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Enhanced cortical effects of auditory stimulation and auditory attention in healthy individuals prone to auditory hallucinations during partial wakefulness

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ABSTRACT

Investigating auditory hallucinations that occur in health may help elucidate brain mechanisms which lead to the pathological experience of auditory hallucinations in neuropsychiatric disorders such as schizophrenia. In this study, we investigated healthy individuals who reported auditory hallucinations whilst falling asleep (hypnagogic hallucinations; HG) and waking up (hypnopompic hallucinations; HP). In an initial behavioural study, we found that subjects with a history of auditory HG/HP hallucinations (n = 26) reported significantly greater subjective sensitivity to environmental sounds than non-hallucinator controls (n = 74). Then, two fMRI experiments were performed. The first examined speech-evoked brain activation in 12 subjects with a history of auditory HG/HP hallucinations and 12 non-hallucinator controls matched for age, gender and IQ. The second fMRI experiment, in the same subjects, probed how brain activation was modulated by auditory attention using a bimodal selective attention paradigm. In the first experiment, the hallucinator group demonstrated significantly greater speech-evoked activation in the left supramarginal gyrus than the control group. In the second experiment, directing attention towards the auditory (vs. visual) modality induced significantly greater activation of the anterior cingulate gyrus in the hallucinator group than in the control group. These results suggest that hallucination proneness is associated with increased sensitivity of auditory and polysensory association cortex to auditory stimulation, an effect which might arise due to enhanced attentional bias from the anterior cingulate gyrus. Our data support the overarching hypothesis that top-down modulation of auditory cortical response characteristics may be a key mechanistic step in the generation of auditory hallucinations.

Introduction

Whilst auditory hallucinations are a characteristic feature of severe neuropsychiatric disorders such as schizophrenia (Sartorious et al., 1974), they also occur in healthy states including partial wakefulness (Ohayon et al., 1996). The occurrence of auditory hallucinations in both pathological and normal states implies that the brain has a generic propensity to hallucinate, and that pathological and non-pathological auditory hallucinations may arise from shared aspects of underlying neurobiological mechanisms (Woodruff, 2004; Hunter et al., 2006). Hence, although the characteristics of auditory hallucinations in the healthy general population may differ from those in people suffering from psychiatric conditions, investigating auditory hallucinations in health may help unravel brain mechanisms leading to the occurrence of pathological auditory hallucinations (Choong et al., 2007).

Hallucinations occurring as subjects fall asleep are termed hypnagogic (HG) hallucinations whereas hallucinations that occur on waking are termed hypnopompic (HP) hallucinations. HG and HP hallucinations are relatively common; in a large sample (n = 13,057) 24.8% of subjects reported having experienced hypnagogic hallucinations and 6.6% reported having experienced hypnopompic hallucinations (Ohayon, 2000). Furthermore, proneness to HG and HP hallucinations is positively correlated with proneness to hallucinations during wakefulness, as measured by the revised Launay–Slade Hallucination Scale (Bentall and Slade, 1985; Jones et al., 2009). Auditory HG and HP hallucinations have typically simple acoustic content (e.g., hearing a name called; Ohayon et al., 1996), whereas the auditory verbal hallucinations (AVH) that are characteristic of schizophrenia are generally more complex and exhibit grammatical sentence structure (Nayani and David, 1996). However, the key shared characteristic is that both auditory HG/HP hallucinations and AVH in schizophrenia are experienced as heard perceptions (Hunter,

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2004; Woodruff, 2004). This implies that their mechanism (in health and disease) involves a spurious representation of auditory signal (in the absence of actual auditory input) occurring within the brain's auditory perceptual apparatus (Hunter et al., 2006).

The idea that auditory hallucinations are associated with apparently spontaneous activation of auditory cortex has been explored in schizophrenia using functional neuroimaging and related techniques to capture brain activity. Numerous studies have found hallucination-related activation in auditory and language processing brain regions including the primary auditory cortex (Dierks et al., 1999; Bentaleb et al., 2002), superior temporal gyrus (Cleghorn et al., 1990; Woodruff et al., 1995, 1997; Lennox et al., 1999; Shergill et al., 2000; Sommer et al., 2008), middle temporal gyrus (Woodruff et al., 1995, 1997; Dierks et al., 1999; Lennox et al., 1999; Shergill et al, 2000; Bentaleb et al., 2002), posterior temporoparietal cortex (Sommer et al, 2008) and Broca's area (McGuire et al., 1993). Although it is possible that hallucination-related activation is underpinned by structural abnormalities in schizophrenia (Barta et al., 1990), it is also noteworthy that spontaneous activation of auditory regions can occur during silence in healthy non-hallucinating subjects (Hunter et al., 2006).

Spontaneous auditory activity leading to auditory hallucinations may come about because of increased sensitivity of auditory regions to internal, top-down, modulatory signals arising in higher cortical regions involved in the deployment of attention (Hunter et al., 2006). It has been hypothesised that states of heightened auditory attention might presage auditory hallucinations (Arieti, 1974; Behrendt, 1998; Grossberg, 2000; Woodruff, 2004; Hoffman, 2010); this idea is supported by the observation that individuals with auditory hallucinations demonstrate electrophysiological evidence of increased effortful attention during auditory processing (increased P300 amplitude; van Lutterveld et al., 2010). A candidate region for top-down modulation of auditory cortex leading to auditory hallucinations is the anterior cingulate cortex (ACC). This region has been found to be activated during the experience of auditory hallucinations in schizophrenia (McGuire et al., 1993; Silbersweig et al., 1995; Shergill et al., 2000). The intensity of ACC activation in this context has also been shown to predict hallucination severity (Cleghorn et al, 1990). Patients with schizophrenia and auditory hallucinations exhibit abnormal ACC activation and effective connectivity during self- and alien-speech processing (Allen et al., 2007; Mechelli et al., 2007). Whilst functional connectivity between the ACC and temporal cortex is thought to be generally reduced in patients with schizophrenia (Vercammen et al., 2010), patients with auditory hallucinations exhibit enhanced temporocingulate connectivity when processing recordings of their own speech compared with recordings of non-self generated speech (whereas non-hallucinating patients and healthy controls show the reverse; Mechelli et al., 2007). In healthy subjects, ACC activation has been demonstrated during auditory hallucinations occurring during meditation in individuals able to produce such phenomena (Szechtman et al., 1998). Activation of ACC has also been shown to accompany spontaneous activation of auditory cortex during silence in healthy, non-hallucinating, subjects (Hunter et al., 2006). Taken together, these studies suggest that ACC can modulate baseline auditory cortical activity in a manner that leads to spontaneous auditory activation and auditory hallucinations in some subjects.

It is possible that increased sensitivity of hallucination-prone auditory cortex to internal signals might reflect a more general state of auditory hypersensitivity manifest as enhanced auditory response to external stimuli. This notion is in accordance with the behavioural observations that: (1) patients with schizophrenia and auditory hallucinations demonstrate increased sensitivity to real speech compared with non-hallucinating schizophrenia patients (although both groups are less sensitive than healthy controls) and (2) patients with schizophrenia and auditory hallucinations demonstrate a significant response bias towards incorrect detection of speech stimuli (i.e., false alarms) whereas non-hallucinating schizophrenia patients and healthy controls do not (Vercammen et al, 2008). In the current study we aimed to investigate the auditory response to external stimulation in healthy individuals prone to HG/HP hallucinations compared with non-hallucinator controls. We also aimed to investigate the effects of auditory attention on cortical activation in HG/HP hallucinators compared with controls. Our overarching hypothesis was that auditory systems prone to hallucinate are unstable because they are hypersensitive to both external (stimulus driven) and internal (attention driven) effects. Our specific predictions were: (1) that individuals prone to auditory HG/HP hallucinations would show an exaggerated temporal cortical response to auditory stimulation compared with non-hallucinator controls and (2) that biasing attention towards the auditory modality would be associated with greater activation of ACC in HG/HP hallucinators than in non-hallucinator controls.

Materials and methods

This study was approved by the University of Sheffield Medical School Research Ethics Committee.

Behavioural study

Subjects

One hundred healthy volunteer participants (56 males) were recruited. Subjects were designated trait positive 'hallucinators' if they reported a history of experiencing HG or HP auditory hallucinations. Subjects were designated trait negative 'non-hallucinators' if they reported the absence of a history of experiencing HG or HP auditory hallucinations. Subjects' sociodemographic details were recorded and they were also assessed using the National Adult Reading Test (NART; Nelson, 1982). Subjects did not have a past history of psychiatric, neurological, hearing or visual disorders and gave informed consent to participate in this study.

Subjective auditory sensitivity

We used a specially devised questionnaire that comprised a series of 23 questions designed to assess subjective auditory sensitivity (e.g., 'Are you distracted by noise made by neighbours above, below or besides where you live, whilst others in your household are not?'). Test–retest reliability was assessed by asking a subset of 20 subjects (hallucinators = 10, non-hallucinators = 10) who had initially completed the questionnaire to complete it again, one month later.

Subjective auditory acuity and impairment

Subjective auditory acuity was assessed using the Hearing Handicap Inventory for Adults (Newman et al., 1990). This is a 25-item self-assessment tool designed to assess the subjective extent of hearing impairment. The inventory consists of an emotional (13-item) subscale and a social/situational (12-item) subscale. The higher the score, the greater the degree of subjective hearing impairment.

Scanning study 1. The temporal cortical response to speech in those with and without a history of HG and HP auditory hallucinations.

Subjects

Twelve healthy right-handed subjects (6 male) who experienced HG and HP auditory hallucinations were recruited for scanning. Twelve non-hallucinator control subjects (6 male) were also recruited. All subjects in our imaging experiments had initially participated in the behavioural study (above). Subjects' sociodemographic details were recorded and they were also assessed using the NART.

Stimuli

Twenty-four unique auditory stimuli were selected from a set used previously in psychophysical experiments (Hunter et al., 2005) and