Network Analysis of Auditory Hallucinations in Nonpsychotic Individuals

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Abstract: *Background:* Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia and can severely disrupt behavior and decrease quality of life. Identification of areas with high functional connectivity (so-called hub regions) that are associated with the predisposition to hallucinate may provide potential targets for neuromodulation in the treatment of AVH. *Methods:* Resting-state fMRI scans during which no hallucinations had occurred were acquired from 29 nonpsychotic individuals with AVH and 29 matched controls. These nonpsychotic individuals with AVH provide the opportunity to study AVH without several confounds associated with schizophrenia, such as antipsychotic medication use and other symptoms related to the illness. Hub regions were identified by assessing weighted connectivity strength and betweenness centrality across groups using a permutation analysis. *Results:* Nonpsychotic individuals with AVH exhibited increased functioning as hub regions in the temporal cortices and the posterior cingulate/precuneus, which is an important area in the default mode network (DMN), compared to the nonhallucinating controls. In addition, the right inferior temporal gyrus, left paracentral lobule and right amygdala were less important as a hub region in the AVH group. *Conclusions:* These results suggest that the predisposition to hallucinate may be related to aberrant functioning of the DMN and the auditory cortices. *Hum Brain Mapp* 35:1436–1445, 2014. © 2013 Wiley Periodicals, Inc.

Key words: auditory hallucination; graph theory; schizophrenia; psychosis; resting state; fMRI; betweenness centrality; degree; default mode network; hub

INTRODUCTION

Auditory verbal hallucinations (AVH) are one of the core symptoms of schizophrenia with approximately 70% of all schizophrenia patients presenting with this symptom [Nayani and David, 1996; Slade and Bentall, 2002]. AVH

can be highly distressing, often disrupt social functioning, and increase risk for suicide and acts of violence [Falloon and Talbot, 1981; Cheung et al., 1997].

It has been hypothesized that hallucinations arise from dysfunctional connectivity in the brain [Friston and Frith, 1995; Northoff and Qin, 2011]. As task execution may

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induce alterations in brain connectivity and network properties, aberrations in functional connectivity are best observed in the absence of external tasks [Jin et al., 2011; Nicol et al., 2012]. For this reason, several studies investigated functional connectivity related to AVH during the resting state. Hoffman et al. [2011] reported increased functional connectivity along a loop comprising language areas and the putamen in hallucinating patients versus nonhallucinating patients. Gavrilescu et al. [2010] observed reduced connectivity of the auditory system, while Rotarska-Jagiela et al. [2010] found associations between hallucinations and connectivity in the hippocampus and a frontotemporal network. In addition, Vercammen et al. [2010] observed a relationship between hallucination severity and connectivity between the left temporoparietal junction (TPJ) and the anterior cingulate and amygdala. As these studies were conducted in schizophrenia patients, this diversity in findings may be partly explained by other clinical symptoms related to the disease such as delusions, cognitive and negative symptoms. Moreover, the use of antipsychotic medication may have affected the results.

Although the previously published functional connectivity studies provide valuable information regarding AVH and schizophrenia, they do not inform us about the functioning of areas in a network context. More specifically, identification of areas with high functional connectivity (so-called hub regions) that are associated with the predisposition to hallucinate can be of particular importance, as these regions may provide potential targets for neuromodulation in the treatment of AVH [McCarthy-Jones, 2012]. As the left hippocampus, inferior frontal gyrus, and superior temporal gyrus (STG) have consistently been implicated during the experience of AVH, we hypothesize that increased functioning of these areas as a hub region is related to the predisposition to hallucinate [Jardri et al., 2011].

These hub regions can be identified using graph theoretical measures, such as connectivity strength and betweenness centrality [Rubinov and Sporns, 2010]. Connectivity strength represents the degree of coupling of a node with the rest of the network, while betweenness centrality is based on the number of shortest paths that pass through a given node in the network. With the former measure, regions can be identified that show a pattern of hypo- or hyperconnectivity with the rest of the brain, while the latter measure identifies regions that are important in bridging different subnetworks [Bullmore and Sporns, 2009; Rubinov and Sporns, 2010].

To circumvent potential confounds associated with schizophrenia, we studied these two hub parameters in individuals with AVH as a relatively isolated symptom [Tien, 1991]. In contrast to schizophrenia patients, in this population AVH occur in the absence of delusions and negative or cognitive symptoms [Sommer et al., 2010a]. Moreover, these nonpsychotic individuals with AVH are not using antipsychotic medication.

In this study, we applied graph analysis to compare resting-state connectivity between 29 nonpsychotic indi-

viduals with AVH who did not hallucinate during image acquisition with 29 matched controls, aiming to investigate whether increased functioning of the left hippocampus, inferior frontal gyrus and STG as hub regions may underlie the predisposition to experience AVH.

MATERIALS AND METHODS

Subjects

Forty-eight nonpsychotic individuals with AVH and 54 controls were recruited via a website: www.verkenuwgeest.nl ("explore your mind"). An extended description of the recruitment and selection procedure is provided in prior studies of our group [Dieren et al., 2010a; Sommer et al., 2010a; van Lutterveld et al., 2010; Daalman et al., 2011]. Briefly, inclusion criteria were: (1) absence of psychiatric disorders other than anxiety or depressive disorder in full remission as assessed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History interview [Andreasen et al., 1992] to exclude axis I pathology and the SCID-II interview to exclude axis II pathology [First et al., 1995], (2) no chronic somatic disorder, (3) absence of alcohol or drug abuse for at least 3 months prior to the assessments. To confirm the absence of drug abuse, urine samples were collected and tested for opiates, amphetamines/XTC, cocaine and cannabis. Additional inclusion criteria for the nonpsychotic individuals with AVH consisted of (4) voices were distinct from thoughts and had a "hearing" quality, (5) voices were experienced at least once a month, (6) drug or alcohol abuse did not precede the first experience of AVH, (7) Because the presence of AVH is related to changes in cortical activity [Jardri et al., 2011], a further inclusion criterion was the absence of AVH during resting-state scan acquisition.

These nonpsychotic individuals with AVH as a relatively isolated symptom can be considered to hold an intermediate position on a continuum of AVH, with healthy individuals at one end and individuals with a psychotic disorder at the other [Strauss, 1969; van Os et al., 2000]. Being an intermediate on this scale, these individuals are affected to some extent as expressed by the presence of subclinical levels of suspicion, a tendency for magical ideation, a somewhat lower Global Assessment of Functioning scale score, and an elevated level of formal thought disorder [Sommer et al., 2010a, b]. However, AVH occur in the absence of delusions and negative or cognitive symptoms in this population [Sommer et al., 2010a]. Moreover, these nonpsychotic individuals with AVH are not using antipsychotic medication. A recent study showed that cortical activation during AVH is similar in these nonpsychotic individuals as in schizophrenia patients [Dieren et al., 2012], suggesting the same neurological substrate may underlie both types of AVH.

The study was approved by the local ethics committee of the University Medical Center of Utrecht. All

participants gave their written informed consent before participation in the study.

Image Acquisition

Imaging was performed on a Philips Achieva 3 Tesla Clinical MRI scanner. Six hundred blood-oxygenation-level-dependent resting-state fMRI images were acquired per subject with the following parameters settings: 40 (coronal) slices, repetition time (TR) = 21.75 ms, echo time (TE) = 32.4 ms, flip angle 10°, field-of-view (FOV) $224 \times 256 \times 160$, matrix $64 \times 64 \times 40$, voxel size 4-mm isotropic. This scan sequence achieves full brain coverage within 609 ms by combining a 3D-PRESTO pulse sequence with parallel imaging (SENSE) in two directions using a commercial eight-channel SENSE headcoil [Neggers et al., 2008]. Since these PRESTO SENSE images have little anatomical contrast, 40 scans with a flip angle of 27° (fa27) were acquired to improve realignment and coregistration during preprocessing. After the functional scans, a high-resolution anatomical scan was acquired (TR/TE: 9.86/4.6 ms, $0.875 \times 0.875 \times 1 \text{ mm}^3$ voxels, flip angle 8°, FOV $224 \times 160 \times 168$, 160 slices) to improve localization of the functional data. Resting-state scans were acquired for 6 min, and subjects were instructed to lie still with their eyes closed, not to think of anything in particular and not fall asleep. The absence of AVH during the scan was established by interviewing the participants directly after completion of the resting-state scan. Head motion was assessed by calculating the mean motion as suggested by Van Dijk et al. [2012]. Mean motion represented the mean absolute displacement of each brain volume as compared to the preceding volume and was calculated from the translation parameters in the x, y and z directions.

Data Analysis

Preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, United Kingdom). First, the fMRI time-series were realigned to the first functional scan to correct for head motion. The realigned time-series were then coregistered to the first fa27 scan. The anatomical scan was hereafter coregistered to the first fa27 scan to provide alignment between the functional time-series and the anatomical image. The T_1 image and the fMRI time-series were spatially normalized to MNI (Montreal Neurological Institute) space. It should be noted that the process of spatial normalization involved the interpolation of fMRI voxels, although common practice in most resting-state fMRI studies, can potentially introduce local artificial correlations between adjacent voxels [van den Heuvel et al., 2008; Hayasaka and Laurienti, 2010; Fransson et al., 2011; Tomasi and Volkow, 2011]. To avoid introducing additional local spatial correlations, the images were not

smoothed. To further remove artificial interdependencies, the mean time courses from the cerebral spinal fluid, deep white matter and six rigid-body parameters were regressed out from the time-series. After this, resting-state time series were band-pass filtered (0.01–0.1 Hz). Furthermore, a binary mask was used to isolate cerebral gray-matter voxels. This mask was created by first reslicing SPM8's gray-matter probability template to the resolution of the functional images ($4 \times 4 \times 4 \text{ mm}^3$). After this, the cerebellar regions were removed using the cerebellar regions in the AAL library [Tzourio-Mazoyer et al., 2002]. Finally, the template was binarized by applying a threshold of 0.55, yielding a total volume in the mask of 10,108 voxels [Zalesky et al., 2011]. To avoid the arbitrary nature of the dichotomizing procedure required to compute unweighted networks, our analysis was based on weighted networks. Recently, Hayasaka and Laurienti [2010] have shown the preferability of using a high spatial resolution in graph analysis. To this end, we focused on voxel-wise instead of region-based networks. Within the gray-matter mask, a weighted undirected network was constructed for all subjects, which was described by the graph $G = (N, W)$, where N is the set of all 10,108 voxels in the mask and $W = \{w_{ij}\}$ is the $N \times N$ symmetric weight matrix, where $w_{ii} = 0$ and w_{ij} the Fisher's z' -transformation normalized Pearson's correlation coefficient r between voxels i and j , with $z' = \text{arctanh}(r)$. Edges with negative z' -values were set to 0. Hereafter, global and local network characteristics were calculated using the C++ Boost Graph Library [Siek et al., 2002]. Figure 1 provides a schematic outline of the analysis pipeline.

Graph analysis

Hub regions were identified using the graph theoretical measures connectivity strength and betweenness centrality. The connectivity strength represents the degree of coupling of a node with the rest of the network. With this measure, regions can be identified that show a pattern of hypo- or hyperconnectivity with the rest of the brain. The betweenness centrality relies on the identification of the number of shortest paths that pass through a node. The more passages, the higher the betweenness centrality. This measure identifies regions that are important in bridging different subnetworks [Bullmore and Sporns, 2009; Rubinov and Sporns, 2010]. In these local graph analyses, the measures were analyzed in voxel-space to be able to locate differences among groups in the brain. In addition, an exploratory global graph analysis was conducted for connectivity strength and betweenness centrality to test for global differences in these measures across groups [Rubinov and Sporns, 2010]. Calculation of these global metrics was performed by averaging the measures across all 10,108 voxels in the gray-matter mask per individual. An extensive description including mathematical forms of these network characteristics is given in Supporting Information S1.

Figure 1.

Analysis pipeline. In the first step, the predefined gray-matter mask was applied to the functional data (A). The second step consisted of calculating functional connectedness between all possible pairs of gray-matter voxels i and j in each subject (B). These correlations were represented as a correlation matrix with each cell holding the level of connectivity between voxel i and voxel j (C), after which a weighted functional brain network was constructed comprising of the positive correlations in the

correlation matrix. This is shown in (D), where the thickness of the green lines indicates the strength of the connectivity between two voxels. After this, hub regions were identified by testing for local differences in connectivity strength and betweenness centrality among groups. Global (average) connectivity strength and betweenness centrality were also calculated for each individual network (E). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

STATISTICAL ANALYSES

Local Graph Analysis

Statistical testing for significant local differences across groups was performed by using a nonparametric permutation test (SnPM) using 10,000 permutations [Singh et al., 2003]. To optimize statistical sensitivity for both spatially extended clusters and high intensity signals, we used a combined threshold based on voxel intensity and cluster volume, using a pseudo- t value of 3 (equally weighted meta-combined or combo test; Hayasaka and Nichols [2004]). The family wise error (FWE) correction threshold to account for multiple comparisons was set at $P = 0.05$. Anatomical labelling of significant activation clusters was performed using the Talairach Client database (<http://www.talairach.org/client.html>) and MRICron (<http://www.sph.sc.edu/comd/rorden/mricron/>) was used for visualization purposes.

After this, the impact of short- and long-range connectivity was explored. Using a Euclidean distance matrix, we calculated the connectivity strength for each participant for the 50% shortest distances and for the 50% longest distances. Each dataset was then analyzed statistically to reveal differences across groups, using the same SnPM analysis as described here above.

Global Graph Analysis

Independent-samples t -tests were employed to test for global differences in overall connectivity strength and betweenness centrality across groups for normally distrib-

uted data. For non-normally distributed data, Mann-Whitney's U test was used.

RESULTS

Data Selection

After scanning, 19 nonpsychotic individuals with AVH were found unsuitable for inclusion, resulting in 29 nonpsychotic subjects with AVH and 54 healthy control subjects included for data analysis. Sixteen of the 19 excluded nonpsychotic subjects were excluded as they had experienced AVH during the resting state, while one subject was excluded because of not closing the eyes during resting-state acquisition, and another subject was excluded because of falling asleep during the scan. An additional subject was excluded because of major artefacts being present in the anatomical scan. Twenty-nine of the 54 control subjects were then selected to enable a good match (on age, sex, handedness and years of education) with the nonpsychotic individuals with AVH. Data on these 29 nonpsychotic individuals with AVH and 29 healthy control subjects were then used for further analyses.

Demographic Variables

The groups did not differ significantly with respect to age, sex, and handedness and years of education. Table I provides a demographic description of the participants. A significant difference was found regarding the number of participants diagnosed with depression in remission (control group: 4, AVH group: 13, $\chi^2 = 6.74$; $P = 0.009$). None of the participants used psychoactive medication.

TABLE I. Subject characteristics

	Controls (<i>N</i> = 29)	Nonpsychotic subjects with AVH (<i>N</i> = 29)	Statistics
	Mean (SD)	Mean (SD)	
Age	41.3 (15.9)	43.1 (13.8)	$t(56) = -0.45$; $P = 0.65$
Sex (male/female)	9/20	9/20	
Handedness (right/ nonright)	22/7	22/7	
Years of education	13.9 (2.3)	13.5 (2.2)	$U(56) = 372.5$; $P = 0.44$
Anxiety disorder	0	0	
Depression in remission	4	13	$\chi^2 = 6.74$; $P = 0.009$

AVH: Auditory verbal hallucinations; *N*: Number; SD: Standard deviation.

Head Motion

Groups did not differ significantly in mean head motion during image acquisition (mean controls: 0.09 mm, s.d. 0.02; mean AVH 0.10 mm, s.d. 0.04 [$t(56) = -1.45$; $P = 0.15$]).

Node Specific Analysis (Local Analysis)

Connectivity strength

A significant increase in connectivity strength in the AVH group compared to the control group was found in a cluster in the right posterior cingulate extending into the cingulate gyrus and the precuneus as well as in a cluster in the left STG extending into the insula. In addition, an increase in connectivity strength was observed in the right middle temporal gyrus (MTG; Fig 2A), indicating that these areas are more important hub regions in the AVH group as compared to the controls. Detailed information about the coordinates of local maxima is shown in Table II. The analysis exploring short- and long-range connectivity showed that increases in short-distance connectivity were present in the AVH group compared to the control group in the three clusters described here above, while increases in long distance connectivity were present in two of these clusters, i.e. in the left superior temporal and the right middle temporal gyri.

Betweenness centrality

A significant increase in betweenness centrality was found in a cluster in the left STG, indicating that this region is a more important hub in the AVH group compared to the controls. In addition, significant decreases were observed in the right inferior temporal gyrus, left

paracentral lobule and right amygdala (Fig. 2B), indicating that these areas are less important hubs in the AVH group compared to the controls. Detailed information about the coordinates of local maxima is shown in Table II.

Global analysis

A significant difference between the groups was found for average connectivity strength (mean controls: 1,734, s.d. 638; mean AVH 1,938, s.d. 550 [$U = 287$; $P = 0.037$]), indicating a pattern of hyperconnectivity in the AVH group compared to the controls. A plot of the connectivity distributions is provided in Supporting Information S2. No differences were observed in average betweenness centrality across groups (mean controls: 0.000085, s.d. 0.000013; mean AVH: 0.000081, s.d. 0.000011 [$t(56) = 1.474$; $P = 0.146$]), indicating that groups were on whole-brain level not different in this measure for hubs.

DISCUSSION

This is the first study to apply graph theory to investigate resting-state brain activity in relation to AVH. We investigated a group of nonpsychotic individuals who experienced AVH in relative isolation to reveal brain characteristics of hallucination-proneness without the confounding variables associated with studying schizophrenia patients, such as delusions, cognitive dysfunction, negative symptoms, medication use and long-term hospitalization. The AVH group showed an increased pattern of overall connectivity as compared to the control group, and our hypothesis that the left hippocampus, inferior frontal gyrus and STG would exhibit increased functioning as a hub region in the AVH group compared to controls could partially be confirmed. The left STG, right MTG and the posterior cingulate/precuneus complex (PCC) were found to be more important hub regions in the AVH group. A second measure to investigate hub regions confirmed that the left STG was more important in the hallucinating group, while the right inferior temporal gyrus, the left paracentral lobule and the right amygdala were less important hub regions.

The increase in overall functional connectivity observed in the AVH group can partially be explained by the observed increase in hub functioning of temporal structures and the PPC, indicating that these regions are more strongly connected with more brain regions [Rubinov and Sporns, 2010]. As such, the present results indicate that temporal areas and the PPC take a more prominent place in the network in individuals with AVH than in nonhallucinating controls. Interestingly, these more important hubs are considered essential parts of the default mode network (DMN), which is a network implicated in wakeful resting [Raichle et al., 2001].

Figure 2.

Local changes in activity in the AVH group compared to the control group in **(A)** connectivity strength and **(B)** betweenness centrality. Data are presented in neurological convention (right is right). $P < 0.05$, FWE corrected. To facilitate interpretation of the results in the top left corner, the AAL template of the precuneus is shown in blue. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Significant local differences and locations of local maxima for connectivity strength, clustering coefficient, path length, and betweenness centrality

Measure	AVH subjects vs. controls	Lobe	Area	Montreal Neurological Institute Coordinates (x, y, z)	T	k
Connectivity strength	Increase	Right limbic	Posterior cingulate	22 -56 10	4.80	25
			Cingulate gyrus	18 -56 22	4.27	
			Precuneus	6 -64 26	4.15	
	Increase	Left temporal	Superior temporal gyrus	-46 -28 6	4.61	20
			Superior temporal gyrus	-54 -32 14	4.02	
			Insula	-46 -36 18	3.52	
	Increase	Right temporal	Middle temporal gyrus	58 0 -14	4.20	11
			Middle temporal gyrus	54 4 -22	3.38	
Betweenness centrality	Increase	Left temporal	Superior temporal gyrus	-50 -32 10	3.86	7
	Decrease	Right temporal	Inferior temporal gyrus	38 -60 -10	4.28	4
	Decrease	Left parietal	Paracentral lobule	-6 -40 70	4.08	4
	Decrease	Right limbic	Amygdala	30 -4 -22	3.78	3

AVH = Auditory verbal hallucinations, k = cluster extent.

PPC

In the DMN, the PPC takes a central position. The DMN consists of two subsystems, with one system involved in memory and associations and another system involved in self-referential processing [Buckner et al., 2008]. Both systems converge in the PPC. As such, increased connectivity with this area may lead to a greater focus on memory processes and self-referential thoughts. Interestingly, a prominent feature of AVH is their repetitive nature, which implies a memory component [Stephane et al., 2003]. This is in line with cognitive models that emphasize the role of memory processes in the genesis of AVH [Badcock et al., 2005; Waters et al., 2006; Jones and Fernyhough, 2009].

Moreover, hallucinations are self-generated and experienced as externally generated. This implies aberrant self-referential processing [Frith and Done, 1989]. The memory and self-referential processes mediated by the PPC in the DMN might therefore be linked to the genesis of AVH. AVH are sometimes compared to screen-savers; when a person is not in the midst of some cognitive task, and is just mind-wandering, AVH may come in. Schizophrenia patients are usually well aware of this feature and apply distraction and focusing as coping strategies to decrease AVH frequency [Haddock et al., 1998; Hayashi et al., 2007]. This association between AVH and mind-wandering also implies a link with the DMN, as these structures increase their activity during periods without explicit cognitive tasks. As such, the PPC may provide a target for neuromodulation to alter AVH proneness. For example, individuals may be trained to decrease activity of this region with a neurofeedback paradigm.

Temporal Structures

The observation that the left STG was a more important hub region in the hallucinating group was further highlighted by a similar increase in the second measure for hubs. Activity in the left STG is usually interpreted in light of auditory processing [Dierks et al., 1999]. Recently, elevated interaction between the auditory cortices and the DMN has been hypothesized to underlie the genesis of AVH [Northoff and Qin, 2011]. However, the increased functioning as a hub region of the left STG could alternatively be seen in light of its involvement in formal thought disorder. Nonpsychotic individuals with AVH show similar increased levels of positive formal thought disorder (i.e. disorganized speech) as schizophrenia patients compared to controls [Sommer et al., 2010b]. This finding is in line with the proposition that AVH and formal thought disorder share a neurobiological substrate [Hoffman, 1986; Strik et al., 2008; Sommer et al., 2010b]. Support for this notion comes from studies that consistently implicated the left STG in AVH [Barta et al., 1990; Dierks et al., 1999; van Lutterveld et al., 2011] as well as in formal thought disorder [Shenton et al., 1992; Kircher et al., 2001; Horn et al., 2009], suggesting that this area may be particularly

involved in a possible common pathophysiological mechanism.

Other Findings

Given the importance of medial temporal lobe structures in the genesis of AVH [Dieren et al., 2010b; Jardri et al., 2011], it is interesting to see that the right amygdala is a less important hub in the hallucinating group. Functional connectivity of the amygdala has previously been linked to the experience of AVH [Vercammen et al., 2010]. These authors found that reduced functional coupling between the amygdala and the left TPJ was associated with increased severity of AVH.

It should be noted that four control subjects and thirteen nonpsychotic individuals with AVH were diagnosed with depression in remission. Nonpsychotic individuals with AVH can be considered to take a halfway position on a continuum of AVH [Strauss, 1969; van Os et al., 2000]. As such, these individuals are affected to some extent as expressed by the presence of subclinical levels of suspicion, formal thought disorder, and a tendency for magical ideation [Sommer et al., 2010a, b]. As depression is a major comorbid symptom in schizophrenia, the higher prevalence of depression in remission in the AVH group may be expected in the framework of these individuals being on a continuum between healthy controls and clinical psychosis [Siris, 2000].

Analysis of short- and long-range connectivity revealed that the hallucination-prone group showed increased short-range connectivity from the left superior temporal and the right MTG and the PCC, while the hallucination-prone group also showed increased long-range connectivity from the left superior temporal and the right middle temporal gyri. These results suggest that, within the broad definitions of short and long connectivity that were used in the present study, the higher connectivity observed in the main analysis in the hallucination-prone group is determined by both increased short-range and long-range connectivity in the temporal cortices, and mainly by increased short-range connectivity in the PCC.

Comparison to Previous Functional Connectivity Studies

To date, several studies used graph analysis to investigate schizophrenia, although these studies did not focus on AVH. In these studies, lower clustering coefficients, alterations in path length and small-worldness, increased connection distance of various regions, and overall decreases in functional connectivity have all been reported [Liang et al., 2006; Micheloyannis et al., 2006; Bassett et al., 2008; Liu et al., 2008; Rubinov et al., 2009; Lynall et al., 2010; van den Heuvel et al., 2010; Zalesky et al., 2011; Ma et al., 2012].

Several studies with a seed-region design specifically addressed AVH by investigating resting-state functional

connectivity in schizophrenia. Hoffman et al. [2011] reported increased connectivity along a loop comprising language areas and the putamen in hallucinating patients versus nonhallucinating patients. A very recent study showed that chronically hallucinating patients had lower connectivity between the left STG and left hippocampus, and this showed a significant negative correlation with the hallucination item of the Positive and Negative Syndrome Scale. Moreover, this reduction in connectivity was significantly stronger in patients who hallucinated during resting-state acquisition [Sommer et al., 2012]. Another study observed reduced connectivity of the auditory system [Gavrilescu et al., 2010], while Rotarska-Jagiela et al. [2010] found associations between hallucinations and connectivity in the hippocampus and a frontotemporal network using an independent component analysis approach. Using a similar approach, Liemburg et al. [2012] observed decreased connectivity between auditory and language networks in schizophrenia patients. As the patients included in these studies also experienced other symptoms of schizophrenia and received antipsychotic treatment, the results may not be specific to AVH. Finally, a recent study investigated spatiotemporal activity patterns related to hallucinations in drug-free adolescents with a brief psychotic disorder [Jardri et al., 2012]. They observed a decrease in coupling between the DMN and the auditory association cortex during AVH. Moreover, a positive relationship between low-frequency oscillations in the DMN and hallucination severity was observed, which extended into symptom-free periods. While the present study observed increased connectivity between an area involved in the DMN and the auditory association cortex (PCC and the left STG) during symptom-free scans, the Jardri et al. study did not observe a relationship between the DMN and auditory association cortex during symptom-free periods.

Limitations and Methodological Considerations

The present results should be interpreted with some caution. Recently, it has been shown that calculation of the shortest path length is dependent on average connectedness of the underlying network [van Wijk et al., 2011]. As we observed an increase in overall connectedness in the AVH group, this could potentially confound the calculation of betweenness centrality, as this measure is dependent on the shortest path length. However, van Wijk et al. also found that for average connectivity values higher than 12 there was convergence to almost constant shortest path length values. In the present study the average connectedness was more than two orders of magnitude higher for both groups, suggesting that the observed differences in connectivity strength did not confound calculation of the betweenness centrality. It is furthermore important to note that the present results should be interpreted in context of the applied spatial scale, as the choice for voxel-

wise or region-based approaches affects network measures [Hayasaka and Laurienti, 2010]. In the present study, the data were spatially normalized to be able to investigate local differences in network metrics across groups. It should be noted that normalization involves the interpolation of fMRI voxels, possibly affecting local correlations. To avoid affecting local correlations as much as possible, the spatially normalized data were not smoothed. Hayasaka and Laurienti [2010] investigated the effect of local correlations by deleting connections between adjacent voxels in a spatially normalized dataset. They observed an effect on clustering coefficient and path length, however no significant effect on the distribution of correlation values was observed, suggesting that connectivity strength is not particularly affected by spatial normalization. Furthermore, the exploratory assessment of differences in short-range and long-range connectivity may be considered to be rather coarse. For example, the Euclidean distance may be a poor approximation for the true axonal distance between regions. For instance, two frontal areas close to the midline that are located in different hemispheres may be separated by a Euclidean distance of 1 cm, while the true anatomical (axonal) distance between the regions is much longer as it includes passing the corpus callosum. Moreover, there are at present no established methods of defining short-range and long-range connectivity, and the cut-offs for short- and long-range connectivity that were used in this study may be considered arbitrary.

Another limitation is that activation of temporal regions has consistently been reported to be associated with AVH [Jardri et al., 2011; van Lutterveld et al., 2011]. Increased connectivity of the temporal cortices may be related to sustained activation of these areas after the occurrence of an AVH. However, the hallucinating group in this study experienced AVH with an average frequency of once every week, rendering this explanation quite unlikely. Another important limitation of this study is that it remains uncertain whether AVH in schizophrenia patients and in non-psychotic individuals can be considered exactly the same phenomenon. A recent study compared the phenomenology of nonpsychotic individuals with AVH and schizophrenia patients. Both groups were similar in several characteristics of AVH. There were no differences in the perceived location of voices (inside/outside the head), the number of voices, loudness, and personification (attribution to a real and familiar person). However, both groups were different in emotional valence of the content, frequency of AVH and control over their AVH. Moreover, age of onset of AVH was at a younger age in the healthy individuals [Daalman et al., 2011], which may suggest a different aetiological origin. However, in contrast with this latter finding is a recent neuroimaging study that investigated brain activity during AVH in both groups. In this study a similar pattern of activation was observed, which is suggestive of similar underlying pathophysiology [Dierker et al., 2012]. There are as such similarities and differences in AVH characteristics between groups. AVH in

the nonpsychotic individuals provide the advantage of studying the symptom in relative isolation and without the confounding factor of antipsychotic medication use, but whether the AVH in both groups should be considered precisely the same phenomenon remains unclear.

In sum, nonpsychotic individuals with AVH showed increased functioning as a hub region in the temporal cortices and the PCC as compared to nonhallucinating controls. These results suggest that the predisposition to hallucinate is related to aberrant functioning of the DMN and the auditory cortices.

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