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Publication Date

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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 represents 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.

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Declarations of interest: none

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 (Synofzik et al., 2010; Synofzik et al., 2013; Voss et al., 2010). 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) (Subramaniam et al., 2012; Vinogradov et al., 2008). 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 (Lowe et al., 2018). In particular, hallucinations are thought to result from the misattribution of patients' internal thoughts as external voices (Voss et al., 2010). 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) (Synofzik et al., 2010; Synofzik et al., 2013). 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 (Subramaniam et al., 2019). 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 (Subramaniam et al., 2019). By contrast, SZ did not manifest mPFC activation, and showed self-agency impairments during the reality monitoring task (Subramaniam et al., 2012). 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 (Fox et al., 2005; Whitfield-Gabrieli et al., 2009). Additionally, aberrant DMN functional connectivity has been shown to predict worsening psychotic symptoms (Whitfield-Gabrieli et al., 2009). 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 (Whitfield-Gabrieli et al., 2009).

In contrast to prior DMN studies in which the mPFC is defined by intrinsic resting-state networks (Fox et al., 2005), to-date no study has explicitly tested this link generalized across 2 different SZ samples - between the mPFC site that underlies self-agency deficits during an explicit reality-monitoring task in one SZ sample (Subramaniam et al., 2012), and linked intrinsic functional connectivity (iFC) metrics within this 'task-evoked mPFC self-agency seed' in a different SZ sample with hallucination symptoms. We hypothesized that aberrant iFC within this mPFC 'self-agency' seed region that previously revealed neural aberrations in SZ during an explicit reality-monitoring task, would reveal aberrant iFC in a different SZ sample, compared to HC, and would positively correlate with hallucination severity in SZ.

Methods

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 (Table 1), and were scanned using fMRI while they completed a resting-state scan, with eyes closed. 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) (Kay et al., 1987). Hallucination severity was assayed using a subscale of the PANSS on a scale of 1 (absent) to 7 (severe).

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, 1mm slice thickness, FOV = 256 mm) and resting-state echo-planar imaging (TR = 2s, 32 slices, 3.5mm slice thickness, TE = 29 msec, FOV = 240 mm; matrix = 64 × 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 v19.c functional connectivity toolbox included functional realignment and unwarp, 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 (Subramaniam et al., 2012). 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 Z 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 iFC, as well as within-group iFC 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 iFC of the mPFC seed related to psychotic symptoms of hallucinations in SZ (Kay et al., 1987).

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 (Fig. 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) (Fig. 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).

Discussion

This is the first study in which we link the neurobiological substrate that underlies self-agency deficits during a reality-monitoring task in one SZ sample with hallucination symptoms that generalized to a different SZ sample during rest. In other words, we show that the neurobiological substrate within the mPFC seed region that revealed neural aberrations that underlie self-agency deficits during a reality-monitoring task in SZ, predicted worsening hallucination severity in a completely different SZ sample during rest. The relation between connectivity strengths in the mPFC seed region with hallucination severity was corroborated in both the within-group and between-group analyses, at statistically significant thresholds, corrected for multiple comparisons. We did not find any correlations between negative symptoms, illness duration or medication. Thus, the present findings suggest that aberrations in the neural architecture of the mPFC specifically underlies self-agency deficits in SZ, which we believe drives their hallucinatory psychotic experiences.

It must be noted, however, that in both our reality-monitoring task and resting state studies, both patient samples constituted chronically-ill patients (i.e. averaging ~20 years of illness); thus, the present findings are not generalizable to recent-onset or at-risk schizophrenia patient populations. We also clarify that we are not stating that the aberrations in connectivity strengths within the mPFC represents the only neural structure that mediates

self-agency deficits and drives hallucination symptoms in SZ, but that the mPFC represents one neural region that plays a crucial neurobiological role in judgments of self-agency (i.e., the awareness that 'I am the originator of my thoughts and actions') that is fundamental for distinguishing the sources of information generated by the "self" from information generated by the "other" (reality-monitoring). Indeed, across convergent evidence from imaging (fMRI, MEG, and EEG) and single neuron studies, the mPFC is the one region that replicably shows increased activity prior to self-generated actions but not during externally-perceived actions (Cabeza and St Jacques, 2007; Fried et al., 2011; Keller and Heckhausen, 1990; Khalighinejad et al., 2018; Passingham et al., 2010; Subramaniam et al., 2018; Subramaniam et al., 2012), thus indicating that mPFC is a robust biomarker of the neural computations that lead to and mediate judgments of self-agency.

In conclusion, both within-group and between-group analyses revealed that aberrant connectivity metrics within our *a priori*-defined self-agency mPFC seed represents one cardinal biomarker that may provide the critical missing link between explicit self-agency task-induced deficits with intrinsic rest states that drives psychotic hallucinatory experiences 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 (Dijkstra and de Bruin, 2016; Etkin, 2018; Sliwinska et al., 2014; Widhalm and Rose, 2019) 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.

Acknowledgments

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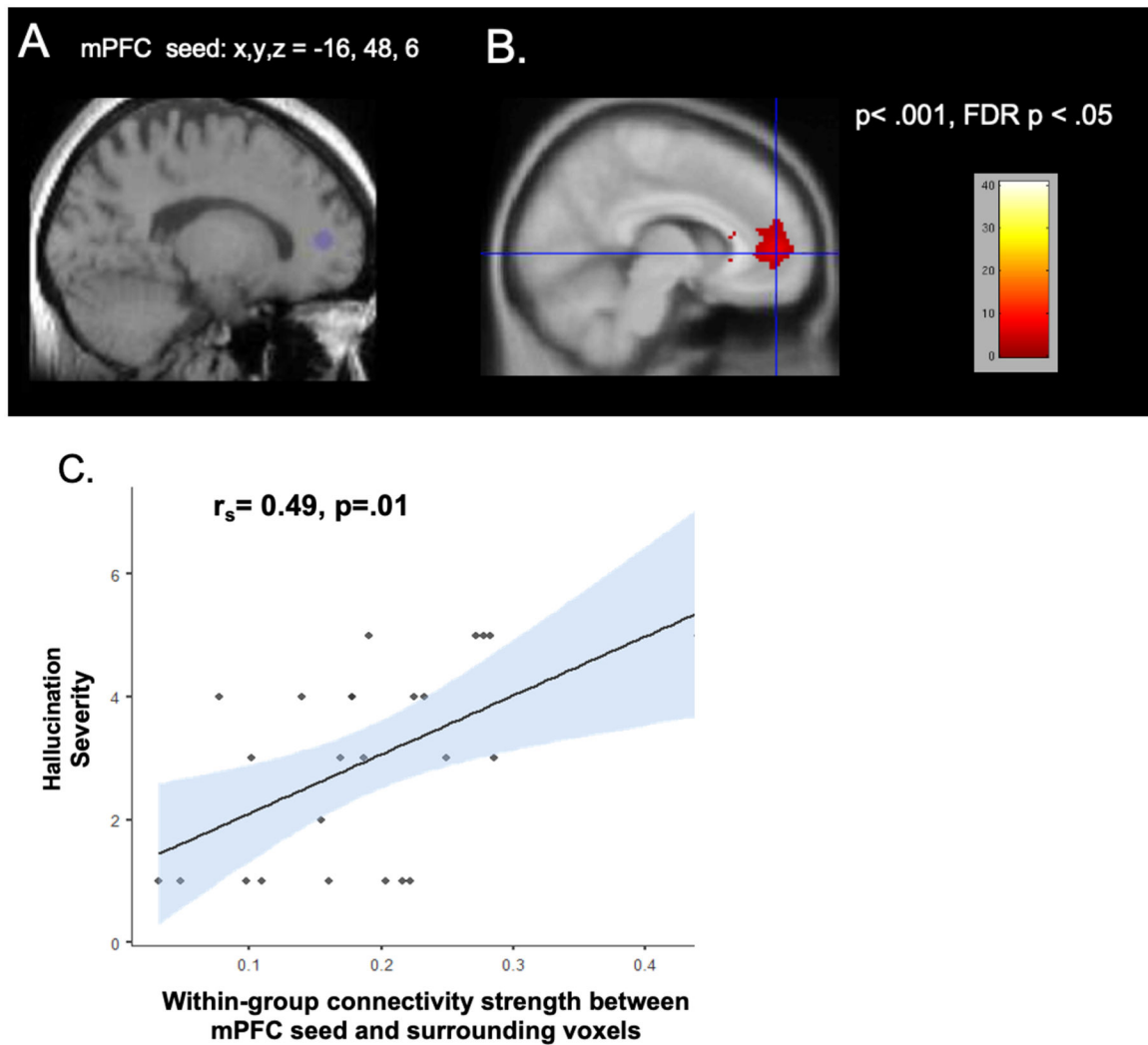
Figure 1.
A. Illustration of mPFC seed 5mm sphere defined from our previous reality-monitoring task in which SZ had revealed aberrant neural activation while making self-agency judgments. **B & C.** Illustrate within-group connectivity strengths between the mPFC seed (shown in A) and surrounding voxels that predicted worsening hallucination severity in SZ.
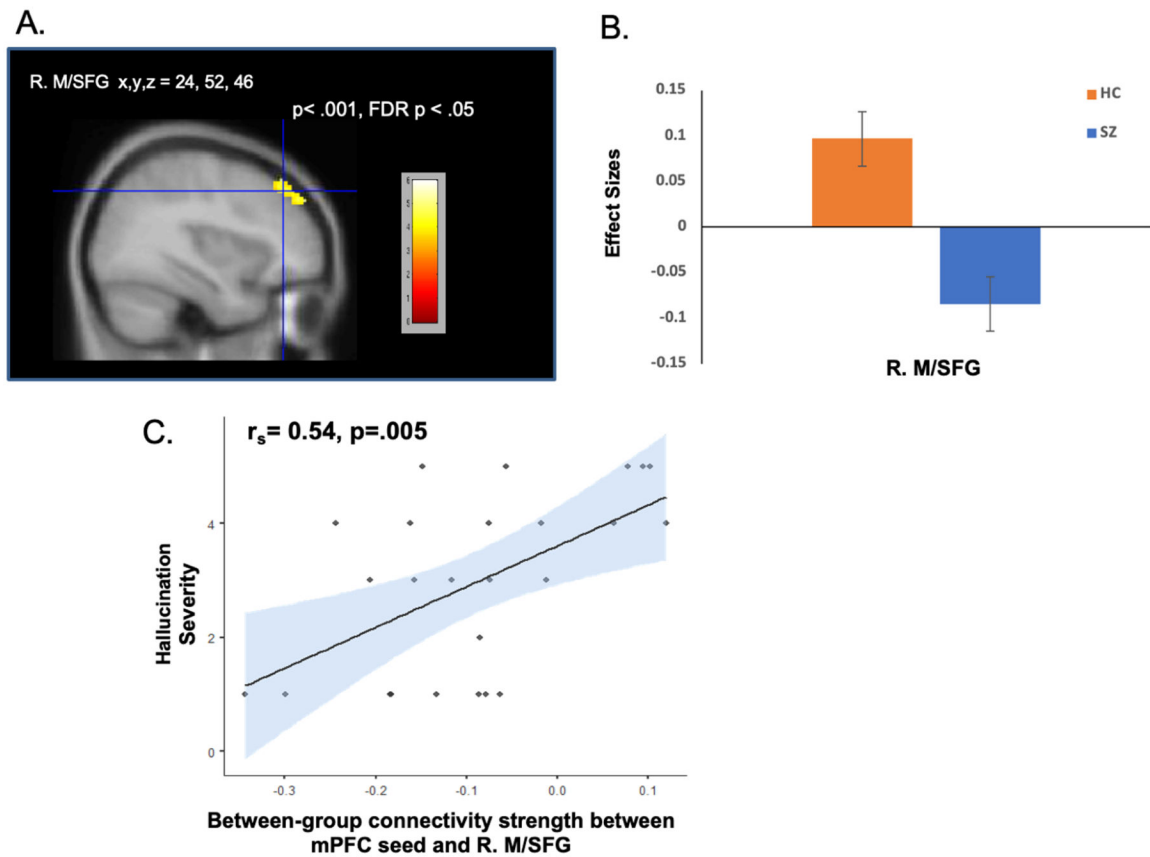
Figure 2.
A. Highly significant between-group connectivity differences between the mPFC seed and R. M/SFG. **B & C.** Illustrate mean connectivity strengths between the mPFC seed R.M/SFG that predicted worsening hallucination severity in SZ.

Table 1.

Demographics (mean, SD) of Healthy Control (HC) and Schizophrenia (SZ) Subjects

	HC	SZ
Age	43 (11.8)	45 (10.3)
Gender	21M, 7F	25M, 7F
Education (years)	14 (0.89)	13 (1.8)

Table 2.

Medication Profile and Symptom Scores of Schizophrenia Patients (SZ)

Antipsychotic Medication[1]	SZ	Within-Group mPFC Correlation p value	Between-Group mPFC Correlation p value
Positive Symptoms	15.80 (4.65)	0.12	0.23
Negative Symptoms	15.64 (5.47)	0.67	0.67
Total Symptoms	63.76 12.87)	**0.004**	0.17
Chlorpromazine (CPZ) Equivalents	321.83 (189.62)	0.10	0.34
Illness Duration	26 (11)	0.34	0.50