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Disrupted network cross talk, hippocampal dysfunction and hallucinations in schizophrenia

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ABSTRACT

Hallucinations characterize schizophrenia, with approximately 59% of patients reporting auditory hallucinations and 27% reporting visual hallucinations. Prior neuroimaging studies suggest that hallucinations are linked to disrupted communication across distributed (sensory, salience-monitoring and subcortical) networks. Yet, our understanding of the neurophysiological mechanisms that underlie auditory and visual hallucinations in schizophrenia remains limited.

This study integrates two resting-state functional magnetic resonance imaging (fMRI) analysis methods – amplitudes of low-frequency fluctuations (ALFF) and functional network connectivity (FNC) – to explore the hypotheses that (1) abnormal FNC between salience and sensory (visual/auditory) networks underlies hallucinations in schizophrenia, and (2) disrupted hippocampal oscillations (as measured by hippocampal ALFF) beget changes in FNC linked to hallucinations. Our first hypothesis was supported by the finding that schizophrenia patients reporting hallucinations have higher FNC between the salience network and an associative auditory network relative to healthy controls. Hippocampal ALFF was negatively associated with FNC between primary auditory cortex and the salience network in healthy subjects, but was positively associated with FNC between these networks in patients reporting hallucinations. These findings provide *indirect* support favoring our second hypothesis. We suggest future studies integrate fMRI with electroencephalogram (EEG) and/or magnetoencephalogram (MEG) methods to *directly probe* the temporal relation between altered hippocampal *oscillations* and changes in cross-network functional communication.

1. Introduction

An estimated 59% of patients with schizophrenia (Sz) report auditory hallucinations (AH); nearly half of those reporting AHs also report visual hallucinations (VHs) (Waters et al., 2014). To address the question of how individuals with Sz come to experience hallucinations, researchers have used non-invasive resting-state functional magnetic resonance imaging (rs-fMRI) to compare spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal in Sz reporting

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hallucinations relative to control subjects. Resting-state functional connectivity (rs-FC) analyses are commonly employed in hypothesis-driven investigations of Sz symptoms and provide an estimate of how correlated or "in synch" BOLD signal activation is across regions of interest. Both VH and AH are associated with abnormal sensory (Clos et al., 2014; Ford et al., 2015; Gavrilescu et al., 2010; Hoffman et al., 2012; Shinn et al., 2013; Sommer et al., 2012), striatal (Amad et al., 2014; Hoffman et al., 2012; Rolland et al., 2015), insular (Clos et al., 2014; Rolland et al., 2015), medial frontal (Amad et al., 2014; Clos et al., 2014), and parahippocampal/hippocampal (Amad et al., 2014; Clos et al., 2014; Ford et al., 2015; Rolland et al., 2015; Sommer et al., 2012) rs-FC. Yet, it remains unclear how these widespread disruptions in rs-FC give rise to hallucinations.

The abnormal salience monitoring model proposes that hallucinations may be driven by abnormal functional communication between resting-state networks (e.g. anatomically distributed brain regions that show consistent functional co-activation at rest) (Palaniyappan et al., 2012a; Palaniyappan et al., 2011). The salience network (SN) contains hubs in the anterior insula and dorsal anterior cingulate cortex, and activates in response to proximally salient cues — from internal changes in bodily state to demanding tasks that require externally-focused attention (Menon, 2015; Seeley et al., 2007). Dynamic causal modeling and Granger causality analyses suggest the right anterior insula regulates activation/deactivation of the default-mode network (DMN) (Goulden et al., 2014; Sridharan et al., 2008). The DMN is associated with internally-directed attention and self-referential processing (Raichle, 2015); network hubs include medial prefrontal cortex, anterior cingulate, precuneus/posterior cingulate cortex, and bilateral angular gyri. Improper monitoring of salient internal events (e.g. auditory-verbal imagery, visual images) plausibly generates hallucinations. Many studies have explored functional network connectivity (FNC) in Sz (Damaraju et al., 2014; Garrity et al., 2007; Whitfield-Gabrieli et al., 2009), yet no study has tested this hypothesis by examining how primary/associative sensory networks interact with the SN/DMN in the context of hallucinations.

A major advantage of the abnormal salience monitoring model is that it accounts for the distributed changes in functional communication observed in Sz reporting hallucinations. However, this network model fails to incorporate the role of the hippocampus in the generation of hallucinations. Across fMRI investigations of the active AH state (e.g. symptom-capture), the left hippocampus shows the highest likelihood of activation (Jardri et al., 2011). One recent study explored low frequency (<0.1 Hz) power of the BOLD signal across brain voxels during rest. This exploratory analysis of amplitudes of low frequency fluctuations (ALFF) found that Sz patients reporting VH and AH had higher ALFF in the left hippocampus relative to patients that reported AH (but not VH). Variability in left hippocampal ALFF was positively associated with reported VH severity, but was negatively associated with AH severity (Hare et al., 2017).

In a magnetoencephalography (MEG) symptom-capture study of AH, transient decreases in hippocampal theta band power (4–10 Hz) preceded reported AHs (van Lutterveld et al., 2012). Hippocampal theta oscillations are measured in local field potentials of humans (Arnolds et al., 1980), and all other mammals studied to date (Green and Arduini, 1954; Lubenov and Siapas, 2009; Vanderwolf, 1969; Winson, 1972). Medial prefrontal neurons and auditory neurons in the inferior colliculus demonstrate spiking preferences at particular phases of the slow hippocampal theta rhythm (referred to as phase-locking) (Hyman et al., 2010, 2011; Pedemonte et al., 1996; Siapas et al., 2005). Researchers speculate that hippocampal theta waves act like the conductor of an orchestra by synchronizing activation of distributed networks, and temporally ordering information (e.g. sensory percepts, motor representations, and memories) (Buzsaki, 2002; Lisman and Buzsáki, 2008). We propose that disrupted hippocampal oscillations destabilize normal network connections in Sz and might plausibly drive abnormal network connections in Sz patients with hallucinations.

The present study models the relationships between hippocampal ALFF, FNC, and targeted symptomology (AH and VH severity) in the resting-state brain. We first test the hypothesis that altered FNC between salience and sensory networks underlies modality-specific hallucinations, predicting that Sz patients with VH will have higher FNC between visual and salience networks relative to all groups, and patients with AH will have higher FNC between auditory and salience networks relative to nonhallucinating Sz patients and HC.

Next, we explore the hypothesis that disrupted hippocampal oscillations destabilize normal functional network connections in Sz. We predict that (1) hippocampal oscillations (measured indirectly as ALFF within the left hippocampal cluster identified in our previous analysis) (Hare et al., 2017) will be associated with FNC in HC; (2) Sz will lack these normal ALFF-FNC relationships, and (3) will have abnormal relationships between hippocampal ALFF and FNC. The poor temporal resolution of fMRI limits our ability to directly test the hypothesis that disrupted hippocampal theta *oscillations* beget changes in FNC. Nonetheless, we establish links between hippocampal BOLD signal fluctuations and FNC, providing preliminary (indirect) support favoring a novel hippocampal binding model that might explain disrupted auditory network functional communication in Sz.

2. Experimental materials and methods

2.1. Subjects

We analyzed 294 resting-state fMRI scans from the Functional Biomedical Informatics Research Network (FBIRN) dataset (Keator et al., 2016). Schizophrenia patients ($n = 141$) and HC ($n = 153$) were matched for age, reported gender, and handedness (Table 1). Raw imaging data were collected from six sites; written informed consent was obtained from all participants. The consent process was approved by University of California Irvine, University of California San Francisco, Duke University/University of North Carolina, University of New Mexico, University of Iowa, and University of Minnesota Institutional Review Boards.

All recruited study participants were between the ages of 18 and 62. All Sz subjects were diagnosed with schizophrenia or schizoaffective disorder by experienced clinicians using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders. Patients were either stable on antipsychotic medication or unmedicated (only 8 out of the 143 Sz subjects were not taking antipsychotic medication at the time of the study). Healthy controls with a first-degree relative with an Axis I disorder or a history of major psychiatric illness were excluded. Exclusion for all participants included history of major medical illness, insufficient eyesight to see with normal acuity with MRI compatible corrective lenses, contraindications for MRI, drug dependence in the last five years or a current substance abuse disorder, an intelligence quotient <75.

The present study draws from the FBIRN Phase III study (see (Hare et al., 2017) (Ford et al., 2015) (Damaraju et al., 2014)). Multiple behavioral/symptom assessments were performed as part of the FBIRN Phase III study including the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984b). The protocol required that symptom assessment ratings be completed within one month of scanning. For a detailed description of the multi-phase FBIRN project including subject characteristics, imaging parameters, and behavior assessments see Keator et al., 2016.

2.2. Grouping of participants

We used the same clinical subgroup sorting strategy used previously in (Hare et al., 2017) and (Ford et al., 2015). Sorting of the 141 Sz into clinical subgroups was achieved by evaluating responses to two SAPS items (Andreasen, 1984a). Item #1 asks if the participant "reports

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