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Archival Report

Functional Connectivity Between Auditory and Medial Temporal Lobe Networks in Antipsychotic-Naïve Patients With First-Episode Schizophrenia Predicts the Effects of Dopamine Antagonism on Auditory Verbal Hallucinations

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ABSTRACT

BACKGROUND: Understanding how antipsychotic medication ameliorates auditory verbal hallucinations (AVHs) through modulation of brain circuitry is pivotal for understanding the pathophysiology of psychosis and for predicting treatment response.

METHODS: This case-control study included examinations at baseline and at follow-up after 6 weeks. Initially, antipsychotic-naïve patients with first-episode schizophrenia who were experiencing AVHs were recruited together with healthy control participants. Antipsychotic treatment with the relatively selective D_2 receptor antagonist amisulpride was administered as monotherapy. Functional connectivity measured by resting-state functional magnetic resonance imaging between networks of interest was used to study the effects of D_2 blockade on brain circuitry and predict clinical treatment response. Hallucinations were rated with the Positive and Negative Syndrome Scale.

RESULTS: Thirty-two patients experiencing AVHs and 34 healthy control participants were scanned at baseline. Twenty-two patients and 34 healthy control participants were rescanned at follow-up. Connectivity between the auditory network and the medial temporal lobe network was increased in patients at baseline (p = .002) and normalized within 6 weeks of D_2 blockade (p = .018). At baseline, the connectivity between these networks was positively correlated with ratings of hallucinations (t = 2.67, p = .013). Moreover, baseline connectivity between the auditory network and the medial temporal lobe network predicted reduction in hallucinations (t = 2.34, p = .032).

CONCLUSIONS: Functional connectivity between the auditory network and the medial temporal lobe predicted response to initial antipsychotic treatment. These findings demonstrate that connectivity between networks involved in auditory processing, internal monitoring, and memory is associated with the clinical effect of dopamine antagonism.

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Auditory verbal hallucinations (AVHs) constitute core symptoms of schizophrenia reported by 40% to 80% of the patients with a diagnosis within the schizophrenia spectrum (1). Although the existing treatment of schizophrenia can still be improved in several ways, patients generally respond to antipsychotic treatment with a reduction of AVHs (2,3). The main target of all current antipsychotic drugs is the D_2-like dopamine receptors expressed predominantly in the striatum (4,5), mainly because there is a strong correlation between the affinity to the D_2 receptor and the effect on positive symptoms such as AVHs (6). Consistent with this, neurochemical studies in antipsychotic-naïve first-episode (ANFE) patients with schizophrenia have demonstrated increased dopamine turnover in the striatum (7). In fact, the effect of D_2 blockade on the relief of positive symptoms is one of the main reasons for the development of the dopamine hypothesis for schizophrenia (7,8). Nevertheless, it is still unclear how blockade of D_2 receptors ameliorates AVHs at the level of large-scale neuronal circuitry.

The existing models for AVHs propose a number of different mechanisms explaining these symptoms as unstable memories (9,10), failure in source monitoring (11–13), interhemispheric miscommunication (14), abnormal top-down and bottom-up predictions (15–20), and mixtures of these mechanisms forming so-called hybrid models (21–25) [models for AVHs reviewed in (26)]. While acknowledging the complexity of each of the AVH models, many models still converge on the idea of abnormal communication between the auditory cortex and the medial temporal lobe (MTL). The unstable

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memory models directly suggest the hippocampal formation as a key structure because AVHs are to be considered as parasitic memories (9) or intrusive and unintended memories (10). The source monitoring (11–13) and hybrid models (21–25) propose the involvement of the MTL in AVHs because the MTL is recognized as one of the key areas of the default mode network (DMN), which is associated with internal monitoring (27).

As reflected in the AVH models, the MTL, including the hippocampal formation, links a wide range of evidence suggesting the importance of this region in the development and treatment of AVHs in patients with schizophrenia. First, in clinical studies, the hippocampal formation has been robustly linked to the pathophysiology of schizophrenia (28) and specifically to the development of auditory hallucinations (29). Second, a well-established preclinical model of schizophrenia suggests a causal link between an early lesion in the MTL and elevated dopaminergic activity in the striatum that is proposed to subsequently induce psychotic symptoms (30). Taken together, the communication between the auditory cortex, MTL, and striatal complex is hypothesized to be a central aspect of the development and treatment of AVHs that is predicted by the network models for AVHs and cuts across clinical and preclinical data.

A direct way of testing the effects of D_2 blockade on large-scale circuitry is to use functional magnetic resonance imaging (fMRI) under resting conditions and estimate changes in functional connectivity. A few previous studies investigating antipsychotic monotherapy in ANFE patients have used compounds with broad receptor profiles such as olanzapine (31) and risperidone (32–35). Although these studies provide evidence of the effect of antipsychotic medication on functional connectivity and the association with clinical symptoms, none of these studies had a specific focus on AVHs.

In a previous study, we investigated pretreatment cross-sectional associations among psychopathology, cognitive measures, and large-scale network structure in ANFE patients in a case-control study (36). In the current study, we applied a longitudinal case-control design on the same clinical cohort with follow-up after 6 weeks of monotherapy with amisulpride to study the effects of D_2 receptor blockade on functional connectivity between networks specifically involved in auditory processing and subsequently test for a possible correlation between network modulations and effects on AVHs. Amisulpride was chosen as a tool compound because it is a selective D_2 receptor antagonist (37). Networks of interest were well-established, atlas-based resting-state networks chosen according to the existing models for AVHs and included the auditory network and the MTL network containing the hippocampal formation and striatum.

We hypothesized that 1) patients with AVHs would be characterized by abnormal connectivity between the auditory network, MTL network, and striatum before initiation of antipsychotic medication; 2) functional connectivity would normalize across time during initiation of antipsychotic treatment; 3) time change in connectivity would be correlated with reduction in AVHs; and 4) connectivity at baseline would predict response to initial antipsychotic treatment with D_2 blockade. In a supplementary analysis for specificity, we tested for differences in functional connectivity between patients with and without AVHs before initiation of antipsychotic medication in a broader model incorporating more functional networks of interest.

METHODS AND MATERIALS

This study was a part of the PECANS (Pan European Collaboration on Antipsychotic Naive Schizophrenia) cohort (ClinicalTrials.gov identifier: NCT01154829). It was approved by the Danish National Committee on Biomedical Research Ethics (H-D-2008-088) and conducted in accordance with the Declaration of Helsinki II. All participants gave informed oral and written consent prior to participation.

Participants

Patients with a first episode of schizophrenia or schizoaffective disorder (ICD-10 criteria) were recruited from psychiatric departments in the Copenhagen area. Only participants who had never received any antipsychotic medication were included. Of a total number of 69 included patients, 32 patients who were experiencing AVHs were scanned with resting-state fMRI at baseline. Twenty-two patients with AVHs were rescanned after 6 weeks of amisulpride monotherapy (see the Supplement for a flowchart of AVH patient recruitment). Twenty-five patients without AVHs from the same cohort were included to perform a supplementary analysis for sensitivity at baseline (9 patients without AVHs were successfully rescanned at follow-up but were omitted from the supplementary analysis due to low statistical power). Healthy control participants (n = 34) matched on age, sex, and parental socioeconomic status were recruited via a specialized research website and scanned at baseline and follow-up. Exclusion criteria for control group participants were any history of psychiatric illness or schizophrenia spectrum disorder (ICD-10 criteria) in first-degree relatives. For all participants, additional exclusion criteria were 1) a severe somatic illness including a history of head injury, 2) antidepressant medication within the past month or during the study, and 3) a current diagnosis of drug dependence (ICD-10). Occasional drug use was allowed, and recent drug intake was tested with a urine test (Rapid Response; Jepsen HealthCare). Benzodiazepines were also allowed until 12 hours before MR scans (demographic data are displayed in Table 1; see the Supplement for data on the 25 patients without AVHs). Other data from the PECANS study have been published in several papers (38).

Clinical Assessments

To confirm a diagnosis of schizophrenia or schizoaffective disorder and exclude psychopathology in control participants, all participants were assessed with a diagnostic interview (Schedule of Clinical Assessment in Neuropsychiatry) (39). Psychopathology was rated with the Positive and Negative Syndrome Scale (PANSS) (40), and patients scoring $\geq$3 at baseline on the PANSS item p3 "Hallucinations" were included in the current analyses as patients with AVHs (data from the clinical assessments are presented in Table 1). Patients without AVHs who were incorporated in the supplementary analysis were defined by a score of $<$2 on the PANSS item p3 Hallucinations (time frame under examination = past week).

Table 1. Demographic Data, Psychopathology Scores, and Drug Dose

	Patients at Baseline, *n* = 32	Patients at Follow-up, *n* = 22	Healthy Control Participants, *n* = 34
Age, Years, Mean (SD)	23 (9.4)	–	25 (5.4)
Sex, Female/Male, *n*	14/18	–	15/19
Duration of Untreated Illness, Weeks, Mean (SD)	60 (75.3)	–	–
Parental Socioeconomic Status, High/Medium/Low	5/14/9 (4 UN)	–	9/16/8 (1 UN)
Handedness (EHI Score), Mean (SD)	79 (39.7)	–	82 (12.4) (3 UN)
Substance Use[a], *n*			
Nicotine	9/7/12/1/3	–	8/15/7/2/1 (1 UN)
Alcohol	4/5/20/2/1	–	1/0/32/0/0 (1 UN)
Cannabis	7/13/2/3/0	–	14/15/4/0/0 (1 UN)
Stimulants	19/12/1/0/0	–	25/7/0/0/0 (2 UN)
Benzodiazepines	23/8/0/0/0 (1 UN)	–	32/0/0/0/0 (2 UN)
GAF-F, Mean (SD)	42 (11.6) (3 UN)	57 (13.2)	–
PANSS Total, Mean (SD)	81 (18.4)	65 (15.9)	–
PANSS Positive, Mean (SD)	21 (4.1)	14 (4.3)	–
PANSS Negative, Mean (SD)	19 (7.5)	20 (6.2)	–
PANSS General, Mean (SD)	41 (9.8)	32 (8.5)	–
PANSS p3 (Hallucinations), Mean (SD)	4 (0.9)	2 (1.1)	–
Amisulpride Dose, mg, Mean (SD)/Range	–	297[b] (188)/50–800	–

EHI, Edinburgh Handedness Inventory; GAF-F, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; UN, unknown.
[a]Substance use categorized as: never tried/tried a few times/use regularly/abuse/dependence.
[b]Excludes 1 patient who discontinued medical treatment with amisulpride 2 weeks before follow-up examinations.

PANSS interviews were video recorded for the purpose of scoring and to ensure that patients reported AVHs.

MRI Data Acquisition

Magnetic resonance data were acquired at baseline before any initiation of antipsychotic treatment and at 6-week follow-up in a Philips Achieva 3.0T whole-body MRI scanner (Philips Medical Systems) with an 8-channel head coil. fMRI data were obtained using a T2*-weighted echo-planar imaging sequence (repetition time = 2 seconds, echo time = 25 ms, flip angle = 75°), with a matrix size of 128 × 128 × 38, and field of view of 230 × 230 × 128 mm^3, resulting in a voxel size of 1.8 × 1.8 × 3.4 mm^3. A total of 300 volumes were acquired, for a total scan time of 10 minutes. Participants were instructed to stay awake with their eyes closed and not to think of anything in particular. Structural MRI was obtained for anatomical reference using a 3-dimensional T1-weighted sequence (repetition time = 10 ms, echo time = 4.6 ms, flip angle = 8°, and voxel size = 0.79 × 0.79 × 0.8 mm^3).

Preprocessing of fMRI Data

First, all fMRI files were denoised with a single-participant independent component analysis approach to reduce the effect of head motion [probabilistic independent component analysis in FSL's MELODIC version 4.1.9 using the MCFLIRT motion correction tool (41) and spatial smoothing with a 5-mm Gaussian kernel]. Single-participant independent component analysis resulted in a varying number of independent components, some of which were judged to be caused by motion and were discarded in a semiautomatic fashion (36). The independent component analysis denoised files were then despiked with the Artrepair toolbox (42). The despiked files were then brain extracted, slice time corrected (interleaved), high pass filtered (150 seconds), and registered to the T1-weighted structural image and to the Montreal Neurological Institute 152 standard space image (43,44). All 4-dimensional files were resampled to 4-mm isotropic voxels. To further reduce the effects of head motion, the files were used as input in a linear regression analysis that included head motion time series estimated along 6 dimensions (x-, y-, z-axes and rotational displacement of pitch, roll, and yaw), together with motion estimates from the previous time point as well as square terms (45). Finally, functional connectivity network masks for all networks (except the striatum; see explanation below) were obtained from the 17-network parcellation atlas provided by Yeo *et al.* (46). Notably, the MTL network represents one of the posterior subnetworks of the DMN in the 7-network parcellation provided in the same paper (46). The striatum network mask was obtained from the striatal connectivity atlas provided by the same group by combining all subdivisions of the striatum to increase the signal-to-noise ratio (47). The networks of interest are displayed on a glass brain in Figure 1.

Statistical Analysis of Functional Connectivity

Functional connectivity was defined as the partial temporal correlation between 2 networks of interest, i.e., before correlating the time series between 2 networks, the time series of all other networks were regressed out of the two in question. A symmetrical correlation matrix was calculated for each

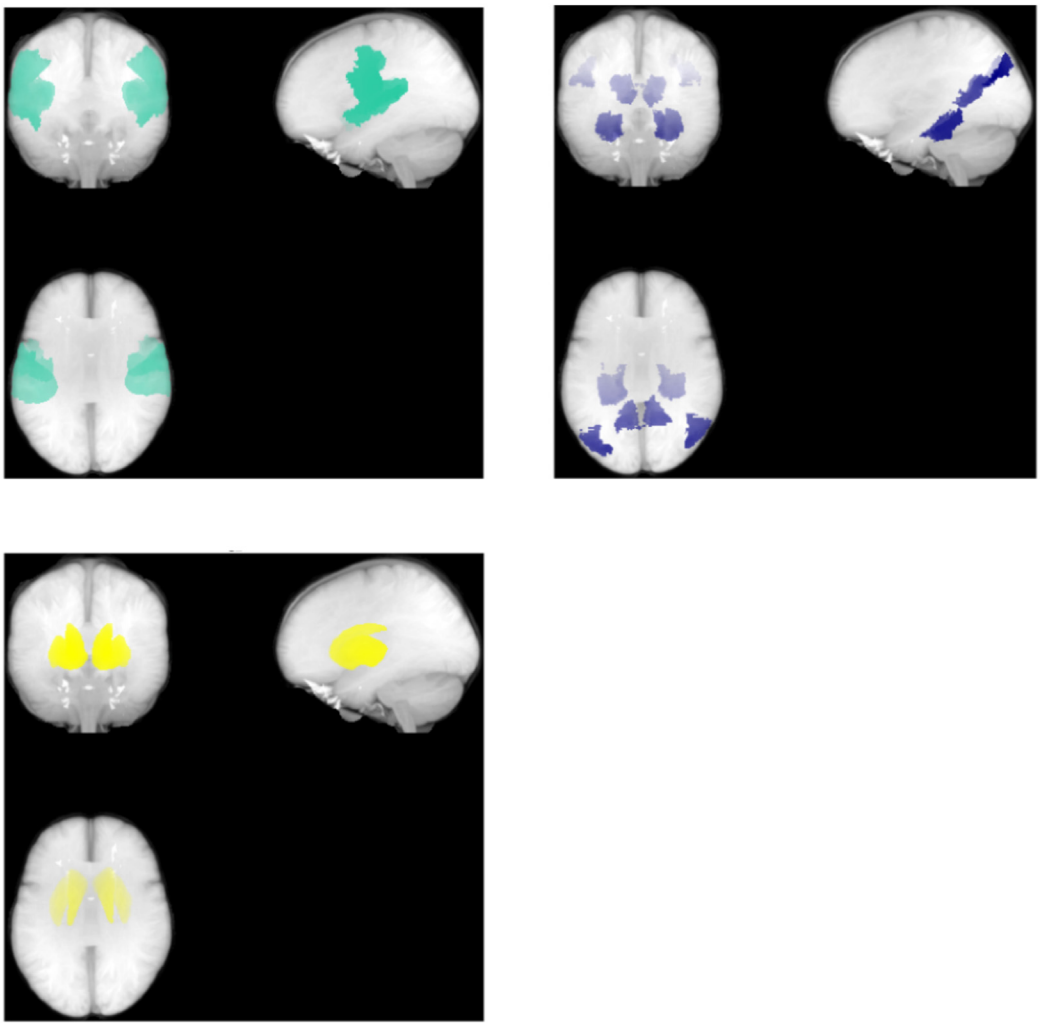

Figure 1. Networks of interest. Networks presented on a glass brain in coronal, sagittal, and axial view. (Upper left panel) Auditory network. (Upper right panel) Medial temporal lobe network. (Lower panel) Striatum.

participant including the pairwise correlations between all networks of interest after Fisher transformation. The correlation matrices were tested for associations using a multiple linear regression analysis with age, sex, and motion summary measures as independent variables. We specifically tested for cross-sectional effects of group and group × time interaction. Furthermore, we included the change in PANSS p3 score as a regressor and tested for a correlation between functional connectivity before initiation of antipsychotic medication and PANSS p3. As a post hoc analysis, we also tested for a correlation between delta PANSS p3 scores and time change in pairwise partial network correlations for pairwise networks showing a correlation with the PANSS p3 at baseline to test whether the clinical effects and network effects of D_2 blockade were associated. As a post hoc analysis, we tested whether pairwise network correlations showing significant correlation with the PANSS p3 at baseline were associated with reduction in PANSS p3 across time to study whether functional connectivity before initiation of medication predicted response to treatment. Finally, as a supplementary test for specificity, we included extra networks from the 17-network parcellation atlas provided by Yeo *et al.* that have been hypothesized to be involved in the formation of AVHs (26). The extra networks included the salience network (dorsal anterior cingulate cortex), somatomotor network (supplementary motor area), temporolateral DMN (superior temporal gyrus), posterior DMN (parietal and posterior cingulate cortices), superior and inferior central executive network (CEN) (prefrontal cortex), and ventral attention network (temporoparietal junction/Wernicke's area) (see the Supplement for a display of all networks included in the supplementary analysis). In this broader model, we tested for a group difference at baseline between ANFE patients with AVHs and ANFE patients without AVHs and for a group × time interaction between ANFE patients with AVHs and healthy control participants. Statistical inference was made using false discovery rate at level $\delta = 0.05$, with a significance threshold defined as $P(j) \leq \delta j/m$ (j is an index running from 1 to m; m is the total number of tests) (48).

RESULTS

Clinical Characteristics

Amisulpride treatment was initiated after baseline examinations and administered in individual doses. The 22 patients who were rescanned after 6 weeks received an average daily dose of 297 mg (range 50–800 mg). The average level of hallucinations (PANSS p3) was reduced from baseline to follow-up from 4.2 to 2.2 (Table 1). One patient discontinued treatment 2 weeks before follow-up examinations (see the Supplement for clinical characteristics of the 25 patients without AVHs who were included in the supplementary analysis).

Functional Connectivity

At baseline, patients with AVHs displayed higher connectivity between the auditory network and the MTL network compared with control participants (p = .002) and lower connectivity between the auditory network and the striatum (p = .031). Baseline connectivity between the auditory network and the MTL network was positively correlated with PANSS p3 (t = 2.67, p = .013) (Figure 2). After 6 weeks, the functional connectivity between the auditory network and the MTL network decreased over time in patients with AVHs compared with control participants (group × time interaction, p = .018). Furthermore, the functional connectivity between the MTL network and the striatum increased over time in patients with AVHs compared with control participants (group × time interaction, p = .013) (Figure 3). The change in functional connectivity between the networks of interest and delta PANSS p3 scores was not correlated ($p < .05$). Finally, the higher functional connectivity between the auditory network and the MTL network was before treatment, the larger the reduction in hallucinations was (t = 2.34, p = .032) (Figure 3). All p values were corrected using the false discovery rate method.

The supplementary test for specificity including extra networks in the model revealed no group difference in connectivity at baseline between ANFE patients with and without AVHs. Moreover, the supplementary analysis of group × time interaction between ANFE patients with AVHs and healthy control participants did not reveal any significant difference in connectivity across time at the corrected level. At the uncorrected level, an additional decrease in functional connectivity in patients compared with control participants was found between the temporolateral DMN and inferior CEN (group × time interaction, p = .038).

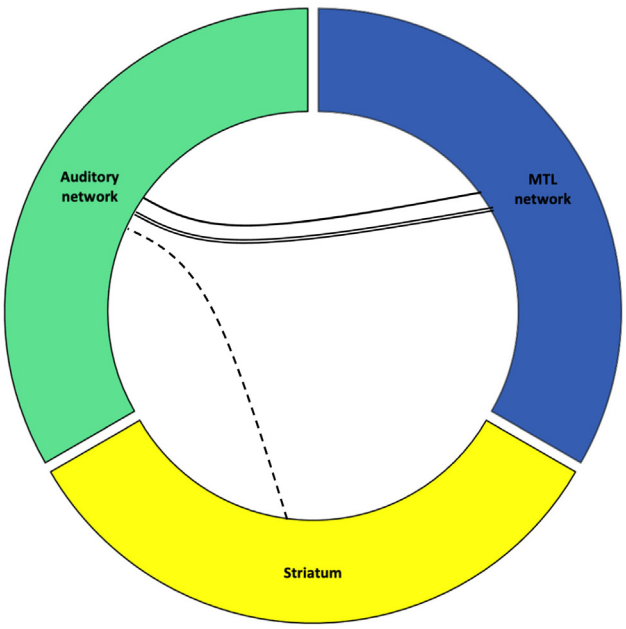

Figure 2. Functional connectivity and association with auditory verbal hallucinations before antipsychotic medication. Full line indicates higher connectivity in patients vs. control participants; dotted line indicates lower connectivity; and double line indicates positive correlation between functional connectivity and Positive and Negative Syndrome Scale p3 in patients. MTL, medial temporal lobe.

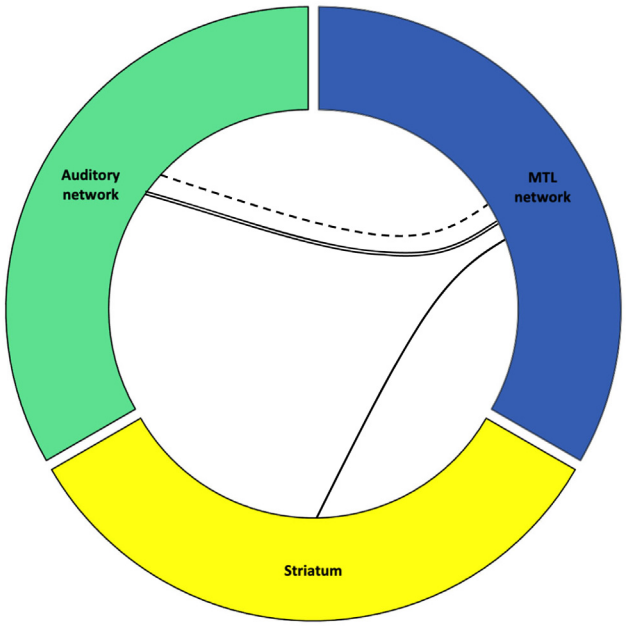

Figure 3. Functional connectivity and association with auditory verbal hallucinations after 6 weeks of antipsychotic medication. Full line indicates increase in patients compared with control participants (group × time interaction); dotted line indicates decrease in patients compared with control participants (group × time interaction); and double line indicates association between functional connectivity at baseline and reduction in Positive and Negative Syndrome Scale p3 across time. MTL, medial temporal lobe.

DISCUSSION

In this study, we investigated the effects of monotherapy with relatively selective D_2 blockade on AVHs and functional connectivity between networks involved in AVHs in patients with schizophrenia who were undergoing initial antipsychotic treatment. We found that the connectivity between the auditory network and the MTL network was increased in ANFE patients with AVHs and that pretreatment connectivity between these networks was associated with the level of experienced

hallucinations. Furthermore, we demonstrated that pretreatment connectivity between the auditory network and the MTL network predicted response to initial antipsychotic treatment and that the connectivity between these networks normalized across time with short-term monotherapy with relatively selective D_2 blockade. The supplementary analysis of sensitivity showed no difference in functional connectivity before initiation of antipsychotic medication between patients with and without AVHs.

Functional Connectivity Before and After Initial Antipsychotic Monotherapy

In general, the findings from the current study are consistent with the previously mentioned network models suggesting abnormal auditory cortex and MTL connectivity in individuals with AVHs. The current findings are also consistent with a few previous studies of ANFE schizophrenia with AVHs reporting aberrant connectivity of brain regions associated with auditory processing, language-related regions, internal monitoring, and memory (49–54), although a direct comparison with previous studies is not possible because of differences in clinical characteristics and connectivity measures. Moreover, increased connectivity between sensory networks and higher-order cognitive networks has been found in patients with AVHs across the psychosis spectrum, indicating that this effect is not specific to schizophrenia (55). The current study extends the existing literature by inclusion of the striatum in the model together with the auditory network and the MTL network. Our finding of decreased connectivity between the auditory network and the striatum suggests that the striatum is involved in the development of AVHs. However, the supplementary test for specificity revealed no group difference at baseline between patients with AVHs and patients without AVHs, indicating that the finding of abnormal functional connectivity is more related to the underlying disorder than to AVHs. On the other hand, a possible difference in functional connectivity between patients with and without AVHs may be subtle compared with the difference in connectivity between patients with AVHs and healthy control participants. Therefore, we suggest that future studies should test for differences in functional connectivity between patients with and without AVHs in larger samples to delineate the nature of AVHs in patients with schizophrenia.

To the best of our knowledge, there have been no previous attempts to study the effects of initial D_2 receptor blockade on functional connectivity in a subgroup of ANFE patients with schizophrenia and confirmed AVHs. The connectivity between the auditory network and the MTL network normalized after 6 weeks of D_2 receptor blockade, indicating relevance for the therapeutic effects of blocking D_2 receptors. A significant group $\times$ time interaction in striatal connectivity was only found between the striatum and the MTL network wherein patients increased across time compared with control participants. This suggests that blocking D_2 receptors in the striatum reduces connectivity of the auditory network through an effect on the MTL network. Importantly, it is also possible that the clinical effect of antipsychotics is partly mediated by blocking extrastriatal D_2 receptors that are found throughout the MTL (28). The supplementary analysis for specificity, including extra networks hypothesized to be involved in the development of AVHs, revealed only one additional decrease in connectivity in patients compared with control participants between the temporolateral DMN and inferior CEN at an uncorrected level. This may suggest that the MTL subnetwork of the DMN, together with the auditory network and the striatum, are specifically involved in the treatment of AVHs with D_2 blockade. On the other hand, the change in connectivity between the temporolateral DMN and inferior CEN both underlines the complex function of the DMN and points to the involvement of the prefrontal cortex in the treatment of psychotic symptoms.

The effects of blocking D_2 receptors found in the current study are likely to reflect downstream effects of manipulating the associative/cognitive cortico-striatal-thalamo-cortical circuits (56,57). These circuits contain parietal and temporal association areas overlapping with areas within the auditory network and the MTL network. Moreover, in a recent comparable and independent study with a large group of ANFE patients with psychosis, we reported highly significant associations between striatal dopamine synthesis and psychotic symptoms (58). Interestingly, the MTL is involved in both internal monitoring as part of the DMN and in memory function. Therefore, the involvement of the MTL in AVHs could reflect either the unstable memory models or the source monitoring models or both. This mirrors the complex nature of the DMN, which is now recognized as a large-scale network consisting of several subnetworks that are associated with different cognitive functions (59).

Importantly, the normalization of connectivity could mirror regression toward the mean caused by a natural variation in the blood oxygen level–dependent signal rather than D_2 receptor blockade, although the ability to predict treatment response from baseline connectivity argues against this.

Functional Connectivity and Short-term Clinical Outcome

As predicted by the network models for AVHs, we found that functional connectivity between the auditory network and the MTL network was positively correlated with the level of hallucinations (PANSS p3). Furthermore, we found that connectivity before initiation of antipsychotic medication between the auditory network and the MTL network was associated with the reduction of AVHs after short-term D_2 blockade. Taken together, these findings indicate that functional connectivity between these networks could be of clinical relevance as a biomarker of AVHs and a predictor of response to treatment. In further support of this interpretation, an earlier study from our group on the same sample that was used in the current study showed that low striatal binding potentials measured before initiation of medication were associated with better clinical response to D_2 blockade (60), confirming previous findings (61).

On the other hand, we did not find a significant association between the change in functional connectivity and the reduction in PANSS p3, which we had expected. Previous studies have found a correlation between changes in connectivity and changes in PANSS positive scores after administration of risperidone (32,33) and between changes in connectivity and changes in PANSS negative scores after administration of

olanzapine in antipsychotic-naïve patients (31). Although these studies did not use AVHs as a specific outcome measure, they indicate a relevant association between changes in functional connectivity and the clinical effect of antipsychotic medication.

Methodological Considerations

Strengths of the current study include 1) exclusion of patients who had received antipsychotic medication before baseline examinations, 2) monotherapy with a selective D_2 antagonist, and 3) rescanning of healthy control participants that enabled modeling of possible time change in functional connectivity in the control participants. One of the limitations of the study is a modest sample size. Furthermore, because all patients in the current study were first-episode patients, it is likely that the non-AVH patients had never experienced significant AVHs before inclusion, i.e., if they had experienced significant AVHs before, they probably would have been diagnosed earlier. On the other hand, it is not certain that they had never experienced AVHs based on the criterion of a PANSS p3 score < 2 during the past week prior to the MRI scan. In addition, although we used a conservative strategy to deal with participant head motion, we cannot exclude residual effects of motion on functional connectivity measures (62–64). Finally, the effects on the blood oxygen level–dependent signal of physiological parameters such as cardiac pulsation and respiration are likely to be undersampled with a repetition time of 2 seconds considering the Nyquist theorem and therefore may affect the results.

Conclusions

The current study revealed increased connectivity between the auditory network and the MTL network in a subgroup of ANFE patients with schizophrenia who experienced AVHs that normalized over time after initiation of D_2 receptor blockade. Functional connectivity between these networks before initial antipsychotic treatment was associated with the level of untreated hallucinations and with the reduction of hallucinations after short-term medication. This indicates the involvement of functional large-scale networks in the development and treatment of AVHs in patients undergoing initial treatment with antipsychotic medication.

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ARTICLE INFORMATION

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