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INVITED REVIEW

Auditory verbal hallucinations: neuroimaging and treatment

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Auditory verbal hallucinations (AVH) are a frequently occurring phenomenon in the general population and are considered a psychotic symptom when presented in the context of a psychiatric disorder. Neuroimaging literature has shown that AVH are subserved by a variety of alterations in brain structure and function, which primarily concentrate around brain regions associated with the processing of auditory verbal stimuli and with executive control functions. However, the direction of association between AVH and brain function remains equivocal in certain research areas and needs to be carefully reviewed and interpreted. When AVH have significant impact on daily functioning, several efficacious treatments can be attempted such as antipsychotic medication, brain stimulation and cognitive–behavioural therapy. Interestingly, the neural correlates of these treatments largely overlap with brain regions involved in AVH. This suggests that the efficacy of treatment corresponds to a normalization of AVH-related brain activity. In this selected review, we give a compact yet comprehensive overview of the structural and functional neuroimaging literature on AVH, with a special focus on the neural correlates of efficacious treatment.

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Introduction

In Kant's view of transcendental idealism, the world we perceive is shaped through an intrinsically generated process and not by external objects as they are. This implies an interaction between the observer and the observed, where the spatial and temporal properties of the perception are constrained by sensory faculties and therefore essentially subjective experiences. This fundamental subjectivity of perception is most vividly illustrated by the phenomenon of hallucinations. Hallucinations can occur in every sensory modality and often accompany a psychiatric, neurological, general medical condition or substance use. In the general population, hallucinations most often occur in the auditory domain and may take the form of auditory verbal hallucinations (AVH) (Beavan *et al.* 2011). This type of hallucination, in disease and health, will be the focus of this review.

In psychiatry, AVH are classified as a psychotic symptom. Indeed, 70% of patients with schizophrenia report AVH (Larøi *et al.* 2012). However, AVH occur across a broad range of psychiatric diagnoses such as bipolar disorder (11–63%; Toh *et al.* 2015), borderline personality disorder (20–50%; Schroeder *et al.* 2013), autism (20%; Kyriakopoulos *et al.* 2015) and post-traumatic stress disorder (50%; Anketell *et al.* 2010). In addition, AVH occur in people with hearing loss (Linszen *et al.* 2016) and in neurological disorders that excite the temporal cortex, such as epilepsy and migraine (Vreeburg *et al.* 2016). Thus, AVH are an important phenomenon in its own right, and can be said to represent an altered state of consciousness from a phenomenological point of view. As pointed out by Hugdahl (2015) and exemplified above, AVH cross the border between different psychiatric disorders, and neurological diseases, since they are found also in Parkinson's disease, Alzheimer's diseases and epilepsy, to mention a few examples. Finally, they cross the border between disease and health, by being present also in a certain percentage of the general population (Sommer *et al.* 2010).

Several theories exist to explain AVH, including overactivation of the auditory cortex (Penfield, 1958), misattribution of internally generated speech (Frith & Done, 1988; McGuire *et al.* 1995), errors in the corollary discharge for labelling internally generated events (Feinberg, 1978; Allen *et al.* 2006) and disturbances in episodic memory retrieval (Copolov *et al.* 2003). A growing body of neuroimaging research has provided

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support for a neurobiological basis of AVH (Hugdahl *et al.* 2009; Jardri *et al.* 2011; Palaniyappan *et al.* 2012; Modinos *et al.* 2013) and also for the efficacy of various treatment strategies. Here, we provide an overview of structural, physiological and functional imaging literature in AVH. Potential underlying mechanisms are discussed with a particular interest for the interaction of available treatment options (pharmacotherapy, brain stimulation and cognitive–behavioural therapy; CBT) with the neurobiology of AVH.

Anatomy and AVH

Early magnetic resonance imaging (MRI) studies reported significant negative associations between superior temporal gyrus (STG) volume (especially Heschl's gyrus; HG) and AVH severity in patients with schizophrenia (Barta *et al.* 1990; Levitan *et al.* 1999). This association was also observed in bipolar disorder with AVH (Stanfield *et al.* 2009). Later, voxel-based morphometry (VBM) studies complemented these findings by showing that volume reductions in the bilateral STG and the left insula are associated with AVH severity in schizophrenia (for meta-analyses, see Palaniyappan *et al.* 2012; Modinos *et al.* 2013).

In schizophrenia patients with AVH, cortical thickness is reduced in HG, Broca's area and Wernicke's area of the left hemisphere, while an increase is observed in the bilateral insula, cingulate gyrus, dorsal middle frontal gyrus and parietal lobe compared with non-hallucinators (Van Swam *et al.* 2012); others report a reduction in right HG (Chen *et al.* 2015). L Mørch-Johnsen *et al.* (unpublished observations) found that cortical thickness, but not area, was significantly reduced in AVH schizophrenia patients, thus extending the VBM studies which only provide data on the tissue volume or density. Interestingly, the only significant reduction, after correcting for multiple comparisons, was in the left STG, and HG. Furthermore, there is evidence that non-clinical hallucinators show an intermediate phenotype compared with controls and schizophrenia patients with AVH. Especially, cortical thicknesses of the left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus were found to show this continuum effect (Van Lutterveld *et al.* 2014).

Furthermore, the occurrence of AVH was classified with an accuracy of 83.6% in first-episode psychotic patients based upon the structural covariance of Broca's area, insula and intraparietal sulcus (Yun *et al.* 2015), suggesting that morphological aspects of these regions are predictive of AVH in psychotic disorders.

Diffusion-weighted MRI studies show that schizophrenia patients with AVH have significantly lower white matter integrity, as defined by fractional anisotropy (FA), in the left arcuate fasciculus compared with controls and non-hallucinating schizophrenia patients (Geoffroy *et al.* 2014; McCarthy-Jones *et al.* 2015). In addition, magnetization transfer of the left arcuate fasciculus is increased in schizophrenia patients and non-clinical hallucinators, suggesting a higher free water concentration due to degradation of axons or glia cells (De Weijer *et al.* 2013). The arcuate fasciculus connects the STG with the inferior frontal gyrus (IFG) and is believed to be a key white matter tract in the language network (Catani *et al.* 2005; Catani & de Schotten, 2012).

Furthermore, AVH are associated with a distributed pattern of connectivity reductions, involving the uncinate fasciculus, corpus callosum, thalamic radiation and fronto-occipital fibers (Knöchel *et al.* 2012; Ćurčić-Blake *et al.* 2013*b*). Alterations in white matter integrity of fronto-temporal tracts have been observed in adolescents with psychotic experiences (mainly AVH), consisting of FA increases in the uncinate fasciculus, arcuate fasciculus and white matter near the striatum (O'Hanlon *et al.* 2015). The uncinate fasciculus connects temporal limbic regions such as the hippocampus and amygdala to the IFG and orbitofrontal gyrus (Kier *et al.* 2004).

The findings of increased white matter connectivity during adolescence and decreases associated with AVH in adulthood may indicate an aberrant developmental trajectory in which early maturation of connectivity in language and emotional brain networks could introduce a mismatch with the maturation of executive control also occurring during this period (Blakemore & Choudhury, 2006), rendering the system more susceptible to errors of self-source monitoring and inhibition (Waters *et al.* 2012). However, longitudinal investigations are much needed to support this.

Blood-flow physiology and AVH

Positron emission tomography (PET), single photon emission tomography (SPECT) and arterial spin labelling (ASL) techniques are used to study changes in blood flow and metabolism associated with AVH. Using fluoro-deoxy-glucose (FDG)-PET, both negative (Gur *et al.* 1995) and positive (Volkow *et al.* 1987; Liddle *et al.* 1992) associations have been reported between hallucination severity and temporal lobe glucose metabolism. Using the same technique, several brain regions including the bilateral supplementary motor area, anterior cingulate cortex (ACC), medial and superior frontal gyri and cerebellum showed a higher glucose metabolism during periods of active AVH compared with silent periods (Parellada *et al.* 2008). Furthermore, antipsychotic-naive patients with AVH showed significantly increased metabolism in the left

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middle and superior temporal gyrus, bilateral middle and superior frontal gyrus and left caudate nucleus compared with those without AVH, while decreased metabolism was observed in the hippocampus, cerebellum and parietal cortex (Horga *et al.* 2011).

Using a within-subject comparison design, a ^{15}O-PET study revealed activation in the thalamus and right striatum, as well as the bilateral parahippocampal gyrus, right ACC and left orbitofrontal cortex during active hallucination (Silbersweig *et al.* 1995). Another symptom-capture study using this technique reports activation in the right medial prefrontal and medial temporal gyrus, left STG, left parahippocampus and left posterior cingulate gyrus (Copolov *et al.* 2003).

Sabri *et al.* (1997) observed a negative association between left thalamic blood flow and AVH severity in never-medicated schizophrenia patients which disappeared after treatment with antipsychotic medication, using SPECT. Furthermore, Gordon *et al.* (1994) found that blood flow in the left temporal lobe negatively correlated with hallucination severity. Within-subject comparison of SPECT data between periods of regular *v.* remitted AVH showed associations with activity in language-related areas such as Broca's region, the left temporal cortex and the ACC (Suzuki *et al.* 1993; McGuire *et al.* 1995). Using ASL, increased perfusion of left HG was found to be associated with the experience of AVH (Homan *et al.* 2013).

Brain physiology studies, thus, show that AVH are related to abnormal metabolism and blood flow in the left temporal cortex, hippocampal complex, thalamus, ACC and frontal cortex. Interestingly, the studies sensitive to state effects (Silbersweig *et al.* 1995; Copolov *et al.* 2003; Parellada *et al.* 2008; Homan *et al.* 2013) consistently show evidence of increased metabolism and blood flow during the experience of AVH *v.* inactive periods. However, studies more sensitive to trait aspects remain equivocal in their findings, possibly related to limited sample sizes (Volkow *et al.* 1987; Liddle *et al.* 1992; Gordon *et al.* 1994; Gur *et al.* 1995; Sabri *et al.* 1997; Horga *et al.* 2011).

Trait-associated brain activation and AVH

Functional MRI (fMRI) studies measuring trait aspects of AVH show that regions including the bilateral ACC), the left superior and middle temporal gyrus and the left premotor cortex are hypoactive in patients with psychosis experiencing AVH during language-related tasks (for a meta-analysis, see Kühn & Gallinat, 2012). These findings are similar to what Hubl *et al.* (2007) and Woodruff *et al.* (1997) found where there was reduced activation in the STG area, particularly on the left, when patients with active hallucinations were exposed to externally presented sounds. Both studies concluded that this phenomenon indicated a kind of 'competition for neuronal resources', between internally and externally generated neuronal activity, where the internal activity 'wins'. See also Kompus *et al.* (2011), who called this phenomenon a 'paradoxical effect'. It could be argued that the reason for lack of increased activity in response to an external sound source is because the hyperactivation caused by the AVH satiates the fMRI-BOLD (blood oxygen level-dependent) response, a kind of ceiling effect that prohibits additional activation caused by the external source. If so, the 'paradoxical effect' suggested by Kompus *et al.* (2011) would be a methodological artefact. This is, however, not a likely explanation, since Hubl *et al.* (2007) used electrophysiology (event-related potential) recordings, which are not dependent on haemodynamic changes. Therefore, the most likely explanation for a 'race model', and 'paradoxical effect', is that AVH cause spontaneous hyperactivity, resulting in increased metabolic demands, seen in the fMRI activation changes.

An important and largely unsolved issue (but see the Discussion), is what changes at the transmitter and receptor level of explanation can explain these changes in neuronal activity (event-related potential) and activation (fMRI) at the imaging level of explanation. To answer questions like these we need to get down to the neurochemistry of AVH, which is a new area for research (Homan *et al.* 2014; Hugdahl *et al.* 2015). Homan *et al.* (2014) and Hugdahl *et al.* (2015) used MR spectroscopy as a new avenue into revealing the neurochemistry of AVH, and Homan *et al.* (2014) reported increased levels of the metabolite *N*-acetylaspartate in healthy controls in frontal areas, while Hugdahl *et al.* (2015) found increased levels of glutamate/glutamine in both frontal and temporal lobe areas in trait-AVH subjects. Findings like these may have important consequences for the development of new, symptom-targeted, drugs that point beyond the classic dopamine hypothesis.

Kang *et al.* (2009) report reduced activation of the amygdala and hippocampus in patients with AVH compared with non-hallucinators and controls in response to a gender discrimination task involving negative auditory stimuli. The connectivity between Wernicke's and Broca's areas is found to be reduced in patients experiencing AVH compared with those without AVH, suggesting a reduced temporo-frontal flow of information during a semantic decision task (Ćurčić-Blake *et al.* 2013*a*).

In contrast, Sanjuan *et al.* (2007) report increased activation of frontal, temporal and limbic regions in schizophrenia patients with AVH compared with healthy controls when confronted with emotional spoken words. Furthermore, patients showed increased

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activation of the parahippocampus and amygdala compared with patients without hallucinations and controls in response to emotional words (Escarti *et al.* 2010). It has also been reported that schizophrenia patients experiencing AVH show temporo-frontal hypercoupling during a speech perception task (Lavigne *et al.* 2015).

Although these findings seem contradictory, they could be explained by differences in experimental setup. Where studies involving a cognitive component to verbal processing (Kang *et al.* 2009; Ćurčić-Blake *et al.* 2013*b*) tend to show decreases in activity and connectivity, studies involving speech perception tend to report overactivation and overconnectivity (Sanjuan *et al.* 2007; Escarti *et al.* 2010; Lavigne *et al.* 2015). These findings thus suggest that AVH are associated with a hypersensitivity to auditory stimuli, while also showing reduced processing of stimuli in association with cognitive demand (Kang *et al.* 2009; Ćurčić-Blake *et al.* 2013*b*). This latter reduced processing may be caused by competition for cerebral resources between the AVH and language-related tasks, possibly related to an attentional bias for internally driven events (Kompus *et al.* 2011). Therefore, these findings seem consistent with both the auditory overactivation hypothesis (Penfield, 1958), as well as the misattribution of internally generated speech hypothesis (Frith & Done, 1988; McGuire *et al.* 1995).

State-associated brain activation and AVH

During the experience of AVH, Broca's area, insula, IFG, left middle and superior temporal gyrus, left inferior parietal lobule and left (para)hippocampal region are consistently reported to show overactivation (Jardri *et al.* 2011; Kühn & Gallinat, 2012).

Activity in right homologues of language regions is associated with the occurrence of AVH, in contrast to production of inner speech, which is strongly associated with left language regions (Woodruff *et al.* 1997; Copolov *et al.* 2003; Sommer *et al.* 2008). The same regions were observed to activate in non-clinical hallucinators, suggesting a common neural network underlying AVH in the psychosis continuum (Diederen *et al.* 2012). Lastly, non-clinical hallucinators show increased connectivity between the bilateral STG, and between the left parahippocampal area and left IFG (Diederen *et al.* 2013).

The period before the onset of AVH is associated with decreased activity in the left parahippocampal gyrus, and also in the left STG and medial frontal gyrus and right IFG (Diederen *et al.* 2010). Hoffman *et al.* (2011) report increased activation of the left IFG compared with its right homologue preceding AVH; the opposite pattern was observed in the left and right posterior temporal area. This activation could correspond to the triggering mechanism of AVH, which may have a component in memory.

Thus, contrary to trait-associated brain activation studies, the literature above clearly suggests that the phenomenon of AVH itself is accompanied by spontaneous over-activity of language-related brain regions and preceded by activity in memory-related areas. Therefore, this literature provides some evidence for the misattribution of internally generated speech hypothesis, the corollary discharge hypothesis (Feinberg, 1978; Allen *et al.* 2006) and episodic memory retrieval hypothesis (Copolov *et al.* 2003). The reviewed studies also cast light on an alternative model, provided by Hugdahl (2009), who suggested that AVH arise because of spontaneous bottom-up hyperactivation, which are not inhibited because of top-down hypoactivation. It was further suggested that bottom-up and top-down processes may be differentially mediated through glutamate overactivity, being the major excitatory transmitter, and γ-amino-butyric-acid (GABA) underactivity, being the major inhibitory transmitter (Hugdahl *et al.* 2015).

Treatment strategies

Pharmacotherapy

Two studies have specifically investigated the efficacy of antipsychotic medication for AVH in patients with schizophrenia by using the P3 item of the *Positive and Negative Syndrome Scale* as the outcome measure (Sommer *et al.* 2012; Johnsen *et al.* 2013). Both studies point out a significant and clinically relevant treatment effect of several first- and second-generation antipsychotics.

Striatal dopamine synthesis and release are elevated in most patients with a psychotic disorder, yet this is not the case in every individual patient (Howes *et al.* 2007; Bonoldi & Howes, 2014). Antipsychotic medication blocks the $D_{2/3}$ receptor, thereby acting downstream of the dopaminergic abnormalities (Howes *et al.* 2012). The efficacy of antipsychotic medication against AVH may thus be related to normalization of dopaminergic signalling. However, one in three patients with psychosis reports antipsychotic-resistant AVH (Johnsen *et al.* 2013), suggesting that AVH are not related to disrupted dopaminergic signalling in these patients. Instead, disrupted glutamine signalling could also be underlying AVH (Hugdahl *et al.* 2015).

Treatment with atypical antipsychotics is associated with a normalization of ACC activation during cognitive demand (Snitz *et al.* 2006), increased activity in the IFG during a verbal fluency task (Fusar-Poli *et al.* 2007), decreased functional connectivity in frontal, temporal

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and subcortical regions including the IFG, STG and parahippocampal gyrus during rest (Lui *et al.* 2010) and an increase in functional connectivity during rest between the striatum and the ACC, dorsolateral prefrontal cortex (DLPFC), hippocampus and anterior insula (Sarpal *et al.* 2015). Although none of these studies specifically investigated AVH as an outcome measure, it is interesting that many of the regions implicated in AVH such as the IFG, STG, hippocampus and ACC also show a normalization of functional responses after treatment. These studies thus provide circumstantial evidence that a normalization of brain function induced by antipsychotic medication may underlie efficacy on AVH in responders. Direct investigation of this putative effect, however, is much needed.

Brain stimulation

Transcranial magnetic stimulation (TMS) is a widely investigated technique for treatment of AVH. Efficacy of 1 Hz-TMS is supported by meta-analysis with an effect size of 0.44 (Slotema *et al.* 2014), reducing frequency and severity of AVH. A large trial with theta-burst TMS reported negative findings (Koops *et al.* 2016).

Usually, the area of stimulation is the left temporoparietal junction as this is found to be most effective (Hoffman *et al.* 2007; Slotema *et al.* 2014). Responders to TMS show increased cerebral blood flow in the left STG preceding 4 weeks of treatment compared with non-responders (Homan *et al.* 2013). Also, decreases in cerebral blood flow of the auditory cortex, left Broca's area and cingulate gyrus after TMS treatment compared with sham are reported (Kindler *et al.* 2013). These findings suggest that the clinical effect of TMS may come from a normalization of the hyperperfusion of the language regions implicated in AVH.

Using FDG-PET, it was shown that metabolism in the left temporal gyrus decreases after stimulation on this area, correlating with AVH severity. Also, a metabolic increase was observed in the right temporal gyrus and the frontal cortex. Furthermore, better treatment response was predicted by higher pretreatment metabolism in the left temporal and parahippocampal regions (Horacek *et al.* 2007). Recently, Klirova *et al.* (2013) reported that metabolism-guided TMS stimulation on the temporoparietal cortex results in stronger treatment effects.

The clinical effect of 1 Hz-TMS is no longer observed after 1 month of follow-up (Slotema *et al.* 2012), indicating that repetitive TMS treatment may need to be applied periodically in order to remain its efficacy. The lack of a long-lasting clinical effect suggests that the observed altered neural dynamics discussed above return to their pathological state at follow-up, but this needs to be investigated. Until now, TMS is mainly used to treat medication-resistant AVH. Given its low risk for side effects it could also be used in earlier stages, even before a first antipsychotic attempted, especially when delusions are absent.

Another emerging treatment for AVH is transcranial direct current stimulation (tDCS), which is based on increasing cortical excitability near the anode (placed over the temporo-parital cortex) and decreasing excitability near the cathode (placed over the prefrontal cortex). tDCS was found to be effective against AVH in medication-resistant schizophrenia patients (Brunelin *et al.* 2012). Mondino *et al.* (2016) showed that active tDCS treatment is associated with a reduction in AVH and a reduction in resting-state functional connectivity between the left temporo-parietal cortex and right IFG. Also, they observed increased resting-state connectivity between the left temporo-parietal cortex and the left angular gyrus, left DLPFC and left precuneus.

Psychological interventions

CBT is the most investigated psychological intervention for AVH, with an average effect size of 0.44 (Van der Gaag *et al.* 2014). The primary aim of CBT is not to reduce the presence of AVH but to accomplish a reappraisal of the meaning of AVH, thereby reducing the emotional reaction and stress in response to them. The neural response to CBT has not yet been studied for AVH specifically, but there are some reports on the effects in relation to positive psychotic symptoms.

Kumari *et al.* (2011) report on the neural response to fearful stimuli before and after CBT for psychosis. Patients receiving CBT showed an attenuated neural response co-occurring with positive symptom reductions after receiving CBT. The regions showing this treatment response comprised the IFG, insula, putamen, thalamus and occipital areas. Mason *et al.* (2016) report that patients receiving CBT for psychosis show a normalization of functional connectivity of the amygdala with the insula and visual areas compared with controls. Also a greater increase in connectivity of the amygdala with the DLPFC and inferior parietal lobule was observed compared with patients receiving treatment as usual. Lastly, the DLPFC showed greater connectivity with other prefrontal regions after treatment with CBT compared with treatment as usual.

In relation to the earlier discussed altered neural response in the amygdala and parahippocampal complex in response to emotional auditory stimuli in AVH (Kang *et al.* 2009; Escarti *et al.* 2010), these studies show that CBT can attenuate the neural response to emotional stimuli. Especially the findings by Mason *et al.* (2016) of the attenuation of amygdala connectivity

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after CBT treatment are in line with the observation of aberrant amygdala response to emotional auditory stimuli, possibly suggesting how CBT for AVH may be efficacious at the neural level.

Discussion

Kant has taught us the subjectivity of perception due to constrains in the sensory faculties, enabling the existence of AVH as a veridical perception. In line with this philosophical framework, the neurobiological correlates of AVH overlap with brain regions associated with the perception of auditory verbal stimuli. Indeed, structural imaging studies converge on the finding of grey matter reductions in the STG, insula and IFG as well as abnormalities in the connecting white matter between these regions. Some findings suggest an atypical developmental trajectory, as well as a dose–response effect between brain structure abnormalities and the psychosis continuum. This suggests that subtle structural brain abnormalities are associated with hallucination proneness, also in the absence of a psychotic disorder.

The metabolic and physiological processes associated with AVH show a strong overlap with the areas that are anatomically affected. However, the evidence regarding these processes is equivocal in terms of the direction of effect, with some studies pointing out increased blood flow and glucose consumption and others finding the opposite effect.

Functional brain imaging studies unequivocally show that language regions are implicated in AVH. However, other regions such as right hemisphere homologues of language regions and the parahippocampal cortex also show abnormal activation during AVH, suggesting that activity outside of primary language regions is a contributor to the occurrence of AVH.

The question remains open as to how the reductions in grey and white matter are related to the disturbances in brain metabolism and activation associated with AVH. Prospective longitudinal studies are needed to further clarify whether the observed structural abnormalities constitute a risk factor or a pathological process post-AVH onset. As argued above, for this question to be resolved it is necessary to move beyond current imaging protocols and search for mechanisms underlying the changes in functional electrophysiology and haemodynamic changes, i.e. looking for alterations and abnormalities at the neurochemistry level. As also suggested above, the use of MR spectroscopy may be a novel and largely untested pathway into the neurochemistry of AVH. Although promising, it is important to also have a critical approach to MR spectroscopy, since there are several unsolved measurement issues, when it comes to both data acquisition, and data analysis, not the least current technical measurement issues with regard to how to best obtain valid data on glutamate and GABA.

Antipsychotic medication is an effective treatment for AVH in psychotic disorders (Sommer *et al.* 2012; Johnsen *et al.* 2013). Imaging evidence suggests that this efficacy may come from a normalization of brain activity in areas typically implicated in AVH. However, a considerable minority of the psychosis patients shows no treatment effect of antipsychotics. Also, antipsychotic medication may not be a favourable treatment strategy for AVH in other diagnoses where a dysregulation of the dopaminergic system is not evident. This suggests that while aberrant dopaminergic signalling may induce AVH in psychotic patients with dysregulated dopaminergic signalling, it is not necessary for AVH to emerge.

There are considerable individual differences in the phenomenology of AVH considering frequency, (negative) emotional content, imperativeness, repetitiveness and omnipotence (Daalman *et al.* 2011; McCarthy-Jones *et al.* 2015). Brain stimulation and CBT are both effective treatments for AVH, yet in different ways. Both treatments appear to have a normalizing effect on activity in the IFG and insula. Selective effects for TMS include a normalized response of the auditory cortex and ACC, whereas tDCS is associated with a normalization of temporofrontal functional connectivity. CBT on the other hand is reported to have normalizing effects on amygdala and DLPFC activation. Interestingly, this shows that interventions effective at the level of reducing AVH occurrence and severity mainly interact with the language network while interventions effective at the level of appraisal may be more involved with the limbic system. This may indicate that while occurrence of AVH is associated with aberrant functioning of the language network, the appraisal and emotional reaction to AVH are mediated by the limbic system. Intervention studies using a combined design with CBT and TMS may be able to elucidate this further.

Although AVH are prevalent in a broad range of disorders and also occur in the general population, current evidence for neurobiological correlates of AVH relies heavily on research in schizophrenia spectrum disorders. A common neurobiology for AVH could be expected considering the overlap in phenomenology over different diagnoses (Slotema *et al.* 2012; McCarthy-Jones & Longden, 2015) and indications that non-clinical hallucinators also show brain abnormalities that lie on a continuum between controls and patients with psychosis (De Weijer *et al.* 2013; Diederen *et al.* 2013; Van Lutterveld *et al.* 2014). However, the finding of unaffected dopamine synthesis in non-clinical hallucinators (Howes *et al.* 2013)

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suggests that differences also exist. A transdiagnostic approach in neuroimaging research is much needed to tease apart the neurobiology of AVH from the clinical context in which they occur.

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Declaration of Interest

None.

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