A Neural Biomarker for Hallucinations: Medial Prefrontal Aberrations in Neural Connectivity Predict Self-Agency Deficits and Hallucination Severity in Schizophrenia

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Abstract

Prior studies have shown that the medial prefrontal cortex (mPFC) represents one neural substrate that mediates judgments of self-agency (i.e., the awareness that “I am the originator of my actions”). Patients with schizophrenia (SZ) manifest cardinal self-agency deficits that contribute to debilitating psychotic symptoms (e.g., hallucinations) and distort reality monitoring. This is the first study in which we examine across 2 SZ samples, the mPFC site that underlies self-agency deficits during an explicit reality-monitoring task (i.e., while subjects distinguish self-generated information from externally-derived information) in one SZ sample, and link intrinsic functional connectivity (iFC) during rest within this a priori task-evoked self-agency seed with hallucination symptoms in a different SZ sample. In particular, we examined the IFC between the mPFC site that underlies self-agency deficits with all other brain regions in SZ using resting-state functional magnetic resonance imaging (fMRI). Resting-state fMRI data were collected from 32 SZ and 28 age, gender, and education-matched healthy control (HC) subjects. Functional connectivity maps were computed for each subject and compared between the HC and SZ groups. Within-group and between-group analyses revealed that aberrant IFC in this a priori-defined mPFC ‘self-agency seed’ predicted hallucination severity. The present findings reveal that the neural aberrations in this mPFC site represent one cardinal biomarker that underlies explicit self-agency deficits during a reality-monitoring task in one SZ sample that generalized to aberrant IFC differences in a different SZ sample and predicted worsening psychotic hallucinatory experiences. This region may represent a key neurobiological target for treatment avenues to improve hallucinatory symptoms.

Keywords: Schizophrenia • Hallucinations • Self-agency • Reality monitoring • Medial prefrontal cortex • Resting-State fMRI

Introduction

Schizophrenia is a severe psychiatric disorder characterized by cardinal deficits in self-agency - the experience and awareness of being the agent of one’s own thoughts, actions and action outcomes [1-3]. These deficits directly contribute to debilitating psychotic symptoms (e.g. hallucinations) and distort reality monitoring (defined as distinguishing self-generated information from externally-derived information) [4,5]. Patients with schizophrenia (SZ) manifest positive symptoms which refer to an excess of normal percepts (e.g. in the form of hallucinations where patients hear voices/see visions that are not really there). Current medications are inadequate with up to 40% of SZ who continue experiencing unremitting positive hallucinatory symptoms [6]. In particular, hallucinations are thought to result from the misattribution of patients’ internal thoughts as external voices [3]. Thus, the psychopathology of hallucinations suggest patients show reduced self-reliance about their own action outcomes, misattributing them as being externally-produced, which is thought to result in patients’ lost sense of self-agency and break from reality (i.e., impaired reality monitoring) [1,2]. Together, these findings compel the need to understand the neurobiology underlying self-agency deficits which we believe drives hallucinatory psychotic experiences in SZ.

We have consistently shown across both functional MRI and magnetoencephalography (MEG) imaging studies that the medial prefrontal cortex (mPFC) represents a critical neural substrate of self-agency in healthy controls (HC) and SZ [7]. In our reality monitoring task, in which subjects distinguish self-generated from externally-derived information, healthy controls (HC) showed mPFC activity during successful encoding and retrieval of self-generated information, which correlated with their accurate identification of self-generated information, indicating mPFC represents a crucial neural correlate of self-agency [7]. By contrast, SZ did not manifest mPFC activation, and showed self-agency impairments during the reality monitoring task [4]. Dysfunction of the mPFC is also prominent in SZ during resting-states within the default mode network (DMN) that is associated with spontaneous, task-independent functional connected networks (temporally correlated activation patterns) during rest [8,9]. Additionally, aberrant DMN functional connectivity has been shown to predict worsening psychotic symptoms. Thus, it is thought that aberrant DMN connectivity during rest reflects reality-monitoring impairments that distort the demarcation between internal thoughts and the external world [9].

In contrast to prior DMN studies in which the mPFC is defined by intrinsic resting-state networks, to-date no study has explicitly tested this link generalized across 2 different SZ samples-between the mPFC site that

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underlies self-agency deficits during an explicit reality-monitoring task in one SZ sample, and linked Intrinsic functional connectivity (fIC) metrics within this ‘task-evoked mPFC self-agency seed’ in a different SZ sample with hallucination symptoms. We hypothesized that aberrant fIC within this mPFC ‘self-agency’ seed region that previously revealed neural aberrations in SZ during an explicit reality-monitoring task, would reveal aberrant fIC in a different SZ sample, compared to HC, and would positively correlate with hallucination severity in SZ [4].

**Participants and Procedures**

Eligibility diagnosis for SZ was determined using the Structured Clinical Interview for DSM-IV (SCID). Thirty two clinically stable, chronically-ill volunteer SZ patients were matched to 28 HC at a group-level in age, gender, and education and were scanned using fMRI while they completed a resting-state scan, with eyes closed (Table 1). SZ participants next underwent clinical neuropsychological assessments. Seven patients did not return to the lab to complete clinical assessments, leaving 25 SZ who completed both resting-state fMRI and clinical assessments. Symptom severity in SZ was assessed with the Positive and Negative Syndrome Scale (PANSS) [10]. Hallucination severity was assayed using a subscale of the PANSS on a scale of 1 (absent) to 7 (severe).

<table>
<thead>
<tr>
<th>HC</th>
<th>SZ</th>
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<tbody>
<tr>
<td>Age</td>
<td>43 (11.8)</td>
</tr>
<tr>
<td>Gender</td>
<td>21M, 7F</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14 (0.89)</td>
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Table 1. Demographics (mean, SD) of Healthy Control (HC) and Schizophrenia (SZ) Subjects.

Resting-state fMRI data acquisition

Data were acquired on a 3 Tesla Siemens Prisma MRI scanner with 64- and 20-channel head and neck coils at the Neuroscience Imaging Center at University of California San Francisco. Participants underwent anatomical T1-weighted imaging (TR=2300 msec, TE=2.98 msec, 160 slices, 1 mm slice thickness, FOV=256 mm) and resting-state echo-planar imaging (TR=2 s, 32 slices, 3.5 mm slice thickness, TE=29 msec, FOV=240 mm; matrix=64 x 64). Data were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and functional connectivity metrics were estimated using the CONN toolbox (http://www.nitrc.org/projects/conn).

Functional connectivity analysis

Resting-state fMRI data were spatially preprocessed, and EPI images were spatially realigned to a mean image and coregistered with the T1-weighted image for each individual by using SPM12. Preprocessing with the default pipeline in the CONN v18.c functional connectivity toolbox included functional realignment, slice-timing correction, structural segmentation and normalization, functional normalization, artifact detection tools (ART)–based functional outlier detection and scrubbing, and functional smoothing with an 8-mm Gaussian kernel in MNI space. A 5-mm-radius sphere was centered on a region of interest (ROI) defined in [4]. The mPFC seed region was generated using the MarsBar toolbox (http://marsbar.sourceforge.net/). Following preprocessing of the EPI images, the magnitude of connectivity was calculated for each subject between the time series for the mPFC seed region with all remaining voxels in the brain, as Fisher transformed correlation values, thresholded at p<.001 uncorrected. Next, second level analyses were performed to examine whether the mPFC seed region showed significantly different between-group differences (HC vs. SZ) in fIC, as well as within-group fIC in SZ using a false discovery rate (FDR) multiple comparison correction thresholded at p<0.05. We used Spearman’s correlations (2-tailed) to examine how within group and between-group fIC of the mPFC seed related to psychotic symptoms of hallucinations in SZ [10].

**Results**

Demographics of HC and SZ are illustrated in Table 1. Symptom scores in SZ are shown in Table 2. Second-level within-group analyses in SZ performed on the average z-maps from the mPFC seed ROI predicted worsening hallucination severity (Figure 1), as well worse overall symptom severity (Table 2). Between-group analyses were performed on the average z-maps from the mPFC seed with every voxel in the brain. We found that connectivity strengths between the mPFC seed region and only one region, the right middle/superior frontal gyrus (R. M/SFG), revealed a significant difference between HC and SZ (p<.001, FDR, p<.05) (Figure 2). Additionally, as predicted, connectivity strength between the mPFC seed ROI and the R. M/SFG correlated with worsening hallucination severity in SZ. We found no correlations in connectivity strength between the mPFC seed ROI with medication (Chlorpromazine equivalents), negative or positive symptoms in either the within or between-group analyses (Table 2; all p’s >.10).

<table>
<thead>
<tr>
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<th>Within-group mPFC correlation p-value</th>
<th>Between-group mPFC correlation p-value</th>
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<tbody>
<tr>
<td>Positive symptoms</td>
<td>15.80 (4.65)</td>
<td>0.12</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>15.64 (5.47)</td>
<td>0.67</td>
</tr>
<tr>
<td>Total symptoms</td>
<td>63.76 (12.87)</td>
<td>0.004</td>
</tr>
<tr>
<td>Chlorpromazine (CPZ) equivalents</td>
<td>321.83 (189.62)</td>
<td>0.1</td>
</tr>
<tr>
<td>Illness duration</td>
<td>26 (11)</td>
<td>0.34</td>
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Table 2. Medication profile and symptom scores of schizophrenia patients (SZ).

Figure 1. (A) Illustration of mPFC seed 5mm sphere defined from our previous reality monitoring task in which SZ had revealed aberrant neural activation while making self-agency judgments. (B, C) Illustrate within-group connectivity strengths between the mPFC seed (shown in A) and surrounding voxels that predicted worsening hallucination severity in SZ.
between the mPFC seed R.M/SFG that predicted worsening hallucination severity in SZ.

In our future research, we now implement non-invasive brain stimulation techniques such as neuronavigated transcranial magnetic stimulation (nTMS) that serve as causal neurostimulation tools to alter the mPFC excitation-inhibition balance and change its activity/connectivity metrics to specifically test its causal impact on improving self-agency and psychotic symptoms of hallucinations.

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References


