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Review article

# Interaction of language, auditory and memory brain networks in auditory verbal hallucinations

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ABSTRACT

Auditory verbal hallucinations (AVH) occur in psychotic disorders, but also as a symptom of other conditions and even in healthy people. Several current theories on the origin of AVH converge, with neuroimaging studies suggesting that the language, auditory and memory/limbic networks are of particular relevance. However, reconciliation of these theories with experimental evidence is missing. We review 50 studies investigating functional (EEG and fMRI) and anatomic (diffusion tensor imaging) connectivity in these networks, and explore the evidence supporting abnormal connectivity in these networks associated with AVH. We distinguish between functional connectivity during an actual hallucination experience (symptom capture) and functional connectivity during either the resting state or a task comparing individuals who hallucinate with those who do not (symptom association studies). Symptom capture studies clearly reveal a pattern of increased coupling among the auditory, language and striatal regions. Anatomical and symptom association functional studies suggest that the interhemispheric connectivity between posterior auditory regions may depend on the phase of illness, with increases in non-psychotic individuals and first episode patients and decreases in chronic patients. Leading hypotheses involving concepts as unstable memories, source monitoring, top-down attention, and hybrid models of hallucinations are supported in part by the published connectivity data, although several caveats and inconsistencies remain. Specifically, possible changes in fronto-temporal connectivity are still under debate. Precise hypotheses concerning the directionality of connections deduced from current theoretical approaches should be tested using experimental approaches that allow for discrimination of competing hypotheses.



*Abbreviations:* ACC, anterior cingulate cortex; AF, arcuate fasciculus; AVH, auditory verbal hallucinations; dACC, dorsal anterios cingulate cortex; DTI, diffusion weighted imaging; EC, effective connectivity; EEG, electroencephalogram; FA, fractional anisotropy; FC, functional connectivity; fMRIt, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MD, mean diffusivity; MTG, middle temporal gyrus; No-AVH, patients without hallucinations; PFC, prefrontal cortex; RS, resting state; SMA, supplementary motor area; STG, superior temporal gyrus; WM, white matter.

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**Contents**



## 1. Introduction

Recent findings from brain imaging have revealed that auditory verbal hallucinations (AVH) in schizophrenia are associated with alterations in brain connectivity (Brown and Thompson, 2010; Jardri et al., 2011) that incorporate both functional and anatomical connections (Allen et al., 2008). These studies have pointed towards a prominent role for language, auditory and memory networks in AVH (Allen et al., 2012; Vercammen et al., 2010). Although many studies have been conducted, some are in discrepancy with each other. For example, some findings point towards increased connectivity within the language and memory networks (Hubl et al., 2004; Shergill et al., 2007), whereas others demonstrate a decrease in fractional anisotropy (FA), implicating decreased connectivity (Catani et al., 2011; De Weijer et al., 2013; Ćurčić-Blake et al., 2015) in the same pathway within the network (Geoffroy et al., 2014). In addition, memory regions have been implicated in AVH (Allen et al., 2012) but their relationship to the language and auditory networks is as yet unclear. Therefore, investigations of the interaction of the language network with the auditory and memory networks appears timely and beneficial to the field.

AVHs are hypothesized to be accompanied by abnormalities both within and between these networks. The most recent comprehensive review related to the neural underpinnings of AVHs (Allen et al., 2012) concluded that there was "insufficient neuroimaging evidence to fully understand the neurobiological substrate of AH." Recent reviews focused on anatomical connectivity of the arcuate fasciculus involved in language functions (Geoffroy et al., 2014) and functional connectivity RS studies in relation to AVH (Alderson-Day et al., 2015, 2016; Northoff, 2014). However, there is no comprehensive review that covers both functional and structural connectivity studies of language, auditory perception and memory processing. In addition, to gather information specific to AVH, it is important to observe changes in connectivity not only in patients with AVH but also in other populations such as non-psychotic individuals with AVH, at-risk mental state and first-episode patients. Previous studies have shown that AVH occur in approximately 5–10% of healthy people – the so-called non-clinical population (van Os et al., 2009; Aleman and Larøi, 2008). These people do not fulfill criteria for a diagnosis of schizophrenia, nor psychosis in general. Furthermore, non-clinical, at-risk mental state and first-episode patients have usually not used medication and exhibit no brain changes associated with duration of illness. Therefore, we will here include connectivity studies that incorporate these AVH populations. In recent years, around 20 new studies have been published on connectivity in relation to AVH, involving fMRI measurements during a task and during the RS, EEG studies and various anatomical studies. Many theoretical models were developed before these new neuroscientific findings, and that it is timely to see how models can be reconciled with connectivity evidence. This implies the need for a new review of neuroimaging studies that may contribute to a novel neurobiological model of AVHs. In order to put these new studies into a theory, we first present the major hypothesis regarding the mechanisms behind AVH and then investigate whether recent literature supports these.

## 2. Major hypotheses in the current literature

In this section, we first outline the most influential hypotheses (or models) of AVH, specifically: Unstable memories and self-monitoring deficits, interhemispheric miscommunication, top-down and bottom-up predictions and Hybrid model. Second, we

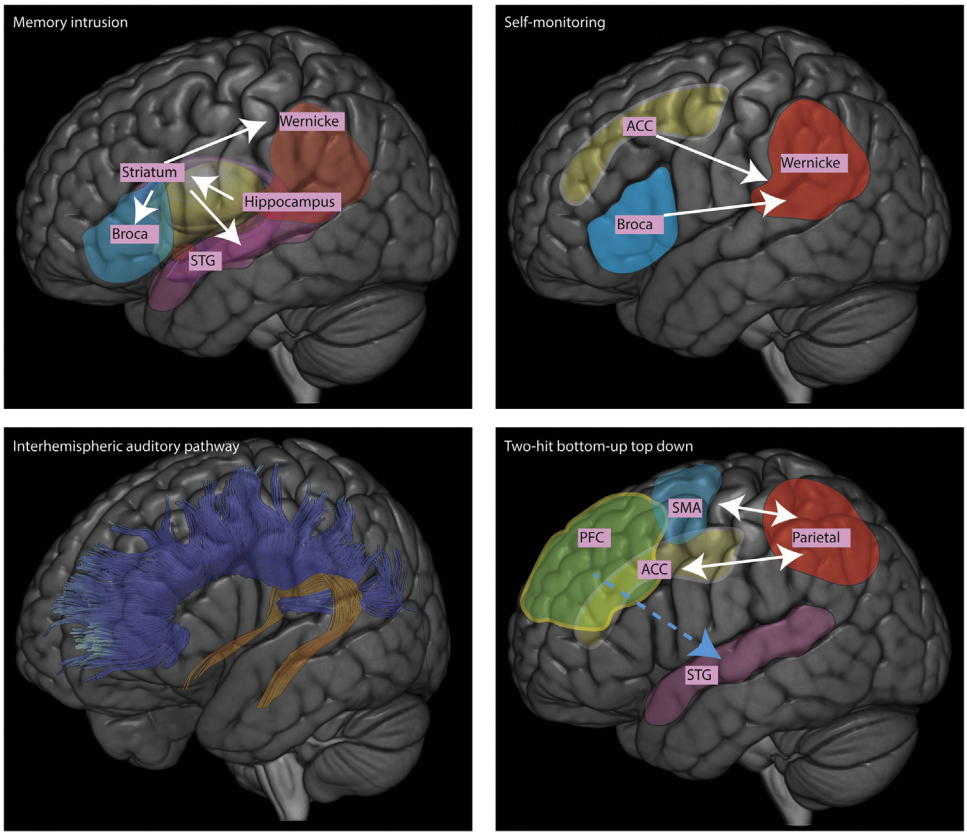


**Fig. 1.** Illustration of different theories. Arrows illustrate the direction of influence. Blue dashed line – increase in excitation.

will review evidence for these models in view of the functional and structural connectivity findings with regard to major networks subserving auditory, language and memory processing. Finally, we will come back to the models and evaluate them in terms of the reviewed findings.

### 2.1. Unstable memories

One early theory proposed that verbal hallucinations may be 'parasitic' memories due to disrupted language production processes which spontaneously and erroneously activate language based memory (Hoffman, 1986). A recent variant of this model proposes that AVH might result from the intrusion and unintended activation of memories and other mental representations (i.e. inner speech, auditory images) (Waters et al., 2006). In support, people who hear voices experience these as intrusive and unwanted (Morrison et al., 1995), as might be expected if memory systems fail to suppress mental associations which are not currently relevant. Problems might arise because of incomplete encoding of memories, increasing their vulnerability to becoming incorrectly primed, or abnormal storage, leading to weak contextual harnessing. In support of this, tangentiality and loosening of associations, types of formal thought disorder have often been reported in patients and healthy individuals with AVH (Sommer et al., 2010). Inhibitory deficits would also contribute to the failure to control the contents of memories (Jardri et al., 2016; Waters et al., 2006). If memory is indeed implicated in AVH, regions engaged would include the hippocampal complex (Fig. 1), and the putamen to translate memories into language experience (Price, 2010) and bring the experience into consciousness (Mhuircheartaigh et al., 2010), as well as speech and auditory network (Wernicke's, Broca's areas; Fig. 2). This theory could provide a neurobiological explanation for the strong association between childhood trauma and AVH, which is present in patients with schizophrenia, with post-traumatic stress disorder and also in non-clinical populations (Daalman et al., 2012). In support, hippocampal deactivations have been observed immediately prior AVH, pointing to the release of memory (Hoffman et al., 2008; Diederen et al., 2010).

### 2.2. Source monitoring

Source monitoring hypothesis proposes that AVH comprise deficits in self-monitoring and reality discrimination (Bentall and Slade, 1985; McGuire et al., 1993; Allen et al., 2007), whereby internally events (thoughts, inner speech, actions) lack 'self' attributes, resulting in broad difficulties in self-recognition.

One approach has been to explain these impairments in terms of sensory-motor predictions from one's own actions via forward modelling and efference copy mechanisms (Feinberg, 1978; Frith et al., 1992). Of these, self-monitoring of inner speech model has been the one most often studied using neuroimaging and neurophysiological monitoring techniques (such as EEG). Neuroscientists have asked about the neural mechanisms that tag self-generated inner experiences as "coming from self" enabling them to be distinguished from externally generated percepts. In nonhuman species, the experiments often involve vocalizations and recording local field potentials from auditory cortical neurons (Eliades and Wang, 2008, 2013). Human studies using EEG-based methods have mimicked this work and the findings (Ford et al., 2002). Regardless of the species, auditory cortex responses are suppressed during vocalization. Connectivity between frontal (perhaps Broca's area) and temporal areas (auditory cortex) has been suggested to be responsible for the auditory cortical

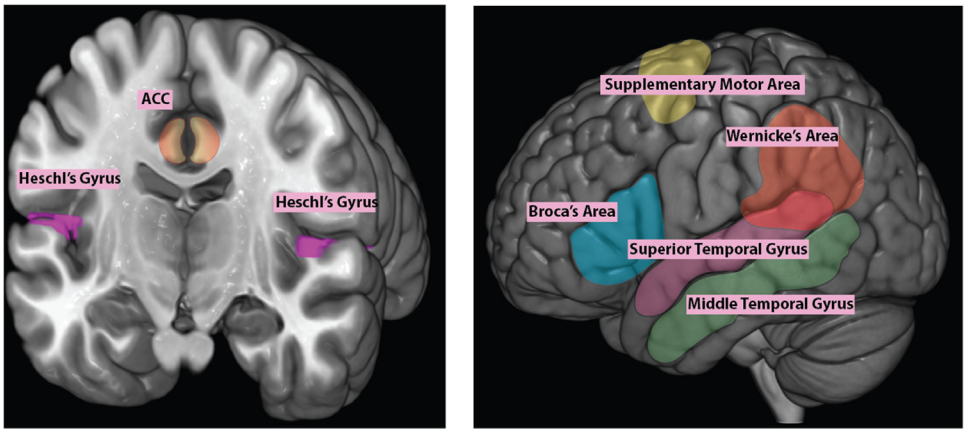


**Fig. 2.** Illustration of language and auditory network. The two network share some regions (such as STG) and are difficult to disentangle from each other. Wernicke area is drawn in the most global manner. Some authors include only TPJ part of the temporal lobe (BA22), but often in articles the Wernicke's area includes parts of parietal lobe with BA 39 and 40 (Mesulam, 1990).

suppression, as the degree of connectivity between these areas during talking is related to the degree of suppression (Ford et al., 2007; Chen et al., 2011; Wang et al., 2014). This communication could signal the arrival of self-generated sensations. Alternatively it may be that perception of speech itself inhibits auditory cortical activity according to the 'saturation hypothesis' (see later). Certainly patients with stressful AVHs find relief by talking to themselves or to others (Nayani and David, 1996; Farhall and Gehrke, 1997; Farhall et al., 2007). One possible mechanism is the reduction of endogenous auditory cortical activity driving AVHs, although other mechanisms (e.g. involving emotion regulation) cannot be excluded. The increased endogenous activity in the auditory cortex in patients with AVH has been observed earlier (Kompus et al., 2011) and the activation in the secondary auditory cortex has been related to AVH (Jardri et al., 2011). Furthermore, the paradoxical deactivation of the auditory cortex during auditory stimuli was reported in a meta-analysis (Kompus et al., 2011) and this could possibly explain the relief that AVH patients experience when they listen to external stimuli. Cho and Wu considered this model insufficient as it does not explain what is to be monitored – i.e. an internal signal still has to arise from somewhere (Cho and Wu, 2013).

A second approach has viewed these 'source-monitoring' problems as memory deficits, involving failure to correctly bind and retrieve memory features to form a cohesive representation of an experience (Mitchell and Johnson, 2009). Together, these deficits speak to the role of the medial temporal lobes (hippocampal complex, perirhinal), because of its role in relational encoding, and more posterior regions and parietal cortex in the retrieval and/or flexible use of relational information during later remembering (Lepage et al., 1998). Prefrontal areas are also involved, but more so for attribution and reasoning. A key white matter structure in this theory is the arcuate fasciculus connecting these areas.

### 2.3. Interhemispheric miscommunication

This hypothesis entails that increased synchrony between bilateral auditory areas may contribute to the underlying neural correlate of AVH (Steinmann et al., 2014b). The theory originates from research into tinnitus, which is an auditory precept of a tone without any corresponding external stimuli. Based on findings of hyper-synchrony between the auditory cortices (Eggermont, 2007), Diesch and colleagues suggested that stronger interhemispheric auditory pathways may facilitate the development and persistence of a positive feedback loop between tinnitus generators located in both hemispheres (Diesch et al., 2012). Studies using several modalities (fMRI, DTI, EEG) support the concept that altered connectivity between bilateral auditory areas via the corpus callosum (Fig. 1) is related to the emergence of auditory AVH (Steinmann et al., 2014b). This idea is based on the observation that the abovementioned pathway is involved in healthy auditory processing and speech comprehension. For example, lesion studies demonstrated a crucial role of this pathway in the integration of prosodic and syntactic information (Friederici et al., 2007). In other words, disturbances in this pathway, crucial for auditory and language processing, may underlie the pathophysiology involved in auditory phantom percepts such as AVH or tinnitus (Steinmann et al., 2014b).

### 2.4. Top-down effect and bottom-up predictions

Another approach that focuses on perception and attentional processes is based on the idea that AVH may be caused by unbalanced mechanisms for bottom-up sensory processing on one hand and top-down mechanisms on the other hand (Behrendt, 1998; Grossberg, 2000; Aleman et al., 2003). It has been reported that patients with more severe hallucinations showed a larger influence of imagery on perception in patients with active AVH, suggesting disturbances in top-down influences on auditory perception (Aleman et al., 2003). They interpreted this as disturbances in top-down influences on auditory perception. The authors suggested that abnormalities in two cognitive mechanisms are simultaneously associated with AVH: (a) deficiency in reality monitoring and (b) increased top-down influence over imagery (restricted to hallucination periods). Metzak et al. found that the default mode network deactivates during reality monitoring, while networks involving the supplementary motor area (SMA), anterior cingulate cortex (ACC) and occipital regions become more activated (Metzak et al., 2015). If there is deficiency in reality monitoring then it is expected that coordinated activation increases (failure to deactivate) in a network involving the default mode network and the superior temporal gyrus (STG) and decreases in the SMA and ACC (Metzak et al., 2015) in association with AVH. Increased top-down influence should be reflected in state studies showing either prefrontal cortex (PFC) or higher order perceptual regions increased connectivity to auditory perception regions such as the STG and middle temporal gyrus (MTG) (Fig. 1).

Later, in the framework of Bayesian inferences and AVH, Friston suggested unbalanced mechanisms for bottom-up sensory processing on one hand and the formation of top-down priors for encoding the bottom-up information on the other hand (Friston,

2005). If for example the bottom-up sensory processing is perception, and the top-down prior expectation is attention, then one might see the cause of hallucinations as perception and attention deficit. This is conceived as a unitary deficit –i.e. predictive coding. Hugdahl et al. also endorsed the idea of an imbalance in top-down/bottom-up influences and suggested that while AVHs originate in perisylvian regions (Hugdahl, 2009), they are in general not as constrained by the PFC in patients as they are in non-psychotic voice-hearers. This would mainly involve abnormalities in the PFC-temporo-parietal connectivity.

Nazimek et al. suggested that AVHs arise from attenuated prediction error processing (Nazimek et al., 2012). Similar to Hugdahl (2009), they suggest the auditory cortices might produce an error signal. They postulate inaccurate top-down processing PFC via thalamus to perception in auditory cortex in voice hearers. This in turn might prevent auditory cortex from generating an error prediction signal when the information is plausible. Thus abnormal interaction of PFC, thalamus and auditory cortices coupled with hypersensitivity of auditory cortex might be at the core of AVH. This theory was based on initial finding of Hunter et al., who showed increased activity during rest in auditory sensory areas of people more prone to hallucinate (Hunter et al., 2006).

### 2.5. Hybrid models of AVH

Ford and Hoffman proposed a hybrid model of spontaneous activations and self-monitoring (Ford and Hoffman, 2013a). They suggested the neural basis of AVH is a hyper-connected cortico-striatal network whereby otherwise nascent activity can gain access to consciousness. This network is responsible for registration of sensory aspects of the experience, including the acoustic vocal characteristics. The non-self-perception of this experience may result from dysfunction of the self-monitoring mechanism. As yet there are no data from a single analysis supporting this hybrid model. However, we will show here that there is evidence from separate studies that both may contribute to the experience of voices. Other authors have also proposed combinations of several hypotheses mentioned above. For example, Aleman and Larøi (2011) combined the top-down account with the self-monitoring account into a single descriptive model of perception and hallucination. Similarly, Waters et al. (Waters et al., 2012) integrated aspects of reduced inhibition, impaired self-monitoring and altered top-down factors into their model of AVH.

In addition, Northoff incorporated several alterations in resting state networks and interactions among them, including auditory areas and areas involved in speech monitoring belonging to the default mode network (ACC), into a resting state hypothesis of AVH (Northoff and Qin, 2011; Northoff, 2014; Alderson-Day et al., 2016).

Many aspects of the models summarized above can be tested using connectivity measures, as obtained with fMRI and EEG. We will now review findings of such studies to compare plausibility of previously mentioned hypothesis.

## 3. Functional connectivity studies

Functional connectivity (FC) refers to the correlations of activity between different brain regions. With time-series derived from functional MRI (fMRI) data, functional connectivity is assessed by calculating the temporal correlation between a blood-oxygenation-level dependent (BOLD) activities in two or more regions (Friston, 2011). Functional connectivity can be calculated from data acquired during rest or tasks. The former method has the advantage of allowing inferences about connectivity to be made without consideration of the cognitive impairment commonly observed in patients with schizophrenia. The latter method has the advantage of, through careful task selection, focusing on brain networks that underlie cognitive operations thought to be involved in AVH. While FC refers to simultaneous activation (such as correlations in fMRI or coherence in EEG), effective connectivity (EC) refers to causal influences of one area over another area. EC approaches allow inferences about the influence one neural system exerts over another (Friston, 2011), have been used, to a lesser extent.

The application of FC analyses to the study of AVHs is motivated by a range of studies demonstrating that inter-region functional coordination plays an important role in determining whether neural activity is experienced consciously as percepts (Cosmelli et al., 2004; Sergent and Dehaene, 2004; Melloni et al., 2007; John, 2002). Here, we reviewed the evidence linking the following networks to AVH: auditory, memory/limbic and language networks (Table 1).

Functional MRI studies have investigated the functional brain networks during the *experience* of hallucinations but also compared the functional brain networks between patients who hallucinate and those that do not, based on reports of hearing hallucination during the past (Allen et al., 2012; Woodruff, 2004). We will refer to brain imaging investigations of groups that hallucinate as *symptom association* studies (also called trait studies), and the experience of hallucinations as *symptom capture* studies (also called state studies).

### 3.1. Auditory network

Sounds are perceived and processed first in primary auditory cortex (PAC) which is located in the superior plane of the superior temporal gyri (STG) called Heschl's gyrus (Zatorre et al., 2002) (Fig. 2) and from there, sounds and voices are processed in the secondary auditory cortex encompassing various parts of the STG, MTG and then also via the thalamus (Zatorre et al., 2002, 2007; Belin et al., 2000; Javitt and Sweet, 2015) sent to higher order areas such are Geschwind's area and other language areas. It has been known for some time that imagery activates the brain areas that overlap with those that sub-serve perception (Kosslyn and Ochsner, 1994; Zatorre et al., 2007). Auditory hallucinations that form even stronger sensory experiences accordingly, activate the auditory cortex (including left STG; Fig. 1), which houses the linguistic auditory perception regions of the brain (Allen et al., 2012; Woodruff et al., 1995a, 1997).

#### 3.1.1. Symptom association studies

The hallucinatory state can be considered a type of challenge state that recombines the naturally occurring resting state networks. A review of the RS literature comparing AVH to NoAVH psychotic patients suggests that connections between aspects of the dorsal anterior cingulate cortex/supplementary motor area (dorsal ACC/SMA (dACC/SMA); overlapping BAs 24/32/8 on the midsagittal plane) and the STG are associated with the severity of AVH (Alderson-Day et al., 2015), which is in line with the RS hypothesis proposed by Northoff (Northoff and Qin, 2011; Northoff, 2014). Specifically, two seed-based studies reported hyper-connectivity in networks involving STG and the dACC/SMA for AVH patients relative to NoAVH (Alonso-Solis et al., 2015; Rolland et al., 2015). The dACC/SMA regions span the fronto-parietal, ventral attention and sensorimotor networks on the medial plane (Yeo et al., 2011), so all are candidates for resting-state-network combinations underlying AVH. These studies also reported hallucination-severity-specific hyperconnection between the STG and many other regions that did not replicate across studies.

As with the RS literature, the task-based literature also provides evidence for the importance of connections between the STG and dACC/SMA, with one source monitoring study directly testing and reporting reduced connectivity in the left STG and dACC/SMA for

**Table 1**
Articles investigating functional connectivity (FC) in one or more of the 3 networks in relation to hallucinations.

| Type Study | Author | HC/AVH/ NoAVH | Type Network | Type study/Task/Analysis | Questionaire | Summary of results |
|---|---|---|---|---|---|---|
| State FC | Raij et al. (2009) | 11 AVH Sz | L/M/A | Button pressing on the onset and offset if AVH, Joystick declination to note reality of AVH; PPI | Subjective reality of hallucinations (SRH)(Hunter, 2004) | SRH **(+)** FC between IFG (B) and: the ventral striatum, the auditory cortex, the right posterior temporal lobe, and the cingulate cortex |
| | Hoffman et al. (2011a) | 23 HC 32 AVH Sz 24 NoAVH Sz | M/L | Baloon pressing during the AVH | | Increased FC in AVH: W to IFG; IFG to putamen |
| | Hoffman et al. (2011b) | 11 AVH SZ 10NoAVH Sz | L | Baloon pressing during the AVH | | Increased FC in AVH: left IFG to right Temporal ROI (MTG and STG) |
| | Thoma et al. (2016) | 11 AVH SZ 4 AVH SzAff | A/L | Button pressing on the onset and offset of AVH; ICA | PANSS; PSYRATS; Semistructured interview to gather qualitative data about their AVH experiences during scanning | Out of 4 common AVH related ICA networks (Insula network; left FTN; bilateral FTN and Auditory cortex and posterior Language Network) only ACPLN **(+)** with AVH occurrence, while Occipital-temporal **(−)** and Medial prefrontal **(−)** with AVH occurence |
| State and Trait FC | Clos et al. (2014) | 49 HC 49 AVH Psychotic patients | L/M | RS | CASH and PANSS | Patients who had AVH during scan:1. Reduced FCb the AG and the surrounding left IPL 2. Increased FC between the thalamus and the left fusiform gyrus/hippocampus; P3**(+)** leftIFG-VMPFC; P3**(−)** thal-righPHG; P3**(−)** thal-rightPrecentralG |
| Trait FC | Lawrie et al. (2002) | 10 HC 3 AVH Sz 5 NoAVH Sz | L | Several Tasks and RS | Krawiecka scale | Reduced FC in AVH: left DLPFC to Midd/STC |
| | Vercammen et al. (2010) | 27 HC 27 AVH Sz | L | RS | AHRS and PANSS | Total AHRS **(−)** conn: left TPJ – bilateral ACC; left TPJ – the bilateral amygdala |
| | Gavrilescu et al. (2010) | 16 HC 13 AVH Sz 13NoAVH Sz | A | RS | | Reduced FC in AVH: interhemispheric PACs, interhemispheric SACs |
| | Escartí et al. (2010) | 31/27/14 AVH chronic, NoAVH never | M-emotion | task-ICA: listening to emotionally charged words | PANSS; PSYRARS; BPRS | Reduced sync. In AVH: STG, IFG and the insula |
| | Sommer et al. (2012) | 49 HC 49 AVH Sz | L/M | RS | PANSS | P3 **(−)** leftSTG-left_hippocampus |
| | Diederen et al. (2013) | 25 HC 25 AVH Non-psychotic | | RS; Seed regression | | Increased FC in AVH: left ST- right ST regions; left ST- right IF regions; left pH region – left IFG; No negative correlations as in control group: left ST- right IF |
| Trait | Mou et al. (2013) | 13 HC 13 AVH Sz 13 NoAVH Sz | | Task: Voice recognition | SAPS-AH | Reduced FC in AVH: tight STG to right SFG; voice recognition accuracy **(+)** FC right STG – right SFG |
| | Shinn et al. (2013) | 28 HC 27 AVH Sz 14NoAVH Sz | A | RS | PSYRATS-AH | Increased in AVH: left HG FC with left frontoparietal regions; Reduced in AVH: left HG FC with right hippocampal formation and mediodorsal thalamus; AVH severity **(+)** FC left HG with: left IFG (Broca's area), left lateral STG, right pre- and postcentral gyri, cingulate cortex, and orbitofrontal cortex |
| | Alonso-Solis et al. (2015) | 20 HC 19 AVH Sz 14NoAVH Sz | A; DMN | RS | History of hallucinations; PANSS | Increased in AVH: FC dMPFC ROI and bilateral: central opercular cortex, insular cortex and precentral gyrus; Decreased in AVH: vMPFC ROI and bilateral paracingulate and dorsal ACC |
| | Rolland et al. (2015) | 16 AVH Sz 14 NoAVH Sz 15 AH/VH Sz | A: mesolimbic pathway VTA-Nacc | RS | | Increased in AVH: FC NAcc with the leftSTG, the cingulate gyri, and the VTA |
| | Lavigne et al. (2015) | 27 HC 10 AVH Sz 13 NoAVH Sz 22 Bipolar | A/L | Tasks: Inner verbal tought and Speech perception; constrained PCA | SSPi | Increased in AVH during Speech perception: FC spfronto-temporal network including speech-related auditory and motor regions |
| | Benetti et al. (2015) | 22 HC 28 AVH ARMS + FEP 18 NoAVH ARMS + FEP | L | Task: Hayling Sentence Completion Task; DTI tractography | PANSS; PSYRATS | Intermediate in AVH between HC and NoAVH (but not sugbuficant): FC LMTG and LIFG: AVH; NoAVH the lowest; |
| | Mechelli et al. (2007) | 10 HC 11 AVH Sz 10 NoAVH Sz | A: dACC/ SMA – STG | Task: Source monitoring; DCM | History of hallucinations; SAPS | Greater (condition) in AVH: EC left STG to ACC for self-initiated than external-initiated speech in patients compared to NoAVH and HC |
| | Ćurčić-Blake et al. (2013) | 31 HC 30 AVH Sz 17 NoAVH Sz | L | Task: Inner speech; DCM | PANSS | Reduced in AVH EC From Wernicke's to Broca's area compared to NoAVH and HC; trend reduced EF from Broca's homologue to Broca's area |
| | de la Iglesia-Vaya et al. (2014) | 31 HC 27 AVH Sz 14 NoAVH Sz | | Task: Emotional word listening; ICA and GC | PANSS; PSYRATS-AH; BPRS | In the patients with AH, the principal causal source was an occipital–cerebellar component, versus a temporal component in the patients without AH and the healthy controls |

**Table 1** (*Continued*)

| Type Study | Author | HC/AVH/ NoAVH | Type Network | Type study/Task/Analysis | Questionaire | Summary of results |
|---|---|---|---|---|---|---|
| | Cui et al., (2016) | 19 HC 17 AVH FEPSz 15 NoAVH FEPSz | M/L | RS; ALF & regional homogeneity; FC | PANSS; AHRS | Increased in AVH right putamen-seeded FC with the left DLPFC and Broca's area relative to those without AVHs |

AVH– auditory verbal hallucinations. NoAVH- patients without AVH; L-Language Network; M – Memory network; A – auditory network; Sz – schizophrenia patients; (+) positive correlation; (−) – negative correlation; PAC- primary auditory cortex, SAC – secondary auditory cortex; PANSS – positive and negative syndrome scale; SRH – subjective reality of hallucinations; PSYRATS – Psychotic Symptom Rating Scale; SAPS- Scale for the Assessment of Positive Symptoms; SANS – Scale for the Assessment of Negative Symptoms; AHRS- Auditory hallucinations rating scale; BPRS – Brief psychiatric rating scale; Cash – Comprehensive Assessment of Symptoms; STG – superior temporal gyrus; STC – superior temporal cortex; AG – angular gyrus; PFC prefrontal cortex; DLPFC – dorsolateral PFC; VMPFC – ventromedial PFC; MTG – middle temporal gyrus; IFG – inferior frontal gyrus; B- Broca's area; ACC – anterior cingulate; Nacc – nucleus accumbens; VTA – ventral tagmental area; ICA- independent component analysis; RS – resting state; PPI – psychophysical interactions; DCM – dynamic causal modelling; PCA – principal component analysis; ALFF – amplitude of low-frequency fluctuation.

AVH relative to NoAVH patients (Mechelli et al., 2007). However, using speech perception, and comparing AVH and NoAVHs patients, another study found increased coordinated activity in the STG and dACC/SMA (Lavigne et al., 2015). The importance of the co-activation of the STG and the dACC/SMA parallels the RS work, and observation of a disconnection is apparently more frequent in the task-based than in the resting-state studies.

Using RS fMRI, Gavrilescu and colleagues investigated inter-hemispheric connectivity in the primary and secondary auditory cortex in patients with and without AVH and healthy controls (Gavrilescu et al., 2010). They used individual seed regions established on functional activation mask maps in response to passively listening to words. They reported AVH patients having reduced interhemispheric FC in both the primary and secondary auditory cortex, as compared to both NoAVH patients and healthy controls. These findings suggest a disruption of multiple auditory functions, both at a basic auditory level and in higher-order language processing abilities.

Iglesia-Vaya et al. presented emotional words to patients with and without AVHs and found differences in connectivity patterns that suggest more cortico-cortical functional synchrony outside language regions in those with AVHs (de la Iglesia-Vaya et al., 2014). Specifically, in the patients with AVHs, the principal causal source was an occipital–cerebellar component, as opposed to a temporal component observed in the patients without AVHs and the healthy controls. The authors concluded that an anomalous process of neural connectivity involves the cerebellum when patients with AVHs process emotional auditory stimuli. Cerebellum is important for brain synchrony and action prediction (D'Angelo and Casali, 2013) by coordinating and modulating cortical activity (Picard et al., 2008).

In reviewing studies that examined inter-hemispheric communication in AVH patients, Steinmann et al. (2014b), noted the strong evidence of a link between AVHs and both structural and functional disruption of inter-hemispheric fibres, whilst accepting that some studies report increased and some decreased connectivity. It is possible that such variability denotes the requirement for an *optimal* level of connectivity to gain healthy function, and that AVH arise when connectivity is either above or below this optimal level (Steinmann et al., 2014b).

### 3.1.2. Symptom capture studies

The auditory system activated during the experience of AVH includes primary (Dierks et al., 1999) and secondary cortices (STG; MTG) as well as other regions such as anterior cingulate, SMA, insula, precentral gyrus, frontal operculum, inferior parietal lobule, hippocampus, and parahippocampal region (Shergill et al., 2000; Raij et al., 2009). The STG (left and right) are almost universally active during AVH (Jardri et al., 2011; Kuhn and Gallinat, 2010). The question is whether such activation (which by definition must be brain-derived) arises within STG or other brain regions, and if so, how its activity relates functionally to other regions that appear to be involved in the experience of hallucinations.

The observation that auditory hallucinations reduce responsivity to external speech within STG and related regions such as MTG has led to the 'saturation theory' whereby the signal driving hallucinations competes for common neurophysiological resources with those used for perceiving external speech (Woodruff et al., 1997; Ford et al., 2009). Hence, we can gain useful inferential knowledge from studying the brain's altered responsivity to external auditory signals during such experiences. This in turn indicates the importance of auditory cortex for the experience of AVHs, as the same apparatus is used in perception of normal speech.

Upadhyay et al. (Upadhyay et al., 2008) found that passive listening to female voices revealed effective connectivity between primary auditory cortex and anterior and posterior STG, regions that have also been demonstrated to be responsible for attributing externality to perceived speech (Hunter et al., 2003), externality being one main factor in how hallucinated voices sound real (Nayani and David, 1996). Interestingly, Jardri et al. found that primary auditory cortex was not systematically active during AVH but when active, this was linked with increased vividness in hallucinatory experiences (Jardri et al., 2013).

Shinn et al. reported a positive correlation between AVHs and functional connectivity between Heschl's gyrus and Broca's area, left lateral STG, anterior cingulate and orbito-frontal gyrus (Shinn et al., 2013). As well as an increased connectivity within auditory regions, their evidence invokes connectivity to regions that could relate to attentional systems in the pathophysiology of AVHs. This is important, as we have known for some time that attention modulates auditory sensory cortex (Woodruff et al., 1995a) and that attention modifies the hallucinatory experience (Nayani and David, 1996). The observation that the STG and anterior cingulate were functionally connected during spontaneous STG activity in acoustic silence adds further weight to the idea proposed by Woodruff (Woodruff, 2004) and Hunter and colleagues (Hunter et al., 2006) that signal within the STG are yoked to attentional systems that could bring the experience of AVHs to conscious awareness. However, the latter was never tested in patients with AVH.

### 3.1.3. Conclusion for auditory networks

Evidence derived from symptom association studies, involving both resting state and tasks, suggests that aberrant connections between the STG and dACC/SMA are common to individuals with AVH. A healthy connection between these regions may play a role in monitoring verbal thoughts and tagging them as coming from 'self'; dysfunction of this connection may reduce the ability to tag these experiences as internal, resulting in AVH. We note that no connectivity studies have directly tested self-monitoring in its physiological sense, although the monitoring process of alerting that "something is wrong", of the need to make behavioral corrections, clearly involves the dACC/SMA (Behrens et al., 2007;

Egner, 2011; Woodward et al., 2008). Similar concepts have been put forward as the breakaway speech and unbidden thoughts account of AVH (David, 1994; Ford and Hoffman, 2013b; Hoffman, 2010). In addition, the altered activity in dACC/SMA is consistent with the recent morphological study showing the para cingulate sulcus is shorter in patients with AH – this area is thought to be involved in reality monitoring (Garrison et al., 2015).

It may also be possible that spontaneous signals within the auditory apparatus (including STG and MTG) in certain circumstances exceed a threshold for conscious awareness, whether by enhanced intrinsic activity or modulated via a reduction in 'top-down' attentional constraint.

### 3.2. Language networks

The most prominent brain areas involved in language processing are Broca's and Wernicke's areas (Fig. 2), in the inferior frontal gyrus and temporal-parietal junction of the left hemisphere, respectively. Lateral frontal and temporal regions of both hemispheres are involved in syntactic processing of connected speech with predominance in the left hemisphere (Friederici et al., 2000), while the right hemisphere has more important role in processing of emotional information (prosody) and tone of spoken language (Meyer et al., 2002; Mitchell et al., 2003). Neoclassical language network includes frontal and temporal areas, as well as the supplementary motor area (SMA) (Fig. 2), ACC, and insula (Mesulam, 1990).

Various mechanisms including misattribution or impaired monitoring of inner speech and perturbed interactions between bottom-up and top-down processes in auditory perception have been suggested as cognitive mechanisms that underlie AVH. Such dysfunction is potentially related to disrupted connectivity between frontal and temporo-parietal brain regions (Allen et al., 2012).

#### 3.2.1. Symptom association studies

Vercammen and colleagues used a region of interest analysis comprising neuronal networks involved in inner speech processing, based around a seed region in the tempo-parietal junction (Vercammen et al., 2010). They found reduced FC between the left temporal-parietal junction and the right homologue of Broca's area in patients with schizophrenia. Furthermore, more severe AVH were associated with reduced FC between the left temporo-parietal region and the bilateral anterior cingulate and bilateral amygdala.

Task based fMRI studies commonly report disruption in the frontotemporal network. One of the first studies by Lawrie and colleagues has shown that FC is reduced between left dorsolateral PFC and temporal regions in patients with schizophrenia during a sentence completion task, compared to healthy controls (Lawrie et al., 2002). Importantly, this FC was negatively correlated with severity of AVH.

EC differences have also been reported between schizophrenia patients with and without AVH. Mechelli and colleagues utilised a source judgment task using pre-recorded single words (self vs other speech) (Mechelli et al., 2007) and estimated the effective connectivity between the temporal lobe and anterior cingulate using dynamic causal modelling (Friston et al., 2003). It was reported that left superior temporal gyrus to anterior cingulate EC was greater for 'self-spoken' words compared to 'other-person spoken' words in patients with AVH. The opposite pattern, i.e. greater EC for 'other-person' spoken words compared to self-spoken words, was observed in both NoAVH patients and healthy controls. Both of these studies (Wang et al., 2011; Mechelli et al., 2007), although employing different analytical approaches, report altered connectivity between temporal and medial PFC areas during source judgments, with the latter study (Mechelli et al., 2007) reporting that this effect is specific to patients with AVH.

Ćurčić-Blake and colleagues investigated EC using dynamic causal modelling in the language circuitry during an inner speech task in patients with AVH and compared it to healthy controls and patients who did not have AVH for at least 6 months prior to participation (Ćurčić-Blake et al., 2013). They found that patients with AVH had decreased connections towards Broca's area, mainly from Wernicke's area, but also from the right homologues of Wernicke's and Broca's areas (interhemispheric connections) to Broca's area. Patients without AVH had intermediate connection strengths. Based on a reduced input from temporal to fontal language areas, the authors suggested that Broca's activity may be less constrained by perceptual information received from the temporal cortex in schizophrenia patients with AVH. This may subsequently affect self-monitoring and lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source. Note that this interhemispheric EC is between frontal areas and might not necessarily involve the auditory interhemispheric pathway discussed in Section 2.3 which is between posterior language and auditory regions.

Shinn and colleagues reported contradictory results (Shinn et al., 2013). They examined primary auditory cortex connectivity in relation to the whole brain and found increased connectivity with the left superior parietal lobule and left middle frontal gyrus, and reduced connectivity to right hippocampal and thalamic regions in AVH patients compared to NoAVH patients.

#### 3.2.2. Symptom capture studies

In a symptom capture study, Raij and colleagues asked patients with schizophrenia to indicate whenever they experienced AVH during resting-state fMRI scans (Raij et al., 2009). Their findings confirmed the involvement of language related networks including the bilateral inferior frontal gyrus (Broca's regions and its right hemisphere homologue), the right posterior temporal lobe (Wernicke's area), the left anterior temporal lobe, and the right anterior cingulate cortex and the parahippocampal cortex during hallucinations. They found that the strength of the connectivity between the left inferior frontal gyrus (IFG) and right ventral striatum, the middle right anterior cingulate cortex, the right posterior temporal lobe, the auditory cortex, and the left nucleus accumbens was positively correlated with subjective experience of the reality of AVH. Moreover, strength of connectivity between the left IFG and parts of the cingulate cortex negatively correlated with subjective experience of the reality of AVH. The stronger the subjective experience of the reality, the weaker the coupling of the IFG with the posterior and rostral anterior cingulate cortex. Thus, this study directly demonstrates complex interaction between language, auditory and memory networks.

Hoffman and colleagues used a bilateral Wernicke's area (posterior STG) delineated seed to investigate FC in patients with schizophrenia with and without AVH, and healthy controls (Hoffman et al., 2011a). They found greater FC between the seed region and IFG in the AVH patients, as compared to NoAVH patients. However, they did not report any difference between AVH patients and healthy controls. Further investigations, using the IFG as a seed region, revealed higher subcortical FC in the putamen in AVH patients with relative to NoAVH patients. Furthermore, stronger FC in AVH patients was seen in a loop linking Wernicke's area, the IFG and the putamen, as compared to both NoAVH patients and healthy controls. In another study, Hoffman investigated time course of AVH and functional connectivity at the various stages of hallucinations (Hoffman et al., 2011b). They found an increased coupling just prior to hallucinations between left IFG (close to Broca's area) and the right temporal areas. Note that all findings regarding button and balloon pressing are partially

confounded by motor planning and imagery specifically for SMA/ACC region (Hanakawa et al., 2008).

*3.2.3. Conclusion for language networks*

In summary, a number of studies have reported alterations in functional connectivity in patients with schizophrenia who experience AVH as compared to those without these symptoms. While most studies report decreased connectivity between language areas and other brain regions, these studies show considerable heterogeneity in their findings. Inconsistency is most likely due to methodological differences between the studies, such us different seed regions and different types of analyses. Nonetheless, these studies also reveal consistencies that likely underlie the experience of AVH. Task-related paradigms demonstrate deficits in source monitoring associated with aberrant frontotemporal FC. Disruption of these mechanisms is consistent with cognitive models which postulate impaired self-monitoring during speech generation.

Similarly, functional connectivity studies, during RS scans, demonstrate disrupted FC in several networks in patients with AVH. The most consistent findings are aberrant connectivity in temporo-parietal language regions and in FC in the primary and secondary auditory cortex in patients with, as compared to patient without AVH and healthy controls. In addition, evidence suggests that AVH are associated with increased connectivity in a cortico-striatal brain network, linking Wernicke's area, inferior frontal gyrus and the putamen.

*3.3. Memory and the limbic networks*

*3.3.1. Symptom association studies*

The most important regions for memory and emotions are the medial temporal lobe regions (Fig. 3). These comprise the amygdala and "the memory regions": the hippocampus, the para-hippocampal gyrus involved in emotional memory (Phelps and LeDoux, 2005; LeDoux, 1996; McGaugh et al., 1996) and together with striatum in associative memory (Sperling et al., 2001).

Sommer et al. investigated FC in patients with chronic AVH during the RS (Sommer et al., 2012). They found a negative correlation of connectivity between the left hippocampus and the left IFG and the severity of hallucinations. However, Diederen and colleagues investigated para-hippocampal gyrus resting-state connectivity in non-psychotic individuals with AVH (Diederen et al., 2013) and found increased resting-state connectivity between the left para-hippocampal gyrus and the left IFG in individuals with AVH as compared to controls. These apparently contradictory findings suggest that presence, severity and stage of illness matter, given that the first study included chronic patients, whereas the latter concerned non-psychotic individuals.

Escarti et al. investigated the limbic networks, defined by independent component analysis (ICA) during listening to emotional words in chronic patients. Patients with AVH had reduced synchrony of these networks in the STG, IFG and the insula as compared with NoAVH patients. The AVH patients had no activation during the task in the insula that was observed in HC and NoAVH patients. Interestingly, AVH patients had increased activation during this task in the amygdala and para-hippocampal gyrus. Amad et al. (Amad et al., 2014) examined connectivity between the hippocampal complex and other regions that included STG in patients with auditory, and patients with auditory *and* visual, hallucinations. In patients with auditory *and* visual hallucinations, FC between the hippocampal complex and: bilateral medial prefrontal cortex and the left caudate nucleus, was increased, and this connectivity was decreased, between the hippocampal complex and STG, left lenticular nucleus, thalamus and right pre-/post-central gyri. These authors argued that their findings fit well with theories of AVHs being 'underconstrained' perceptions that arise when the impact of sensory input on the activation of thalamocortical circuits and synchronization of thalamocortical gamma activity is reduced (Behrendt, 2003). They note that this relationship is reinforced by the fact that the frontal and temporal regions, anatomically connected to the thalamus through the lentiform nucleus, were strongly functionally connected with the hippocampus in the patients with AVH.

*3.3.2. Symptom capture studies*

Few studies have assessed potential co-activation of memory-related structures during the experience of AVH. A meta-analysis

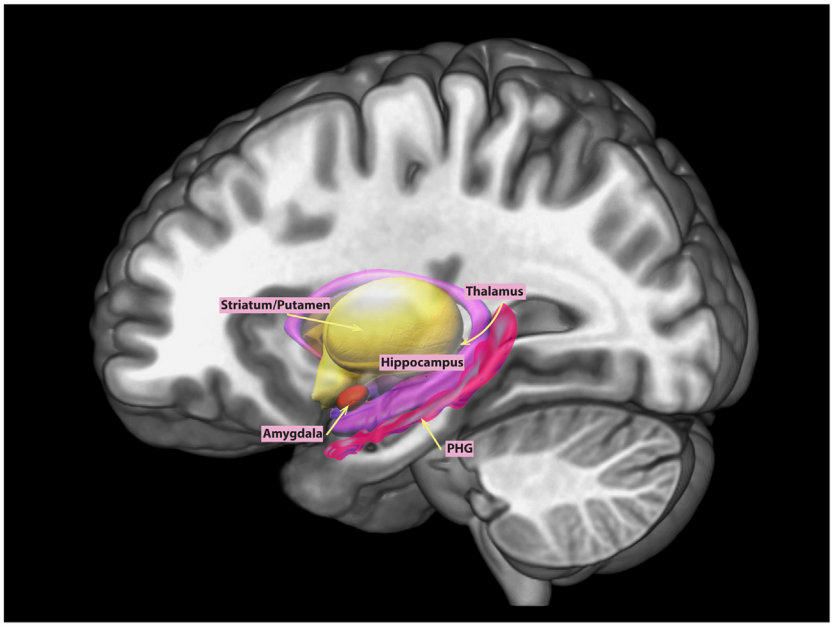


**Fig. 3.** Illustration of memory/limbic network including striatal regions (a possible intermediate step between hippocampus and auditory regions). PHG – para-hippocampal gyrus.

showed involvement of the hippocampus and para-hippocampal gyrus during the experience of AVH (Jardri et al., 2011), suggesting that memory retrieval plays a role in these experiences. Interestingly, two studies that differentiated between signal changes during AVH and signal changes preceding the AVH found that the hippocampal complex was mainly involved in the time period directly before the AVH and not so much during the AVH itself (Diederen et al., 2010; Hoffman et al., 2011b). This may suggest that a memory occurs and subsequently activates the areas that were also active during the initial experience, i.e. the language related areas. Thus, it is conceivable that a decrease in memory inhibition enables the "escape" of memory fragments that lead to a re-lived experience. Memory fragments are usually inhibited during focused attention (Benoit et al., 2015), but may become less inhibited during times of daydreaming and relaxation, when the default mode network is more active. Indeed, patients often mention their hallucinations occurring most frequently at times when focused attention is low, at the beginning and end of the day (Krans et al., 2015; Nayani and David, 1996). Also, in healthy subjects AVH can occur at the borders of sleep, when focused attention is extremely low. In addition, viewing AH as a result of memory-intrusions may help understand the striking association between psychological trauma and this type of hallucination (Chou et al., 2014), observed in patients as well as in non-clinical people with AVH (Daalman et al., 2012). These mechanisms are consistent with the general idea that top-down cortical inhibition over sensory cortex is reduced allowing spontaneous sensory activity to reach conscious awareness (Hunter et al., 2006).

Regarding the striatal involvement, Hoffman and colleagues investigated FC in patients with AVH, patients without AVH, and healthy controls (Hoffman et al., 2011a). They found that FC summed along a loop of Wernicke to IFG to putamen is robustly greater for AVH patients when compared with healthy controls and patients without AVH. Even though this study is based on the language area, greater connectivity between putamen and Broca is in line with the hypothesis of spontaneous generation of memories because according to that theory, putamen is translating memories into language and distributing them to language areas.

#### 3.3.3. Conclusion for memory/limbic network

In summary, there is clear evidence that the memory network interacts with language areas in an aberrant way in patients with AVH as well as in non-psychotic individuals. There is a clear differentiation of the strength of this interaction during rest or during a task as compared to the experience of hallucination. Namely, most symptom association studies point towards reduced connectivity between the memory and language areas in patients with AVH compared to those without. However, there is a clear increase in the connectivity during and prior to experience of AVH (symptom capture studies).

## 4. Anatomical connectivity

Anatomical connectivity refers to physical connections between brain regions – bundles of myelinated axons known as white matter (WM). In the past 20 years novel MRI sequences and analysis techniques have enabled non-invasive investigation of brain anatomy including both the morphology and connections. The most important methods for investigation of brain connections are based on the estimation of WM the diffusion tensor imaging (DTI) (Jones et al., 1999).

In brain regions with a high density of aligned axons (such as WM pathways), water will have a preferred direction in which it can diffuse, which can be measured by diffusion weighted imaging. This directionality is called anisotropy. The most widely used outcome is the fractional anisotropy (FA) coefficient, estimated per voxel. FA has been proven to reflect the integrity of the axonal membrane and myelin sheet (Beaulieu, 2002), as well as the local coherence of myelinated axons (Cercignani and Horsfield, 2001). However, decreases in FA do not always imply aberrant integrity, but can also indicate crossing fibers (see for example (Hoeft et al., 2007; Soares et al., 2013)). Other DTI-derived metrics (such as mean diffusivity and radial FA) may also be of interest in AVH since they may reflect different pathophysiological processes occurring in WM than in FA, but are less commonly reported.

In the next section we will review the most important findings regarding WM quality and AVHs (Table 2).

### 4.1. Anatomical connectivity of auditory regions

There is a large body of evidence implying faulty auditory processing in patients with AVHs (Javitt and Sweet, 2015; Steinmann et al., 2014b). Increased activation has been observed in the primary auditory cortex during rest, which decreases during auditory tasks (Kompus et al., 2011). Furthermore, decreases in the primary (Modinos et al., 2013) and secondary auditory cortex GM volume (reviewed by Allen et al. (Allen et al., 2012)) suggest that there are abnormalities in the top-down regulation of the auditory cortices, which poses questions regarding the underlying WM integrity of pathways connecting auditory regions.

The auditory cortices consist of the posterior part of Heschl's gyrus (known as the primary auditory cortex) and the secondary auditory cortex protruding to the planum temporale and the superior bank of the posterior superior temporal gyrus (Belin et al., 2000). The WM pathways projecting from the auditory regions that are involved in higher order auditory processing are the arcuate fasciculus and the interhemispheric pathways in the posterior part of the corpus callosum. The arcuate fasciculus is involved in both auditory and language processing (Duffau, 2008). Therefore, the association of abnormalities in the arcuate fasciculus with AVHs is described in more detail in Subsection 4.3.

Another important pathway connects the primary and secondary auditory cortices between hemispheres – the isthmus and splenium of the corpus callosum. Previous findings regarding the interhemispheric auditory pathway are contradictory at first glance. Hubl et al. (2004) found that acute patients with AVH had increased FA values in the posterior parts of the interhemispheric commissures of the corpus callosum. Similar findings were obtained by Mulert and colleagues (Mulert et al., 2011b), who found that within the first episode patient group, subjects who heard voices had significantly increased FA in the auditory tract compared to patients who did not have this symptom. Both findings suggest increased connectivity along the interhemispheric auditory pathway in AVH patients. Meanwhile, Knöchel and colleagues investigated FA and mean diffusivity (Knochel et al., 2012), a measure of the compactness of axons and intercellular space (Beaulieu, 2002). In contrast to the abovementioned two studies, it was found that a decrease in the corpus callosum volume was associated with the severity of AVH and that the mean diffusivity values in the isthmus of the corpus callosum correlated significantly with the severity of AVH in patients with paranoid schizophrenia. This is in principle opposite to the finding of increased FA values in the same area. Wigand and colleagues reported decreased FA in AVH patients over the entire pathway compared to patients without AVH in chronic patients (Wigand et al., 2015). In addition, in the midsagittal section of the auditory tract – a similar part of the posterior corpus callosum to that studied in previous investigations the AVH group displayed decreased FA in the midsagittal section. It is worth noting that AVH occur in heterogeneous conditions, and that reduced corpus callous isthmus size (found in

**Table 2**
Articles investigating anatomical connectivity using diffusion tensor imaging (DTI), diffusion spectral imaging (DSI), magnetic transfer imaging (MTI) or stimulation of a white matter tract.

| Author | HC/AVH/NoAVH | Type Network | Type study | ROI tracts | Questionaire | Summary of results |
|---|---|---|---|---|---|---|
| Hubl et al. (2004) | 13 HC 13 AVH Sz 13 NoAVH Sz | A/L/M | DTI tractography; a special line-scan technique | | PANSS, CGI | Increased in AVH: 15 clusters: along AF (6clusters left; 4 clusters right); Cingulate bundle (limbic); Interhemispherical commissural fibers of the CC; Reduced in AVH; 2 clusters: ILF |
| Shergill et al. (2007) | 40 HC 33 Sz | M/A | DTI voxelwise | | BPRS | Propensity to AVH **(+)** with FA in SLF and anterior cingulum |
| Seok et al. (2007) | 22 HC 15 AVH Sz 15 No AVH Sz | L | DTI voxelwise + ROI | ROI's from ANOVA of 3 groups: 2 clusters cingulum bundle, 3in SL, 1 the middle cerebellar peduncle | PSYRATS-AH | Increased in AVH: mean FA in middle part of SLF; PSYRATS-AH **(+)** FA in left frontal SLF |
| Szeszko et al. (2008) | 33 HC 33 Sz | L | DTI whole brain; FA | | | Severity of AVH **(+)** FA in IFOF; Actually with all modalitiies of hallucinations (V, tactile etc) |
| Lee et al. (2009) | 22 HC 21 ChrSz | L | Line scan diffusion imaging | Left & Right STG | SAPS & SANS | MD**(+)** in LSTG (WM) with SAPS-Auditory Hallucination; MD**(+)** in LSTG (WM) with "Voices Conversing" |
| Mulert et al. (2011a, b) | 10 HC 5 AVH FEP (paranoid) 5 NoAVH FEP (paranoid) | A | DTI; fibre tractography; average FA over the whole tract | Homotopic auditory areas via the CC | PANSS | Increased in AVH: FA in the interhemispheric pathway – HC intermediate between NoAVH and AVH; FA values trendwise **(+)** and AVH symptoms |
| De Weijer et al. (2011) | 42 HC 44 AVH Sz | M//L | DTI-FA; MTI-MTR; Fiber tracking FACT | AF; cortical spinal tract, cingulum and UF | PANSS and PSYRATS | PANS_pos **(+)** with MTR in L&R AF |
| De Weijer et al. (2011) | 36 HC 35 AVH Sz 35 AVH non-psychotic | M/L | DTI-FA; MTI-MTR; Fiber tracking FACT | AF; cortical spinal tract, cingulum and UF | PANSS | Increased AVH vs HC: **MTR** in AF; Reduced in AVH Sz only vs HC: FA in all bundless |
| Knöchel et al. (2012) | 15 HC 16 Sz 16 FD-relatives | A | DTI & VBM; automatized segmentation of CC | whole and segmented CC | PANSS and RHS | Severity AVH **(−)** FA in CC; Severity AVH **(−)** VBM volume in CC; |
| Whitford et al. (2014) | 26 HC 24 Sz | M | | Cingulum; 5 subconecctions of Cingulum | SAPS & SANS | SAPS (4 item subscale) &Hallucinations subscale **(−)** FA in the I1 sub-connection (cingulum to rostral and caudal ACC) |
| Bracht et al. (2014) | 22 HC 24 Sz | M | DTI Probabilistic tractography SPM8 | NAcc connectionsto: VTA, NAcc, amygdala, mOFC, lOFC and dlPFC | PANSS P3 + P1 | P3 + P1 **(+)** PIBI FA values Nacc-Amygdala |
| Wu (2014) | 18 HC 18 SZ | L | DSI | ventral stream-IFOF and dorsal stream-AF; semantic task | PANSS | GFA **(−)** with symptom severity (hallucination/ delusions) in AF and IFOF and lateralization during semantic task |
| Wigand et al. (2015) | 33 HC 24 AVH Sz 9 NoAVH Sz | A | DTI; streamline tractography | interhemispheric Auditory Pathway (AP) | | Reduced in AVH: FA over entire AP; FA and Mode in Midsagital section of AP; Increased in AVH: radial diffusitivy in Midsagital section of AP. |
| Ćurčić-Blake et al. (2015) | 14 HC 17 AVH Sz 14 AVH Sz | L/A | DTI TBSS | left: IFOF, UF, SLF, AF, cingulum; Bilateral ACR | | Reduced in AVH: FA in left: anterior IFOF, UF, ACR, AF (anterior and long parts of the AF – frontal regions such as BA44, and temporal regions), CC medial and posterior part—the forceps major, the cingulum, corticospinal tract and the ATR |
| Benetti et al. (2015) | 22 HC 28 AVH ARMS + FEP 18 NoAVH ARMS + FEP no Sz | L | DTI tractography; fMRI task Hayling Sentence Completion Task | Left AF | PANSS; PSYRATS | Intermediate in AVH between HC and NoAVH (but not sugbuficant): FA in AF; NoAVH the lowest; |
| Oestreich et al. (2015) | 40 HC 39 AVH Sz 74 NoAVH Sz | L | DTI tractography | IFOF segmented in 4 regions: frontal, fronto-temporal; temporal; occipital | DIP items 51, 52 and 53 | Reduced in AVH: FA fronto-temporal fibers of the left IFOF |
| McCarthy-Jones et al. (2015) | 40 HC 39 AVH Sz 74 NoAVH Sz | L | | left long direct segment of AF | | Increased in AVH: Radial Diffusivity left long segment AF; Reduced in AVH: FA Left long segment of AF (less than NoVAH and HC) |
| Koubeissi et al. (2016) | 3 epliepsy patient | L | Stimulation of left AF | left AF | | Complex AVH occur upon stimulation of AF |

FA – fractional anisotropy; GFA – generalized fractional anisotropy; MTR – magnetic transfer ratio; MD – mean diffusivity; AF – arcuate fasciculus; IFOF – inferior fronto-occipital fasciculus; UF – uncinate fasciculus; ACR – anterior corona radiata; ATR – anterior thalamic radiation; CC – corpus callosum; SLF – superior longitudinal fasciculus; AP – auditory pathway; For other abbreviations see the legend of Table 1. Note that MTR and MD are considered to be inversely proportional to FA, thus increases in FA are often correlated with decreases in MTR and MD.

schizophrenia in a meta-analysis (Woodruff et al., 1995b) may also be related to delusions which occur in the same condition (Woodruff et al., 1993).

In summary, several studies have reported abnormalities in auditory pathways, interhemispheric as well as within one hemisphere. However, their findings are contradictory with respect to the direction of differentiation. The main trend seems to be that in the first episode patients or acute patients fractional anisotropy is increased, whereas in chronic patients FA decreases. Nevertheless, the results are in line with our previous suggestion that any departure from healthy connectivity causes an imbalance in functioning and is at the core of AVH.

### 4.2. Memory limbic regions

The phenomenology of AVH strongly implicates the involvement of brain regions subserving both retrieval of memories and the experience of negative emotion. Memory impairment is well documented in schizophrenia but has not been investigated intensively in relation to AH (Aleman et al., 1999). Nevertheless, theories/empirical evidence of impairments in memory (Section 2.1 of this paper) and emotional processing, added to the negative emotional connotation of AVH in patients with schizophrenia (Hill and Linden, 2013), demands further investigation of the memory/limbic network.

The memory/limbic network is involved in emotional processing and regulation, self-monitoring, memory and attention. It comprises the following areas: the anterior cingulate, involved in error monitoring and emotional processing and learning (Bush et al., 2000); the hippocampus, generally involved in memory processes (Squire et al., 2004); the parahippocampal gyrus involved in contextual associations closely related to memory (Aminoff et al., 2013); the amygdala, involved in emotional processing and emotional learning (McGaugh et al., 1996); the entorhinal cortex, which is closely associated with memory functions of the hippocampus(Squire et al., 2004); the perirhinal cortex, which has a function in sensory integration, semantic and long-term memory (Murray and Richmond, 2001; Murray et al., 2005). The largest white matter pathways connecting these regions are the uncinate fasciculus and the cingulum.

The uncinate fasciculus connects lateral and medial prefrontal cortices to the uncus, the entorhinal and perirhinal cortices, and the temporal pole/anterior temporal lobe (Von Der Heide et al., 2013). A recent review suggests that uncinate fasciculus has a role in valence-based biasing of decisions. Given this function, the uncinate fasciculus appears to be a good candidate to play a role in the emotional part of AVH.

Thus far only one study, using tract-based spatial statistics, has found evidence of an association of white matter abnormalities within the uncinate fasciculus and AVH (Ćurčić-Blake et al., 2015). Specifically, patients with hallucinations with lower FA values had more severe AVH. As mentioned above (Section 4.1), Hubl et al. (2004) found no difference in FA in the uncinate fasciculus in AVH compared to patients who had never experienced AVH. Both studies had relatively small samples., In a larger sample (42 patients with AVH), De Weijer and colleagues found no correlation between FA in uncinate fasciculus and symptom severity (De Weijer et al., 2011).

The cingulum is the long-range white matter tract placed underneath the cingulate cortex. It connects the ACC, the posterior cingulate cortex, the isthmus of the cingulate gyrus and the parahippocampal cortex. Decreased FA in various parts of the cingulum has consistently been observed in schizophrenia patients (Hubl et al., 2004; Shergill et al., 2007; Knöchel et al., 2012). However, the relation with hallucinations remains puzzling. Even though a few studies have found no association of cingulum integrity with AH (Knöchel et al., 2012), several other studies have found differences between patients with and without AH along this tract.

In one of these studies, Shergill et al. (2007) compared healthy controls and patients with various severity of AVH. The authors reported that higher FA in the superior longitudinal fasciculus and anterior cingulum was associated with a propensity to experience auditory hallucinations, although overall FA was lower overall in patients compared to healthy volunteers (Shergill et al., 2007). Similarly, Hubl et al. (2004) demonstrated reduced anisotropy in the cingulate bundle in patients without AVH compared to patients who had experienced AVH, but this was restricted to the left hemisphere. In contrast, Whitford et al. (2014) found a negative correlation of FA values in Subsection 4.1 of the right cingulum with the hallucination subscale of SAPS. This subsection of the cingulum projects into the rostral anterior cingulate gyrus and the caudal anterior cingulate gyrus. These two regions assume different roles, the former being involved in emotional processing and the latter in cognitive processes for memory and executive functioning. The authors proposed that this negative correlation is in line with suggestions that AVH arise from abnormal interactions between cognition and emotion. Seok et al. found increased values of FA in the left caudate cingulum in patients with AVH as compared to patients without (Seok et al., 2007). However, the correlation with symptom severity was diminished after a correction for antipsychotic use was made. Ćurčić-Blake et al. (2015) found a negative correlation of the hallucination severity with FA in the left cingulum.

In support of the relationship between AVH and limbic network abnormalities, Bracht et al. (2014) reported a positive correlation between severity of both hallucinations and delusion (summary score) and connectivity between amygdala and the nucleus accumbens using probabilistic tractography methods. However, this study did not aim to investigate AVH per se (Bracht et al., 2014).

In summary, most studies have found altered FA values in cingulum with AVH, and contradictory results cannot be explained by the duration of illness because increases were seen in both chronic and acute patients. These discrepancies are probably caused by the use of different acquisition methods or analysis methods, but the general consensus nevertheless points towards abnormal anatomy of the memory/limbic network in relation to AVH.

### 4.3. Language network

A recent meta-analysis included DTI studies highlighting the results on the most important fronto-temporal fiber tract, which integrity is essential for a functioning language network, the *arcuate fasciculus* (AF) (Geoffroy et al., 2014). AF plays a central role in language perception and production. Four out of five papers retained in the meta-analysis reported decreased FA of the left (but not right) AF of patients with AVH as compared to patients without AVH (Seok et al., 2007; Catani et al., 2011; De Weijer et al., 2011; Ćurčić-Blake et al., 2015). Similar results were recently obtained when comparing ultra-high-risk and first-episode-psychosis individuals following AVH episodes with NoAVH subject (Benetti et al., 2015).

However, one study included (Hubl et al., 2004) as well as studies not eligible for being included in the above mentioned meta-analysis demonstrated increased connectivity within the language network in these patients (Shergill et al., 2007; Rotarska-Jagiela et al., 2009; Knöchel et al., 2012).

Seok et al. also found increased FA in different white-matter tracks, like e.g. in the caudal part of the left cingulate gyrus and the left *inferior longitudinal fasciculus*. These authors reported a positive correlation between AVH severity and the left *superior longitudinal fasciculus* FA – the region with the highest white matter density in AVH compared to all other groups (Seok et al., 2007).

Abdul-Rahman and colleagues specifically investigated WM abnormalities in particular loci along the AF as well as its regional lateralization in schizophrenia (Abdul-Rahman et al., 2012) by examining different WM along the whole extent of the AF. This study revealed that schizophrenia patients had lower FA in the frontal aspects of the left AF compared with healthy controls. On the contrary, patients exhibited greater left FA and axial diffusivity lateralization in the temporal segment of AF found correlated with the severity of delusions and hallucinations.

The most recent study, comprising 74 patients with no history of AVH, and 39 patients with lifetime AVH found that FA was

specifically decreased in the AF (longitudinal part) in patients with AVH as compared to other patients and healthy controls (McCarthy-Jones et al., 2015). This study involved the highest number of schizophrenia patients without AVH so far. Radial diffusivity was increased in this segment of the AF, suggesting that insufficient myelination or demyelination affects the AF longitudinal segment in AVH patients.

It seems that later studies point to an increased FA of the arcuate fasciculus in AVH, while previous reports as well as meta-analyses rather evidenced a reduced FA for this bundle. Hypothetically, it might be that a basic dysfunction (in the fronto-temporal connection) could lead to compensatory structural changes in connectivity without reaching a good functional balance. Such differences in findings may be related to unselected sample of schizophrenia patients in seminal papers (e.g. (Agartz et al., 2001)). Patients recruited in first DTI studies were most of the time not classified according to symptoms, but only as responding or not to diagnosis criteria for schizophrenia. One the strength of subsequent conducted DTI studies is clearly the well selected study population (AVH+ vs NoAVH) to enable a distinction between disease-specific and symptom-specific effects.

Another important tract involved in language processing is the inferior fronto-occipital fasciculus, connecting frontal with temporal and parietal parts of the brain and running inferior to the AF (Forkel et al., 2012). Duffau and colleagues used intra-operative electrostimulation (Duffau, 2008) and found that the inferior fronto-occipital fasciculus has an important role in the semantic processing of language. With the aim of investigating this region further, two comprehensive studies focused on the integrity of the inferior fronto-occipital fasciculus in AVH (Ćurčić-Blake et al., 2015; Oestreich et al., 2015). Even though different techniques were used, both studies found decreased FA in the fronto-temporal part of the left inferior fronto-occipital fasciculus.

The debate is still open and the potential influencing variables are not well enough controlled. There are differences in the studied populations (life time history vs present state of AVH) or methodological contrasts (controls vs schizophrenia patients with subsequent correlation analysis vs selected study groups covering patients with or without AVH), like differences in the meta-analysis methods (data collection as well as analysis: here e.g. voxel based vs tract based vs regions of interest) and last but not least according to difference in the methods, according to which the anatomical regions have been defined. An increase in the total number of whole-brain DTI studies referring to validated white-matter templates would pave the way to coordinate-based meta-analyses, providing a peak effect size and signed maps of positive or negative differences in AVH patients (Peters et al., 2012).

## 5. EEG-based connectivity analyses

This paragraph focuses on studies using EEG investigating altered connectivity in patients with AVH. EEG is a direct measurement of neural activity. EEG oscillations, or intrinsic coupling modes, have been demonstrated to reflect the key mechanisms mediating functional connectivity in the brain (Engel et al., 2013). Moreover, recent developments of non-invasive brain stimulation such as transcranial alternating current stimulation offer a frequency- and probably mechanism-specific alteration of brain function (Herrmann et al., 2015), suggesting that an improved understanding of altered oscillatory coupling between brain regions underlying AVH might provide a direct link to specific network-modulation or even new concepts for treatment.

It is important to note that there has been substantial methodological progress in the field of EEG-connectivity analyses during the last few years. While earlier studies using sensor-level EEG-coherence measurements were at increased risk of problems due to volume conduction, the analysis in source-space and the addressing of the phase-lag between brain regions have been successful steps towards valid EEG-based connectivity results (Pascual-Marqui et al., 2011). Currently, several different analysis-strategies for EEG-based connectivity are used, such as the investigation of phase-coherence (Ford et al., 2007).

Briefly, the rationale for using EEG to study AVH can be the following. It has been proposed that a potential mechanism for information processing by the brain is synchronization of distant neuronal assemblies (Varela et al., 2001; Fries, 2005; David and Friston, 2003). Therefore, if there is altered anatomo-functional connectivity in AVH as shown previously from DTI studies, the functional consequence is a corresponding alteration of neuronal synchronization, and thereby impaired information processing potentially leading to hallucination. In principle, the pathophysiology of AVH thus predict impaired EEG synchronisation during sensory processing in patient s with AVH, as shown in a series of studies (Kwon et al., 1999; Gallinat et al., 2004; Uhlhaas et al., 2008; Uhlhaas and Singer, 2010; Engel et al., 2013).

Here we will present EEG studies with a focus on self-monitoring of self-generated sensations, interhemispheric miscommunication (Summarized in Table 3).

### 5.1. Self-monitoring of self-generated sensations

Ford et al. demonstrated greater sensor-level coherence during talking than listening between fronto-temporal regions in all frequency-bands in healthy subjects. Interestingly, a lack of EEG-theta band coherence between frontal and temporal lobes during talking was associated with a tendency to hallucinate in patients with schizophrenia (Ford et al., 2002), while there was no condition x group interaction for other frequency bands (delta, alpha, beta and gamma). Using electrocorticogram recordings from treatment-resistant epilepsy patients, Chen et al. investigated phase synchrony between Broca's area and auditory cortex in the gamma band during a vocalizing/listening task (Chen et al., 2011). Here, pre-speech neural synchrony was correlated with the subsequent suppression of the auditory cortical response to the spoken sound. This can be interpreted as a gamma-band mediated neural instantiation of the transmission of a copy of motor commands (Chen et al., 2011). Using EEG and source estimation, Wang et al. in a talking/listening paradigm demonstrated that inferior frontal gyrus activity 300 ms before speaking was associated with suppressed processing of speech sounds in auditory cortex around 100 ms after speech onset. Frontal-temporal source coherence was increased in lower frequencies (delta/theta frequency range) in the pre-speech timeframe in comparison to the talking timeframe. These findings suggest that an efference copy from speech areas in prefrontal cortex is transmitted to auditory cortex, where it is used to suppress processing of anticipated speech sounds (Wang et al., 2014).

### 5.2. Interhemispheric miscommunication

Using sensor-level EEG analysis, Sritharan et al. compared timeframes during AVH with timeframes without AVH in seven schizophrenic patients. While they did not find significant changes in the coherence between Broca's region and Wernicke's area (as estimated from the scalp EEG electrode positions), the authors reported a significant increase of alpha-coherence between the left and the right superior temporal cortices during AVH (Sritharan et al., 2005). Using sensor-level EEG-coherence analysis, Henshall et al. investigated upper alpha and upper beta band coherence from six pairs of electrodes in schizophrenic patients with and without AVH. Relative to both healthy controls and patients without AH, coherence was lower in patients with AH (Henshall

**Table 3**
Articles investigating FC using EEG.

| Type Study | Author | HC/AVH/ NoAVH | Type Network | | Methods analysis | ROI tracts | Questionaire | Summary of results |
|---|---|---|---|---|---|---|---|---|
| State | Sritharan et al. (2005) | 7 AVH Sz patients | L/A | State, Microswitch pressing during hallucinations | Alpha-band average coherence | Sensor level looking at groups of electrodes over: Broca's, Wernicke's area and interhemispheric auditory | | NS Change: coherence between Broca's and Wernicke's areas; Increased during AVHs: coherence between the left and right ST cortices |
| | Angelopoulos et al. (2011) | 8 AVH Sz 7 NoAVH Sz 16 HC | A/L | State, Optical switch pressing on the onset and offset of AVH; | Phase coupling | T7 and T8 electrodes | PSYRATS-AHRS; PANSS | Increased during AVH: phase coupling between T7 and frontal regions; Increased during hallucinations synchrony in alpha band |
| | Koutsoukos et al. (2013) | 8 AVH Sz | A/L | State, Optical switch pressing on the onset and offset of AVH; | Phase coupling between theta and delta oscialtions | | | Increased during AVH: phase coupling between theta and delta significant in the left fronto-temporal regions |
| | Kindler et al. (2011) | 8 AVH Sz (paranoid) 1 AVH acute polimorphic psychotic disorder | | State, Button pressing on the onset and offset of AVH; | Topographical microstates (sensory level; classes A-D; based on Global field power) | All sensors | | Shorter during AVH: microstate D (frontal positve power, occipital negative power) |
| Trait | Ford et al. (2002) | 10 HC 7 AVH Sz 5 NoAVH Sz | L | Tasks: Talking and listening own speech | Coherence | Bilateral: Frontal, Temporal | BPRS; SAPS | Reduced in AVH: Left Fronto temporal Coherence produced in talking condition |
| | Henshall et al. (2012) | 17 HC 19 AVH Sz 17 NoAVh Sz | A | Task listening pure tone or word | Transfer Times (IHTT) | sensor level interhemispheric auditory | | Longer in AVH: IHTT for word listening only; IHTT fir word listening was shortest in HC; No difference in IHTT fro pure tone |
| | Henshall et al. (2013) | 17 HC 19 AVH Sz 17 NoAVh Sz | A | Task listening pure tone or word | Coherence: upper alpha and upper beta band | sensor level interhemispheric auditory | | Reduced in AVH: Interspheric coherence in alpha band |
| | Mulert et al. (2011a,b) | 16 HC 18 Sz | A | task auditory steady state response | Source localization: gamma band synchrony | Source localization: STG, MTG, Heschl's gyrus | SAPS | Auditory hallucination scores **(+)** phase synchronization between the PAC but not for the SAC. |
| | Ford et al. (2007) | 24 HC 12 Sz | L/A | task talking and listening own utterances (such as “ah”) | Pre-speech neural synchrony | sensor level right and left frontal, temporal and parietal | BPRS; SANS | Reduced in AVH: pre-speech synchrony; In HC pre-speech synchrony correlated with suppression of responsiveness to the spoken sound (corollary discharge); |
| | Koenig et al. (2012) | 26 HC 18 AVH Sz 11 NoAVH Sz | A | Auditory stimulation with click-tones at 20, 30 and 40 Hz | spectral amplitude maps & GFS | sLoreta-bilateral: Heschl's gyrus STG, angular gyrus, IFG and ACC; Global measures were from all sensors | Oulis Auditory Hallucinations Rating Scale | Reduced in AVH: Global Activation and GFS only at 40 Hz; While HC and NoAVH Sz have increased GFS during task, AVH have decrease; sLoreta gave no reulsts |
| | Griskova-Bulanova et al. (2016) | 25 HC 15 AVH Sz 11 NoAVH Sz | | Auditory stimulation with click-tones at 40 Hz | Phase locking for early- and late-latency – gamma responses | | Oulis Auditory Hallucinations Rating Scale | Longer in AVH: time of peak response |

GFS – global measure of phase-locking; IHTT – interhemispheric transfer time; NS – not significant; For other abbreviations see the legend of Table 1.

et al., 2013). Moreover, Henshall et al. demonstrated altered (increased) interhemispheric transfer times after auditory stimulation in schizophrenic patients with AH after the presentation of words. This finding can be attributed to transcallosal dysfunction in patients with AH (Henshall et al., 2012). Using source estimation and the analysis of phase synchronization, Mulert et al. found reduced interhemispheric gamma-band phase coupling between auditory areas in schizophrenic patients during an auditory steady state response (ASSR) task. Moreover, there was a significant positive correlation between auditory hallucination symptom scores and gamma- phase synchronization between the auditory cortices (Mulert et al., 2011a), which is in line with the respective anatomical findings (Hubl et al., 2004; Mulert et al., 2012). This may reflect that there is an *optimal* level of connectivity for healthy functioning and that AVH arise when the connectivity is either above or below this optimal level. Recently, Steinmann et al. demonstrated that gamma-band phase coupling between bilateral auditory areas is related to conscious perception in dichotic listening tasks in general, suggesting that altered conscious auditory perception during dichotic listening tasks of patients with AH might be related to disturbed gamma-band phase synchronization (Steinmann et al., 2014a, 2014b).

Given the variety of EEG-based connectivity analysis strategies, there are a number of additional interesting findings. Koutsoukos et al. investigated altered coupling between theta and gamma EEG rhythms to be associated with the experience of AVH. The average differences of theta-gamma-coupling between hallucinatory and resting stages were significant in the left temporal area (Koutsoukos et al., 2013). Kindler et al. demonstrated the shortening of class D microstates during AVH (Kindler et al., 2011). Using simultaneous EEG-fMRI, class D microstates have been suggested to be related to a right-lateralized frontoparietal network associated

with attention reorientation (Britz et al., 2010). Koenig et al. used measure of phase synchrony and demonstrated a left-lateralized phase synchrony –decrease in patients with AVH during 40 Hz auditory stimulation, in contrast to a phase synchrony –increase in healthy subjects or patients without AVH (Koenig et al., 2012; Griskova-Bulanova et al., 2016).

In summary, there is support from EEG studies to both the concept of self-monitoring of self-generated sensations and the concept of interhemispheric miscommunication underlying AVH. Recent methodological advances in EEG-based connectivity analyses have strengthened the validity of these results.

## 6. Discussion

### 6.1. General summary

We have reviewed literature concerning the anatomical and functional connectivities implicated in AVH in the language, auditory and memory/limbic networks. Even though some contradictory results can be found, there is clear consensus that these networks are disturbed specifically in patients with AVH. While inter-hemispheric connectivity appears to be increased in the early stage of illness, a decrease is observed in the later stages. In healthy people with hallucinations, an increase in inter-hemispheric connectivity has been observed, similar to early stage patients. The majority of large studies on chronic schizophrenia patients that incorporate both a control group and a group of patients without AVH find decreases in anatomical or functional connectivity of language areas (De Weijer et al., 2013; Oestreich et al., 2015; McCarthy-Jones et al., 2015; Ćurčić-Blake et al., 2013), but other studies (with smaller sample sizes; see Table 2) have found exactly the opposite (Hoffman et al., 2011a; Benetti et al., 2015). Most of these studies, excluding those that limited investigation to just a few regions of interest, found abnormalities in a combination of networks rather than in a single network. Even though most hypotheses are specific in terms of directional influence between regions, for example the influence of cognitive control areas over auditory perception areas, no clear causal hypothesis has been tested so far.

These networks are not independent of each other but rather interconnected. As observed in anatomical studies, some of the regions involved have functions in multiple networks. The best such example is the superior temporal area where the secondary auditory cortex overlaps with Wernicke's area (Bethmann and Brechmann, 2014). Patients with AVH exhibit abnormal anatomical and functional connections in all three networks. In at least two networks, auditory and language, the direction of the abnormality is unclear. However, regarding the FC during hallucinations, one pattern clearly emerges. Namely, 7 out of 8 symptom capture studies (4 fMRI and 3 EEG) investigated connectivity strengths in these networks all found increases in FC between the auditory and language networks during AVH. In addition, two studies (Raij et al., 2009; Hoffman et al., 2011a) found connectivity increases in the cortico-striatal loop during hallucinations. Thus, a clear pattern of increased interaction among the auditory-language and striatal brain regions occurs while patients hallucinate. This finding could explain why AVH are such realistic experiences of speech: increased coordinated activity in this circuitry has been observed during speech perception relative to inner verbal thought (Lavigne et al., 2015). However, the number of symptom capture studies is still low, and more data are needed in this regard.

Regarding fronto-temporal connections some studies found increases in the connectivity strengths but others found decreases. A consensus about how to interpret these discrepancies may currently not be within reach, as more information is needed on the role of these networks in hallucinations. It is possible that the differences arise from different measurement or analysis techniques (Alderson-Day et al., 2016), or the use of different questionnaires. Additionally, differences in connectivity could arise due to considerable heterogeneity within the category of AVH. More specifically, sub-categories of AVH have been proposed, particularly in the context of schizophrenia – e.g., command hallucinations, third-person hallucinations, and thought echo (Blom and Sommer, 2010; McCarthy-Jones et al., 2014). It has been suggested that different sub-types of AVH have different neurological underpinning (Blom and Sommer, 2010). However, none of the connectivity studies reviewed here investigated specific sub-categories of AVH. Only Oestreich summarises AVH experiences (Oestreich et al., 2015) based on the Diagnostic Interview for Psychosis (DIP) (Castle et al., 2006). This may also be relevant to the non-specificity of the presented findings and deserves to be investigated in more detail. Another possibility is that the strengths of connections change over the course of the illness. This seems to be the case for interhemispheric auditory pathway based on both FC and auditory cortex reported here. Specifically, connectivity strengths are stronger for first episode patients, but they are lower in patients with a more chronic form of psychotic disorder. During acute psychosis, frequent AVH may have a training effect on the white matter tracts as they are heavily used during this experience, which may induce them to grow. This is in line with findings of Hillary and colleagues in patient with neurological disease (Hillary et al., 2015). Their review of 126 studies showed that after the onset of illness overall connectivity is increased but diminishes in the later stages of the degeneration (Hillary et al., 2015). Nevertheless, one plausible conclusion is that an *optimal* level of connectivity is necessary for healthy functioning and that AVH arise when the connectivity is either above or below this optimal level.

### 6.2. Evidence for theoretical proposals regarding AVH

The results of several studies supported the hypothesis of AVH as arising from spontaneous activation caused by memory intrusions. Two studies found evidence for a specific role of connections between memory regions and Broca's area (the language production area) (Sommer et al., 2012; Diederen et al., 2013) and Hoffman showed that the FC between the putamen and language areas is very important for AVH (Hoffman et al., 2011a). However, all of these studies showed that a more complex network of regions is involved, suggesting that the hypothesis of spontaneous memory intrusions is too limited to account for the data. Also, none of these studies looked at the actual influence of one region on another, while the hypothesis of spontaneous memory intrusion has a specific information flow assumption: the memories produced by memory regions enter the putamen which feeds them towards language production and comprehension regions (see Fig. 3). This specific assumption of information flow direction should be investigated in order to truly test the hypothesis.

Support was also found for the self-monitoring theory of AVH. The EEG connectivity findings of Ford et al. (2002) are very similar to those of Lawrie and colleagues using fMRI (Lawrie et al., 2002): both reported diminished connectivity between the fronto-temporal speech production region and speech comprehension areas in patients with AVH. Lawrie et al. concluded that their data " . . . represent further evidence that AVH in schizophrenia are related to the defective monitoring of inner speech, that is, the temporal processing of subvocal speech is not constrained by prefrontal input, indicating that the speech is self-induced." There were no group differences in activations associated with sentence completion, indicating that functional connectivity differences occur also in absence of measurable activation differences. Again

this theory is based on the specific directional influence from higher cognitive areas towards perception areas (see Fig. 1). One study used effective connectivity between monitoring and language areas and interpreted their findings as evidence of source monitoring deficits in the people with AVH and as support for the self-monitoring deficit theory of AVH (Mechelli et al., 2007). Note that the distortion found in the previous paper was for the reverse connection, i.e., from the STG towards the ACC (which is the monitoring area), which suggests more that there is "trouble" with perceptual input to the monitoring area.

Regarding interhemispheric connections, we already mentioned that there is substantial evidence for disturbances here. These results suggest that interhemispheric miscommunication between bilateral auditory areas in patients with AVH is already present during the first episode (Hubl et al., 2004; Mulert et al., 2012), but alters during the course of the disease (Wigand et al., 2015). Interestingly, there is a strong relationship between the structure and function of interhemispheric connectivity between the bilateral auditory areas and conscious auditory perception in general (Westerhausen et al., 2009; Steinmann et al., 2014b). This might explain why a relationship between interhemispheric auditory connectivity and auditory phantom perception is found not only in the context of AVH in schizophrenia, but also for example in the context of tinnitus (Diesch et al., 2012).

Finally, the issue of top-down control versus bottom-up miscommunication was also supported by several studies. For example, Shinn and colleagues found aberrant connectivity between Heschl's gyrus and Broca's Area, the left lateral STG, anterior cingulate and orbito-frontal gyrus (Shinn et al., 2013). However, even though most of these theories have a clear hypothesis about the inhibition or excitation exerted by one region on the other one (such as the PFC over the PAC), an examination of directionality was clearly missing from the summarized research. Indeed, only three studies so far have investigated the influence of one area on another (Mechelli et al., 2007; Ćurčić-Blake et al., 2013; de la Iglesia-Vaya et al., 2014). All three studies found specific AVH-related changes to connections from the perceptual towards higher cognitive areas. More specifically, all three studies found that decreases in the connections from the temporal lobe to the frontal language and monitoring-related areas play an important role for patients with AVH. We can thus propose that AVHs are derived from auditory cortical activity, and it is highly likely that spontaneous activity caused by the intrusion of external auditory signals (that recruit neurophysiological resources overlapping with those responsible for AVH perception) is normally inhibited in this receptive sensory area, so it is when this inhibition is reduced that AVHs reach conscious awareness.

Based on the reported findings we suggest that there are aberrations in connectivity that are complex and that dynamically change as the illness evolves, specifically between the language, memory/limbic and auditory networks that are of importance for AVH in schizophrenia. Furthermore, the evidence presented here supports can be taken to partially support all the accounts mentioned in the Introduction and does not allow any individual theory to be favoured. Nonetheless, a close examination of the results summarized in Tables 1–3 yields strongest available evidence for the "unstable memories" and "top-down versus bottom-up influences" hypotheses. This is a matter of interpretation though, and obviously one could argue that the combined evidence is most in favour of the "hybrid models" we mention in Section 2.5. For certain hypotheses, such as the interhemispheric miscommunication hypothesis, less studies have been conducted that allow to evaluate the hypothesis. Thus, in that case one should keep in mind that the absence of evidence does not imply evidence of absence. Another important issue is that most studies did not explicitly test different hypotheses against each other nor did their design permit strong conclusions in that regard. Thus, with the exception of Mechelli et al. (2007) who directly tested the self-monitoring hypothesis using causal connectivity, none of the other studies were specifically designed to test directionality of connectivity related to a single hypothesis. For example, anatomical studies do not distinguish directional influence and thus cannot support causal influences embedded in hypotheses. Moreover, deficiencies in white matter tracts do not necessarily reflect functional connectivity deficiencies. Several studies support more than one hypothesis, and reveal abnormalities in 2 or 3 networks (see Tables 1–3). Thus, at this point the available evidence is consistent with hybrid hypotheses in which all three networks and the striatal network are involved. Further studies should be directed towards discerning which of the four abovementioned scenarios (Ford and Hoffman, 2013a; Aleman and Larøi, 2011; Waters et al., 2012; Northoff, 2014) is most plausible by adopting a more specific experimental paradigm and using causal inference analysis methods.

In patients with schizophrenia, errors already occur at the perception level (Gold et al., 1992). Not only is information from speech omitted, but due to deficiencies in functioning and interaction of the memory/limbic and auditory networks, patients fill in words or emotional intonation that are not present. This is well documented in the study of schizophrenia (Fridberg et al., 2010) and is specifically correlated with positive symptoms (Brebion et al., 1999). This "filling in" is often referred to as memory intrusion and false memory alarms. One consequence is the construction of memory of false negative events, which is specific for schizophrenia as compared to healthy controls. However, healthy controls with a propensity to AVH are more likely to report hearing a word that fits the context of a sentence when it is not actually presented (Vercammen and Aleman, 2010). It is curious that "filling in" seems to take place at the semantic processing level in nonclinical subjects with a propensity to AVH. This is in line with abnormal top-down influences on auditory perception in the case of hallucinatory experiences (Behrendt, 2006; Grossberg, 2000), as described in Section 3.3.

Thus, there is already extensive interaction of these three networks at a perceptual level, which may lead to the memory problems regarding auditory-verbal information. In patients, these memories are more negative and this may be related to faulty interhemispheric communication (as the language areas in the right hemisphere are involved in the emotional connotation of speech (Heilman et al., 1975; Wildgruber et al., 2006) and memory impairment.

These arguments do not yet explain the generation of AVH. We reviewed evidence here that language pathways are abnormal in patients with schizophrenia. This imbalance in anatomical connections, reflected by functional miscommunication, suggests that the regions involved (primarily Broca's area and the superior temporal regions including Wernicke) either receive too little, too much or erroneous input. It is possible that all three scenarios are in play. We suggest here that in the absence of input or with decreased input, these regions still try to communicate in an aberrant way. Indeed, evidence from RS studies suggests that the RS connectivity in schizophrenia patients is disrupted (Alderson-Day et al., 2015). Northoff predicts that elevated resting state activity in the default mode network and auditory cortex coupled with their unaltered communication can enhance the development of AVH (Northoff, 2014; Northoff and Qin, 2011). One possible consequence is a predisposition to the over-activation of language regions in the absence of correct input (Jardri et al., 2011). Indeed in one study, Broca's region starts to search for extra information either due to missing input or to an overflow of abundant signals. For example specifically Broca's area (BA44) was activated by

unintelligible speech presented at low signal-to-noise ratios (Zekveld et al., 2006), suggesting that Broca's area is recruited in an effort to make semantic sense of what we are hearing. This is consistent with 'over-activation' of Broca's area during AVH (Sommer et al., 2008). This may prompt the auditory regions to start producing information, even their activation during hallucinations is not consistently reported in the literature (see for overview (Jardri et al., 2011)). Another possibility is additional intrusion of 'faulty' memories of negative voices, such that threatening inner speech is then produced. Furthermore, a lack of self-monitoring (described in several of the sections here) coupled with abnormal functioning of the fronto-temporal and interhemispheric networks, causes the inner produced voices to be perceived as coming from the outside.

In summary, the language, auditory and memory/limbic networks are highly interconnected in the perception of speech. All three networks exhibit anatomical and functional abnormalities in schizophrenia patients. We propose that previous research may have focused too narrowly on the language network only and that the resulting miscommunication between all three networks may be at the core of AVH in schizophrenia. Precise hypotheses concerning the directionality of connections deduced from current theoretical approaches can and should be tested using existing RS connectivity data. This may help to provide conclusive evidence for or against major theories regarding the mechanism of AVH.

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