical activity associated with auditory hallucinations: inferior frontal/insular, anterior cingulate, temporal cortex bilaterally, right thalamus and inferior colliculus, and left hippocampus and parahippocampal cortex. However, no activation was observed in the primary auditory cortex. Shergill and colleagues were also able to provide information regarding the temporal course of AVH in these patients. Activation in the left inferior frontal and right middle temporal gyri was evident 6–9 s before patients signalled the onset of the hallucination, whereas activation in the bilateral temporal gyri and the left insula coincided with the perception of the hallucination. This supports the hypothesis that during hallucinations activation in cortical regions mediating the generation of inner speech may precede the engagement of areas implicated in the perception of auditory verbal material (Shergill et al., 2004).

In the most recent neuroimaging activity study of hallucinations, Van de Ven et al. (2005) studied six hallucinating schizophrenia patients using fMRI. They applied a data-driven analysis method known as spatial independent component analysis (ICA) that does not rely on a predefined model of brain activity. Such analysis methods are capable of separating relevant spatial networks from activity patterns related to other sources such as head movement. The authors observed auditory cortex activity (including Heschl's gyrus) during hallucinations in three of the six patients. Thus, it would appear that some but not all patients activated primary auditory cortex during auditory hallucinations. Van de Ven et al. (2005) also asked the patients to indicate the occurrence of hallucinations by button press. The time courses of regional brain activation found with ICA showed large variability in the shape, amplitude, and time of onset relative to self-reports. This supports the added value of using data-driven methods that do not rely exclusively on introspection. However, there was a clear association between the average of the time courses and the button-presses indicating hallucinations, suggesting that the researchers targeted the right component.

In addition to group studies of patients a number of interesting case studies contribute to the literature. These studies also suggest that hallucinations in a given modality involve areas that normally process sensory information in that modality. Furthermore, these studies have investigated the degree of modality-specific neural correlates of non-auditory hallucinations. For instance, Izumi et al. (2002) found evidence of differing patterns of regional cerebral blood flow during musical hallucinations versus verbal hallucinations. Shergill et al. (2001) studied a patient with both auditory and somatic hallucinations, and used neuroimaging (fMRI) to identify differences in brain activation underlying both. This analysis revealed that somatic hallucinations were primarily associated with activation in areas classically associated with tactile processing (e.g. primary somatosensory cortex, posterior parietal cortex, thalamus), whereas auditory hallucinations were primarily associated with activation in a distinct set of brain areas, particularly the right temporal cortex. Kasai et al. (1999) report right auditory cortex dysfunction (based on SPECT) during musical hallucinations in a cognitively intact 88-year-old woman. Finally, Mori et al. (2006) observed increased rCBF (based on SPECT) in left temporal regions and in the left angular gyrus in a patient with Alzheimer's disease.

In total seven studies report left lateralised, two report right lateralised, and four studies report bilateral temporal lobe activation during hallucinations. The one study of patients with visual hallucinations also reports bilateral activation in associated sensory cortex (ventral extrastriate visual cortex). Ten activation studies report non-sensory cortical and subcortical areas involved in the experience of hallucinations. Although the exact role of these areas is not yet clear, a possible hypothesis is that activity in subcortical areas and modality-specific association cortices, account for these conscious perceptual experiences. Inappropriate anterior cingulate activation may reflect impairments in the monitoring of speech and erroneously tags internally

generated imagery as originating from an external source. What is clear however is that studies have consistently observed activity in either language-production areas or in the primary auditory cortex during auditory hallucinations. This strongly implicates the temporal lobe, more specifically the middle or superior temporal gyri. For visual hallucinations, activity is observed in secondary visual cortex.

4.2. Cognitive studies

Cognitive studies are based upon paradigms intended to uncover specific cognitive processing abnormalities or biases associated with the predisposition to hallucinate. The simplest studies just present sensory stimuli in the same modality as the hallucinations in patients with hallucinations. The rationale behind these cognitive 'interference' studies is that lower activation in perceptual areas in response to external stimulation during periods of hallucination as compared to periods without hallucination would suggest that hallucinations and the processing of external auditory stimuli compete for common neurophysiological mechanisms. Studies by David et al. (1996) and Woodruff et al. (1997) provide evidence that sensory areas may be 'occupied' during the experience of hallucination. These investigators found that the auditory association cortex (superior temporal gyrus) is less responsive to external auditory stimulation during hallucinations compared to when they are absent. They interpret this as indicative of physiological competition for a common neural substrate by the hallucinations. This finding was confirmed in a recent study involving 15 patients with schizophrenia with daily auditory hallucinations for at least 3 months prior to the study (Plaze et al., 2006). They were studied with fMRI while listening to sentences or to silence. Severity of hallucinations correlated negatively with activation in the left STG in the speech minus silence condition, suggesting that auditory hallucinations compete with normal speech for processing sites within the temporal cortex in patients with schizophrenia. For visual hallucinations, an identical finding has been reported, with respect to visual cortex and a reduced activation to visual stimuli (Howard et al., 1995).

In another study in which patients with AVH were scanned while they listened to external speech Copolov et al. (2003) report limbic regions as being more active in hallucinators. It is suggested that the observed pattern of activation is consistent with models of auditory hallucinations as mis-remembered episodic memories of speech.

The above studies support the notion that hallucinations have sensory qualities as they involve perceptual brain areas. However, the origins of such perceptions are less clear. Much of the cognitive literature suggests that AVH arise through externalised thoughts due to defective source or self-monitoring of inner speech (for reviews see (Ditman and Kuperberg, 2005; Seal et al., 2004)). Functional imaging studies have investigated the hypothesis of defective verbal self-monitoring in schizophrenia patients with auditory verbal hallucinations. McGuire et al. (1995) studied the neural correlates of inner speech and verbal imagery in schizophrenia patients with and without AVH. In the inner speech task, volunteers were asked 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, hallucinators showed reduced activation in the left MTG and the rostral supplementary motor area, regions that were strongly activated by both normal volunteers and non-hallucinating patients. The authors concluded that a predisposition to verbal hallucinations in schizophrenia 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. (2000b) investigated the functional anatomy of auditory verbal imagery in patients with auditory hallucinations. Schizophrenia patients with a history of prominent auditory hallucinations and a healthy control group were scanned while generating inner speech or imagining external speech. Patients showed no differences while generating inner speech but experienced a relatively attenuated response in the posterior cerebellar cortex, hippocampi, lenticular nuclei, right thalamus, temporal cortex and left nucleus accumbens during verbal imagery. The authors concluded that this pattern of activation in patients with hallucinations was due to attenuation in regions implicated in 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. In a parametric study of inner-speech generation this group again examined brain areas implicated in processing inner speech in patients with auditory hallucinations (Shergill et al., 2003). Participants were trained to vary their rate of inner-speech generation. When the rate of inner-speech was increased, the patients with schizophrenia showed a relatively attenuated response in the right temporal, parietal, parahippocampal and cerebellar cortex. These findings were again interpreted as evidence for defective self-monitoring of inner-speech in patients experiencing hallucinations. Healthy volunteers show activation in brain regions involved in speech generation (left inferior frontal cortex) and perception (temporal cortex) during the generation and monitoring of inner-speech (Shergill et al., 2002). However, verbal self-monitoring seems to be particularly associated with temporal, parahippocampal and cerebellar activations (Frith and Done, 1988). In patients prone to hallucinations activation in these regions was relatively attenuated compared to control participants.

A small number of studies have directly addressed neural correlates of explicit source/self-monitoring in healthy individuals and patients with and without hallucinations. McGuire et al. (1996b) implemented a verbal self-monitoring task in a PET study with healthy volunteers. In the first

condition volunteers were shown words and asked to read them aloud. In a second condition volunteers were asked to read the word aloud but heard the investigator saying the word instead of themselves (alien feedback). On half the trials the speech that the volunteers heard was distorted by elevating the pitch. Distortion of the volunteers' speech while they read aloud led to a bilateral activation of the lateral temporal cortex. A similar pattern of activation was evident when volunteers read aloud, but the word they heard was spoken by someone else. These data suggest that self and externally generated speech are processed in similar regions of the temporal cortex. A subsequent fMRI study using the same task in a healthy control group confirmed these results (Fu et al., 2006). Furthermore, in this study the use of an event related design allowed correct and misattributed source judgements trials to be isolated and analyzed separately. Fu et al. (2006) report that correct source attributions for self-speech were associated with greater temporal activation than misattributions supporting the self-monitoring theory that a mismatch between expected (signalled via a feed forward signal or 'corollary discharge) and perceived auditory feedback leads to greater temporal activation. However, it should be noted that 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; Allen et al., 2007b). In brief 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. Yet the model does not explain why the patient experiences a particular external author (Pacherie et al., 2006). Frith proposed that the experience of externality may arise from a faulty belief system. An alternative account proposed by Jeannerod (1999) and Jeannorod and Pacherie (2004)) proposes that the attribution of one's own action to an external agent is because of abnormal activation of neural networks that are involved in representation of actions of the self (both overt and covert) and others. Functional imaging evidence of such a shared system in humans demonstrates that the neural circuits involved in action execution and action observations overlap (see Blakemore and Decety, 2001; Grézes and Decety, 2001 for reviews). However, to date this model has not been applied to speech monitoring in patients with hallucinations.

Using a speech-monitoring task in which participants made judgements (self/other) about the source of pre-recorded speech, Allen et al. (2007a) studied the neural correlates of source misattribution in patients with and without AVH, and healthy controls. Patients with AVH were more likely to misattribute their own speech externally than non-hallucinating patients and controls. Moreover, compared to both control groups, patients with hallucinations showed altered activation in the STG and anterior cingulate when making misattribution errors. The authors suggest that the misidentification of self-generated speech in patients with AVH is due to abnormal activation in the anterior cingulate and temporal cortex and may be related to impairment in the explicit evaluation of auditory verbal stimuli. This study is interesting as it implicates the anterior cingulate gyrus in source monitoring processes.

Using healthy volunteers Aleman et al. (2005) also examined the neural basis of cognitive processes that might be involved in hallucinations. The study investigated whether speech perception areas would activate during inner speech, using a performance-based task. The results showed that making metrical stress judgments of visually presented words activates speech perception areas in the left superior temporal sulcus. Volunteers were asked to imagine hearing somebody else reading the word out loud. Speech perception areas did not activate in a control condition in which volunteers 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. Aberrant over activation of the latter could account for the perceptual characteristics of voice hallucinations.

All twelve cognitive studies report activation in the sensory corticies although the laterality of these activations varies considerably. Four of these studies also report non-sensory activation although the precise networks activated depends on the cognitive tasks that were used. Early cognitive studies using interference paradigms suggest that hallucinations and the processing of external auditory stimuli compete for common neurophysiological resources in the superior temporal gyrus. Studies have also examined the monitoring of inner speech and the neural correlates of source misattribution in both healthy volunteers and patients with AVH. Patients with hallucinations demonstrate attenuated activation in cingulate, premotor, cerebellar, temporal and subcortical regions thought to subserve the monitoring of inner speech. The misattribution of inner speech may be particularly associated with altered engagement of the temporal and anterior cingulate corticies.

5. Cerebral asymmetry and connectivity in patients with hallucinations

A long-standing hypothesis regarding the etiology of schizophrenia posits variations in the dimension of language lateralization are associated with the illness. For example, Crow (1998) argues that symptoms of schizophrenia can be understood as a failure to establish dominance of language in one hemisphere, with consequent disruption of the mechanisms of 'indexicality' that allow the speaker to distinguish thoughts from speech output. Several authors have asserted that AVH may arise from aberrant activation in the right hemisphere (Olin, 1999). This hypothesis goes back to the influential book by Julian Jaynes (1976), *the origin of consciousness in the breakdown of the bicameral mind.* According to Jaynes, human beings

lacked conscious awareness until 1000 BC. In ancient times human behaviour was controlled by a "bicameral mind", with the left hemisphere as the site for speech whereas the right hemisphere mediated supernatural voices of gods and demons (i.e. hallucinations). The workings of such a bicameral mind would still be reflected in mental disorders such as schizophrenia. Reduced cerebral lateralization of language in schizophrenia has been documented in a substantial number of studies (Sommer et al., 2001). However, a quantitative examination of neuroimaging studies of hallucinations found a predominance of left hemisphere activation, and thus failed to support Jaynes' hypothesis of distinct roles of both hemispheres in language versus hallucinations (Sommer et al., 2002). Four studies however, do report altered lateralization in patients with hallucinations. Shapleske and colleagues compared structural brain asymmetry of the planum temporale (PT) and sylvian fissure (SF) of patients with no history of hallucinations (30 patients) and patients with a strong definitive history of AVH (44 patients) in addition to 32 matched healthy volunteers (Shapleske et al., 2001). They failed to find differences between the groups on these measures. The only significant finding was a modest correlation between leftward asymmetry of the sylvian fissure and hallucinations within the prominent hallucinator group.

In a functional MRI study of language activation Sommer et al. (2001) reported a correlation between hallucinations and decreased lateralization in patients with schizophrenia. Consistent with this, a recent study by Weiss et al. (2006) has also implicated aberrant asymmetry in patients with AVH. Using a verbal fluency task in unmedicated patients Weiss and colleagues report that patients with schizophrenia showed reduced language lateralization in the frontal cortex, because of a more bilateral activation of Broca's area compared with primarily left hemisphere activation in healthy controls. Furthermore, the decrease in lateralization was correlated with severity of hallucinations. However, the sample size was very small in this study, just 7 patients. Stephane et al. (2006) used PET to scan 18 patients with schizophrenia and 12 healthy volunteers whilst they read single nouns. The subset of patients with AVH showed reversed laterality in the supplementary motor area compared to the controls groups (greater in the right hemisphere). The authors conclude that abnormal laterality if the supplementary area activity accounts for the failure to attribute speech generated by one's own brain to ones self.

Integration between distributed brain regions in patients with and without hallucinations has also been examined by a small number of studies. Using magnetic resonance DTI, Hubl et al. (2004) investigated the integrity of white matter tracts in the brains of schizophrenic patients with and without hallucinations and a healthy comparison group. DTI assesses the directionality of water diffusion (anisotropy), which is restricted by boundaries such as white matter fibres. Reduced anisotropy implies a loss of white matter integrity. Patients with AVH, were shown to have significantly higher anisotropy values relative to both control groups in the lateral temporoparietal section of a major fiber 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 a region related to the acoustical processing of external stimuli. Shergill et al. (2007) used DTI to the integrity of the major white matter fasciculi, which connects the frontal, temporal and parietal cortices, and the corpus callosum in patients with schizophrenia. Across all patients there was reduced anisotropy in regions corresponding to the longitudinal fasiculi bilaterally and in the genu of the corpus callosum. Within the patients group AVH were associated with relatively increased anisotropy in the superior longitudinal fasciculi and in the anterior cingulum.

Two studies have also investigated functional and effective connectivity using fMRI data. In neuroimaging studies, functional connectivity is defined as cross correlations over time between spatial remote brain regions (Friston et al., 1993). Studies of effective connectivity; however, aim to indicate the contributory influence of each region on another (Bullmore et al., 2000; Friston et al., 1996). In a study of functional connectivity by Lawrie et al. (2002) 8 patients with schizophrenia and 10 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 regional brain responses between the two groups correlation coefficients between left temporal cortex and left dorsolateral prefrontal cortex were significantly lower in the patients with schizophrenia and were negatively correlated with the severity of auditory hallucinations. The authors conclude that frontotemporal functional connectivity is reduced in schizophrenia and may be associated with auditory hallucinations. However, it should be noted that patients were recruited to this study based on a diagnosis of schizophrenia rather than upon AVH status.

Mechelli et al. (2007) assessed effective connectivity in patients with and without AVH and in healthy volunteers. Using the fMRI data previously reported by Allen et al. (2007a) the hypothesis that source misattributions are associated with poor functional integration within the network of regions that mediate the evaluation of speech was tested. In healthy volunteers and patients without AVH, connectivity between the left superior temporal and the anterior cingulate cortex was significantly greater for alien than for self-generated speech. In contrast, the reverse trend was found in patients with AVH. The authors conclude that in patients with AVH, the tendency to misattribute their own speech to an external source is associated with impaired effective connectivity between the left superior temporal and anterior cingulate cortex.

Although this finding is based on external rather than internal speech, the same mechanism may underlie the faulty appraisal of inner speech in AVH.

In summary, although evidence for altered asymmetry in patients with hallucinations is inconclusive, four published studies provide evidence for disrupted connectivity between the temporal, prefrontal and anterior cingulate cortex. Alterations in both structural and functional integration of language and attentional networks may be crucial to understanding the neural substrate of these intriguing phenomena.

6. Towards a neuroanatomical model

Based on the findings discussed in this review, we propose a model describing a network of brain areas and their respective contributions to the hallucinatory experience. The model assumes several alterations in grey matter volume, activation, and functional connectivity of a network of brain regions whose interplay subserve the integral process of conscious perception (Fig. 1). Hyperactivation of the secondary sensory cortex (i.e. associative perceptual areas) is central to this model. With regards to auditory hallucinations a number of the studies report activation in the left posterior STG (analogous to the secondary auditory cortex) and Heschl's gyrus (primary sensory cortex) in patients whilst they are experiencing hallucinations. The secondary sensory cortex is crucial for perception of objects (Haxby et al., 1994), whereas the primary perceptual cortex is concerned with processing of more low-level aspects of a percept, such as line orientations in the case of primary visual cortex (Tootell et al., 1998), or tones in the case of primary auditory cortex (Formisano et al., 2003). Spontaneous neural activity in these regions, observed in healthy volunteers (Hunter et al., 2006) as well as patients may prime sensory regions for 'over-perceptualization'.

Given the widely reported involvement of non-sensory regions in patients with hallucinations any neuroanatomical model clearly needs to encompass a distributed network of cortical and subcortical regions. Compared to the non-hallucinating brain, the hallucinating brain is characterised by reduced grey matter volumes in the temporal cortex, stronger activation in subcortical centres, reduced control by the dorsolateral prefrontal cortex, aberrant activation from emotional attention centres (rostral/ventral anterior cingulate), and attenuated activation of the dorsal anterior cingulate, supplementary motor area and cerebellum which are thought to be involved in monitoring processes. Dysfunction in this 'top-down' network applies to hallucinations in any modality and can account for the often-emotional content, sense of externality and non-volition that accompany the experience. For speech hallucinations, typically experienced in psychotic illness, altered activation in speech production areas (i.e. inferior frontal gyrus) and altered coupling with monitoring areas (anterior cingulate) and language reception areas (Wernicke's area) is postulated. Our model hypothesises bottom-up dysfunction through over activation in secondary (and occasionally primary) sensory cortices that lead to the experience of vivid perceptions in the absence of sensory stimuli. The hallucinatory experience is 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. Finally, over activity of cortical and subcortical regions involved in the regulation of emotion (parahippocampal gyri, cingulate, orbitofrontal cortex) contribute to the often affect laden characteristics of hallucinations. Aberrant

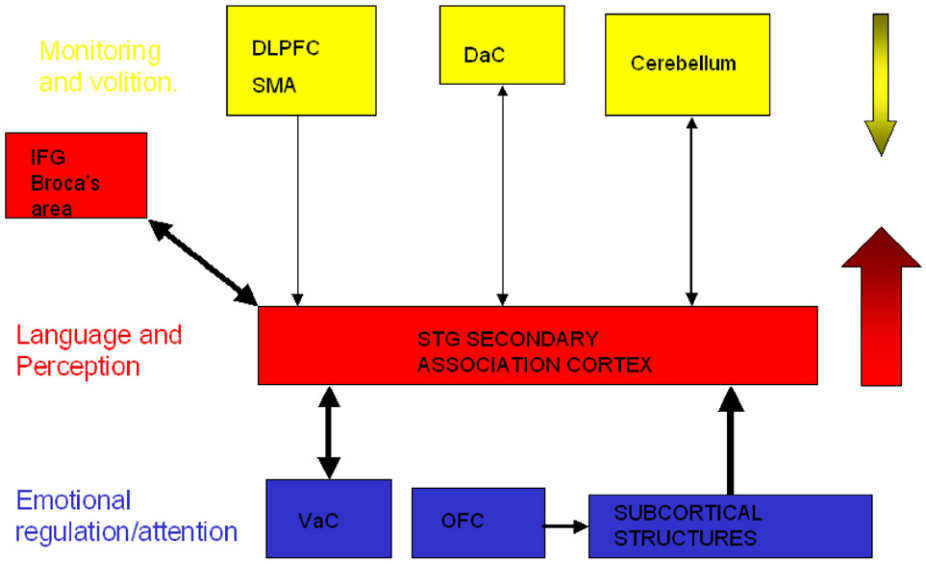

Fig. 1. Schematic diagram of brain regions involved in hallucinations: DLPFC = dorsolateral prefrontal cortex, SMA = supplementary motor area, DaC = dorsal anterior cingulate, Vac = ventral anterior cingulate, IFG = inferior frontal gyrus, OFC = orbitofrontal gyrus, STG = superior temporal gyrus. Thick lines represent increased connection strength, thin lines represent decrease connection strength.

connectivity between sensory corticies and frontal regions may be central to this dysregulation. The importance of fronto-temporal interactions has also been acknowledged by Peled (1999) who postulates a disconnection model as central to schizophrenia. With regards to AVH, altered connectivity between the superior temporal, inferior frontal gyrus and anterior cingulate cortex may cause dysfunctional activation in language processing areas.

It should be noted that although the model is novel, it integrates several aspects that have been proposed before by others. For example, the importance of fronto-temporal interactions was recognised previously (McGuire and Frith, 1996; Silbersweig and Stern, 1996). However, it is important to note, that previous authors in general favoured a disconnection model, in which frontal regions fail to prime perceptual centres regarding the internal origin of self-generated speech (i.e. failure of a corollary discharge mechanism). Our account also acknowledges the possibility of reduced control by monitoring centres in the anterior cingulate gyrus, dorsal frontal cortex and supplementary motor cortex. This may account for the repeated observations of the functional 'hyperactivity' in the sensory cortex during hallucinations. This would manifest via altered connectivity between distributed sensory and non-sensory regions. However, such a model is speculative and clearly needs to be examined by future research designed to address this hypothesis directly. Furthermore, the relationship between reduced grey matter volumes in primary and secondary sensory regions and functional 'hyperactivity' in these regions still remains unclear.

However, we also hypothesise an increased activation or hypercoupling of speech production centres in the inferior frontal cortex and speech perception areas in left temporoparietal cortex. Hoffman et al. (2007) provided some evidence for such a hypercoupling between temporoparietal and inferior frontal regions in the dominant hemisphere as an underlying pathophysiology of AVH. This is consistent with the available DTI evidence that reports increased anisotropy in the arcuate fasciculus that connects these language areas. A similar increased connectivity from emotional centres in the caudal anterior cingulate could boost activation of speech perception areas through attentional arousal mechanisms mediated by the thalamus. Evidence for this model is limited however; with only two studies reporting increased structural connectivity between language regions. These hypotheses await a more thorough investigation and would be supported by work that integrated both structural and functional connectivity methods in patients with AVH.

The role of emotion also deserves more attention. A recent study compared brain activation in patients with schizophrenia with persistent hallucinations to that in controls in an auditory emotional paradigm based on the most frequent words heard by patients with auditory hallucinations (Sanjuan et al., 2007). The authors found stronger activation of frontal lobe, temporal cortex, insula, cingulate and amygdala in patients when hearing emotional words in comparison with controls. Although this study lacked a patient group without hallucinations, the results suggest a relevant role for emotional response with regard to the neural basis of auditory hallucinations. Furthermore, in the studies by Dierks et al. (1999) and Shergill et al. (2000a, b) additional activations in regions responsible for the processing of emotion (e.g. the amygdala-hippocampus complex and insula) was also reported. According to Kircher et al. (2005) activation in these regions may be associated with the anxiety typically experiences when hearing voices.

Another area of research into hallucinations that has gathered momentum over recent years has involves the use if repeated transcranial magnetic stimulation (rTMS). The efficacy of slow (1 Hz) rTMS as a treatment for AVH in patients who do not respond to antipsychotic medication has been examined in several studies. Hoffman et al. (2003) studied 24 patients with treatment resistant AVH who were randomly allocated to rTMS treatment (focused on the left temporoparietal cortex) or sham treatment group for 9 day. Hallucinations were robustly improved by rTMS relative to sham. In a recent meta-analysis Aleman et al. (2007) reports on 15 treatment studies using 1 Hz rTMS centred on the left temporoparietal cortex. The meta analyses reported a mean weighted effect size of treatment gain for rTMS versus sham in ten studies involving 212 patients. Furthermore there were no effects of rTMS on composite scores for positive symptoms suggesting its specificity as a treatment for AVH. The results provide evidence for the efficacy of rTMS as an intervention that selectively alters neurobiological factors underlying AVH and provide further evidence for the role of the posterior temporal cortex in auditory hallucinations.

More research is needed into the neural basis of non-auditory hallucinations in non-schizophrenic patients. For instance, studies could examine visual hallucinations characteristic of Parkinson's disease and Charles Bonnet syndrome. Although top-down factors have been implied in these types of hallucinations (Collerton et al., 2005), we would suspect a stronger role of aberrant functioning of thalamo-cortical perceptual circuits per se, i.e. without a monitoring component. However, the lack of studies to date makes it difficult to establish a unifying model that can account for hallucinations across modalities.

The importance of how patients are recruited and assess needs to be considered. Clearly, this has not been consistent across studies and may have contributed to variable results of neuroimaging studies. Indeed, the different ways hallucinating and non-hallucinating patients are defined could potentially lead to the same person meeting the criteria for a hallucinator in one study and a non hallucinator in another (Ditman and Kuperberg, 2005). Finally, medication effects need to be considered. Many of the studies reported in this review negate this problem by either using a non-hallucinating patient group matched for medication or studying the same patients when they are actively hallucinating and then again when

their symptoms have remitted. However, a substantial number of studies do not control for the effects of medication (usually antipsychotics) upon neural activation measured by either fMRI or PET making these studies more difficult to interpret.

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