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Monitoring Self & World: A Novel Network Model of Hallucinations in Schizophrenia

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MONITORING SELF & WORLD: A NOVEL NETWORK MODEL OF HALLUCINATIONS IN SCHIZOPHRENIA

by

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Under the Direction of Jessica A. Turner, PhD

ABSTRACT

Schizophrenia (Sz) is a psychotic disorder characterized by multifaceted symptoms including hallucinations (e.g. vivid perceptions that occur in the absence of external stimuli). Auditory hallucinations are the most common type of hallucination in Sz; roughly 70 percent of Sz patients report hearing voices specifically (e.g. auditory verbal hallucinations). Prior functional magnetic resonance imaging (fMRI) studies have provided initial insights into the neural mechanisms underlying hallucinations, implicating an anatomically-distributed network of cortical (sensory, insular, and inferior frontal cortex) and subcortical (hippocampal, striatal) regions. Yet, it remains unclear how this distributed network gives rise to hallucinations impacting different sensory modalities.

The insular cortex is a central hub of a larger functional network called the salience network. By regulating default-mode network activity (associated with internally-directed thought), and fronto-parietal network activity (associated with externally-directed attention), the salience network is able to orient our attention to the most pressing matters (e.g. bodily pain, environmental threats, etc.). Abnormal salience monitoring is thought to underlie Sz symptoms; improper monitoring of salient internal events (e.g. auditory-verbal imagery, visual images) plausibly generates hallucinations, but no prior study has directly tested this hypothesis by exploring how sensory networks interact with the salience network in the context of hallucinations in Sz.

This dissertation project combined exploratory and hypothesis-driven approaches to delineate functional neural markers of Sz symptoms. The first analysis explored the relationship between Sz symptom expression and altered functional communication between salience and default-mode networks. The second analysis explored fMRI signal fluctuations associated with modality-dependent (e.g. auditory, visual) hallucinations. The final analysis tested the hypothesis that abnormal functional communication between salience and sensory (e.g. auditory, visual) networks underlies hallucinations in Sz. The results suggest that there are three key players in the generation of auditory hallucinations in Sz: auditory cortex, hippocampus, and salience network. A novel functional network model of auditory hallucinations is proposed to account for these findings.

INDEX WORDS: fMRI, Schizophrenia, Hallucinations, Salience network, Hippocampus

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1 INTRODUCTION

1.1 Schizophrenia

More than 3.5 million Americans are diagnosed with schizophrenia (Sz), a mental disorder impacting roughly 1% of the world population. To be diagnosed, individuals must report two or more of the following symptoms for at least six months: delusions, hallucinations, disorganized speech, disorganized/catatonic behavior, or negative symptoms.[1] *Negative symptoms* refer to a loss of normal behavior such as diminished emotional response, while *positive symptoms* refer to abnormal thoughts, perceptions, or behaviors that are not normally present in the general population. Individuals must report at least one positive symptom (e.g. delusions, hallucinations, disorganized speech) to be diagnosed with the disorder.

Symptoms tend to emerge in late adolescence or early adulthood. As symptoms become more frequent and severe, they can interfere with social relationships, or make it difficult to hold down a job. Estimates of unemployment in Sz range from 80-90%.[2,3] The burden often falls on family or other members of the community to provide care and financial support. Without such support, individuals with Sz can end up on the streets. A year-long study of over 10,000 patients with severe mental illness reported that 20% of Sz patients were homeless.[4]

Hallucinations are vivid perceptions that occurs in the absence of corresponding external stimuli.[5] Auditory hallucinations (AHs) are common in Sz, while hallucinations impacting other modalities (e.g. visual, olfactory, gustatory, somatosensory/tactile) are less common. Roughly 60-80% of individuals with Sz report AHs[6–8], while about 27% report visual hallucinations (VHs).[6]

At a minimum, these involuntary perceptual experiences can be distracting. But even worse, the hallucination content (e.g. what exactly the patient sees, hears, etc.) oftentimes makes

these experiences intolerable. An extensive survey asked 100 Sz patients about their experiences of hearing voices (e.g. auditory *verbal* hallucinations), and reported that three out of five patients reported that the voices abused and degraded them (calling them 'slut', 'gay' and other derogatory terms).[9]

Given that AHs are one of the most prevalent, debilitating symptoms of Sz, patients need promising treatment options. Unfortunately, auditory verbal hallucinations remain resistant to pharmacological treatment in over 25% of cases.[10] Researchers have used non-invasive techniques such as functional magnetic resonance imaging (fMRI) to identify the underlying neural mechanisms of AHs and VHs, in an effort to develop innovative therapies that target these specific symptoms. These studies are reviewed in the following section.

1.2 Hallucinations and the Brain

1.2.1 Symptom-Capture Studies of Auditory Hallucinations

Prior symptom-capture studies of AHs have compared the blood oxygen level dependent (BOLD) fMRI response during periods where Sz patients actively report hearing voices or other sounds (e.g. "ON periods") relative to periods where they do not report these experiences (e.g. "OFF periods"). Symptom-capture studies require that individuals with Sz have fluctuating AHs, and substantial insight into their experiences to indicate ON versus OFF periods (usually indicated with button presses to avoid motion artifacts associated with verbal report). Consequently, the number of subjects enrolled in AH-capture studies tends to be low ($N < 10$), which limits the inferences that can be made regarding the larger Sz population.

Given these challenges, Jardri et al.[11] performed a coordinate-based meta-analysis of ten symptom-capture studies of AHs in Sz patients. For each of the ten studies, clusters of brain activation associated with AH "ON periods" were modeled as Gaussian distributions and were

then converted to a 3-dimensional activation map. The union of activation maps was calculated on a voxel-by-voxel basis to obtain estimates of the likelihood of activation of brain regions. The left hippocampus showed the highest likelihood of activation during active AHs; Broca's area (in left inferior frontal gyrus), bilateral insular cortex, and left auditory cortex (in the superior temporal gyrus) were also more active during active AH episodes.[11] These findings suggest that activation of a distributed network gives rise to AHs in Sz.

1.2.2 Symptom-Capture Studies of Visual Hallucinations

There have been no prior symptom-capture studies of VHs in Sz patients. A previous symptom-capture study of VHs was successfully performed on a single patient with Parkinson's disease[12], but a discussion of these results falls outside the scope of this chapter.

1.2.3 Resting-State Functional Markers of Auditory Hallucinations

Trait-based approaches using tools like resting-state fMRI circumvent methodological challenges of symptom-capture studies. Resting-state fMRI analyses explore fMRI signal fluctuations during a rest period (usually less than 10 minutes). During the scan, the subject is instructed to stay awake and rest with his/her eyes open or closed and is not given formal instructions to perform particular task(s). Researchers can use resting-state fMRI to explore how features of the fMRI signal relate to traits in a given sample. Researchers interested in neural markers of hallucinations can compare resting-state fMRI signal fluctuations in patients that report hallucinations as a symptom relative to those that don't report hallucinations.

Resting-state functional connectivity analyses (rs-FC) are the most common type of resting-state fMRI analysis. This correlational analysis determines the level of coherence of the resting-state BOLD signal in different brain regions. If BOLD activation in one region is

consistently correlated with BOLD activation in another region across time points of the resting-state scan, it is inferred that the two areas of the brain are functionally (if not directly) connected.

In Sz, AHs are associated with rs-FC changes in regions that mirror those reported in symptom-capture studies of AHs. Gavrilescu et al. found that Sz patients reporting AHs had reduced interhemispheric connectivity between left/right primary auditory cortices and between left/right secondary auditory cortices relative to both Sz patients that did not report AHs, and healthy control subjects.[13] Sommer et al. found reduced rs-FC between left auditory cortex and both the left hippocampus and left insula/operculum in Sz patients reporting AHs relative to healthy controls.[14] Importantly, this study failed to include a clinical control group without AHs, so it is difficult to say which of the observed changes in brain function are related to hallucinations (versus Sz diagnosis). Thus, there is available, but limited, evidence suggesting that *reduced* auditory cortex functional communication underlies AHs in Sz.[13,14]

Other studies report that AHs are associated with elevated auditory cortex rs-FC. In one study, reported AH severity was positively correlated with rs-FC between left primary auditory cortex and Broca's area in the left inferior frontal gyrus.[15] Another study explored rs-FC summed across a loop linking secondary auditory cortex (Wernicke's area), inferior frontal gyrus, and putamen, and found that rs-FC across this loop was significantly greater for Sz patients reporting AHs relative to patients without AHs, and healthy controls.[16] In sum, the trait to experience AH in Sz patients is associated with aberrant patterns of rs-FC with auditory cortex in the superior temporal gyrus[13–17], inferior frontal gyrus[15,16], insula[14,17], putamen[16], hippocampus.[14,17] These brain regions overlap with regions showing elevated likelihood of activation during the active AH state.[11]

1.2.4 Resting-State Functional Markers of Visual Hallucinations

The relatively low prevalence of VHs in Sz (~27%) makes it difficult to recruit large numbers of patients for resting-state fMRI analyses of VHs. In addition, the high prevalence of AHs in Sz (~70% of Sz cases) often precludes researchers from studying VHs in isolation; most Sz patients reporting VHs as a symptom also report AHs. Given these challenges, previous rs-fMRI analyses of VHs in Sz have compared patterns of rs-fMRI activation of Sz patients reporting both VHs and AHs relative to a patient group that reports AHs but not VHs. Relative to patients reporting AHs (but not VHs), patients reporting both VHs and AHs have hyperconnectivity between: (1) amygdala and both the visual cortex (mainly Brodmann area 18) and inferior frontal gyrus[18]; (2) nucleus accumbens (in the striatum) and widespread regions including bilateral parahippocampal gyri, insula and putamen[19]; and between (3) hippocampus and both left caudate and bilateral medial frontal cortex.[20] Thus, the trait to report VHs is linked to abnormal rs-FC between a distributed network of cortical (frontal, occipital) and subcortical (amygdala, nucleus accumbens, hippocampus/parahippocampus) regions.

1.2.5 Summary

Both VHs and AHs are associated with abnormal sensory[13–18], striatal[16,19,20], insular[17,19], medial frontal[17,20], and parahippocampal/hippocampal[14,17–20] functional connectivity during rest. This network of regions largely overlaps with those identified in symptom-capture studies. A compelling theory of hallucinations in Sz must account for these widespread alterations in activation and functional communication.

In the following section, I review three theories of AHs in Sz. Each theory proposes that AHs stem from disrupted cognitive mechanisms ranging from memory deficits to self-monitoring deficits to salience monitoring deficits. Each theory then postulates neural

mechanisms that explain these cognitive deficits. Importantly, these three neuroscientific explanations of AHs are pitched at a different level of analysis (e.g. neurophysiological, functional systems/networks, etc.). Below, I describe the central features of each theory, and address how well each theory accounts for the evidence gleaned from neuroimaging analyses.

1.3 Theories of Hallucinations

1.3.1 Memory Intrusion Theories

Memory intrusion theorists propose that AHs in Sz arise from a combination of deficits in (1) intentional inhibition, which result in involuntary intrusion of auditory representations into consciousness, and (2) binding contextual cues to particular memories, such that Sz patients with AH can't form complete representations of past events.[21] The theory predicts that Sz patients with AH will have disrupted function of brain regions involved in intentional inhibition (e.g. prefrontal cortex, anterior cingulate cortex and subcortical thalamic/striatal regions) and those involved in context memory (e.g. hippocampus and connections to prefrontal cortex). Taking into account prior research findings, this theory accounts for much of the evidence. Yet, the theory fails to account for the role of the auditory cortex in the generation of AHs.

1.3.2 Predictive Coding and Self-Monitoring Theories

Predictive coding theories of cognitive function assume that a central function of the brain is to make predictions, monitor prediction errors (e.g. mismatches between predicted outcomes and actual outcomes), and update and improve predictions.[22] Self-monitoring theory is a subtype of the more expansive predictive coding framework. To understand the details and significance of self-monitoring theory, consider the following example. Suppose that I'm on a hike in the Georgia mountains. Self-monitoring theorists assume that every time I take a step, (1) my motor cortex sends a motor command to my leg; (2) a copy of this command is made (e.g. efference

copy); (3) I receive sensory feedback from my leg (regarding position, contact with the ground, etc.). The central assumption of self-monitoring theory is that higher-level brain centers monitor each of our actions by comparing predicted consequences (encoded by efference copies) to actual sensory feedback that we receive.

Self-monitoring mechanisms serve at least two important functions. First, self-monitoring is essential for an ongoing sense of agency. I relay this feeling to others when I make claims like "I was walking up the mountain, and my foot slipped." Notice that even in the case where I slip – an instance of a prediction error – I still have the unshakeable sense that it was *me* who was walking, and it was *me* who slipped. According to the self-monitoring theorist, this feeling of agency is tied to ongoing predictions that are made by sensorimotor systems. Efference copies are only generated when *my motor system(s)* sends commands to different parts of *my body*. In this sense, efference copies serve as tags of self-generated actions. Consider the hiking example once more but assume that no efference copy is made when I take a step. If a primary function of the efference copy is to tag self-generated actions, the absence of an efference copy might lead me to infer that I did not cause my foot's movement; some other force or agent must therefore be responsible for my foot's movement.

Second, self-monitoring allows us to quickly detect cases of prediction errors. Again, consider the case in which my foot slips. In this case, there is a mismatch between my prediction and the actual outcome. If my self-monitoring centers are working properly, they should immediately detect this prediction error and signal to motor and cognitive systems to adjust accordingly (e.g. focus my attention, brace for impact, etc.).

Prior research suggests that the auditory cortex signals prediction errors. When healthy adult human subjects hear themselves speak, early responses of the auditory cortex (peaking ~90

ms after hearing speech sounds) are dampened relative to when they passively listen to speech played back.[23] Auditory dampening effects are thought to occur, because efference copies convey predictions that attenuate auditory responses to sounds predicted by the model (e.g. one's own speech).[24] When researchers manipulate feedback that subjects receive during talking (e.g. pitch-shifted or alien feedback) to induce prediction errors, these auditory dampening effects are not observed.[24] In this way, auditory cortex activity signals predicted outcomes (e.g. attenuated activity) and prediction errors (e.g. large fluctuations in activity).

Horga et al.[25] hypothesized that prediction error signals in the auditory cortex would be deficient in Sz patients with auditory verbal hallucinations. To test this hypothesis, they modeled activity in the auditory cortex as a function of prediction signals and prediction error signals during a speech decision-making task. Patients with auditory verbal hallucinations had reduced prediction error signals in the right auditory cortex relative to heathy controls. One shortcoming of this study is that it did not include a clinical control group of Sz patients that did not hear voices. Thus, it is unclear whether these predictive coding deficits in the auditory cortex are unique to Sz patients with auditory verbal hallucinations.

Another study included a clinical control group and found that nonhallucinating Sz patients showed auditory dampening responses similar to controls during speaking relative to the prediction error conditions (e.g. pitch-shifted or alien feedback).[26] Patients with AH failed to show this dampening response during speaking, suggesting that they may have a distinctive predictive coding deficit (e.g. failure to successfully monitor their own speech).

Functional communication between speech perception centers in auditory cortex (e.g. Wernicke's area) and speech production (motor) centers in the inferior frontal gyrus may be responsible for these observed auditory dampening effects. Phase synchrony of gamma

oscillations (35 – 50 Hz) during talking is associated with auditory dampening effects.[27] These findings are consistent with the central assumptions of the self-monitoring framework. Motor centers must relay prediction signals (e.g. efference copies) to sensory regions to successfully attenuate activity to sensations that are predicted by the model.

To explain AHs, self-monitoring theorists propose that sensorimotor circuits that are critical for monitoring *inner speech* (e.g. "the little voice inside each of our heads") are disrupted. Schizophrenia patients consequently fail to recognize their own inner speech as their own. The self-monitoring theory of AH emphasizes the role that auditory cortex and inferior frontal gyrus play in the generation of hallucinations.[27] But this theory fails to account for the important roles that subcortical (e.g. hippocampal, striatal) regions play in the generation of hallucinations. Multi-network models of AHs may fare better at explaining prior research findings.

1.3.3 Triple Network and Salience Monitoring Theories

Recent advances in human neuroimaging have allowed researchers to delineate *functional networks* (e.g. anatomically-distributed brain regions that show consistent patterns of functional co-activation). Triple network theorists propose that dysfunctional cross-network communication gives rise to widespread symptoms of Sz. Before we can make sense of how *dysfunctional* network communication might give rise to Sz symptoms, we must first understand the general functions that these networks perform in healthy subjects.

In the early 2000s, researchers observed that regions spanning the anterior midline (medial frontal/anterior cingulate cortex), posterior midline (posterior cingulate cortex extending into precuneus), and posterior lateral cortex (bilateral angular gyri) were consistently co-active during periods of internally-directed thought.[28,29] Activity in this so-called default mode network (DMN) decreases when healthy subjects perform tasks requiring externally-focused attention,

and activity in lateral fronto-parietal networks increases. It is thought that the DMN plays an important role in supporting internal mental processes (thought, imagery, memory).[30] Efficient switching between DMN and fronto-parietal network states may be required to flexibly adapt to our surroundings and orient our attention to the most pressing matters (rewards, threats, meeting a deadline at work, recognizing a car drifting in the lane on the highway to avoid a collision, etc.)

A third network, the salience network (SN), is thought to play a critical role in orienting our attention to the most pressing matters; central hubs of this network include the bilateral anterior insular cortex, and dorsal anterior cingulate cortex.[31,32] Findings from Granger Causality and dynamic causal modeling analyses in healthy subjects demonstrate that activation of SN hubs predicts subsequent activation of DMN activation and fronto-parietal networks.[33,34] Studies of those with traumatic brain injury reveal that diminished white matter integrity of fibers connecting dorsal anterior cingulate and anterior insular cortex disrupts DMN activation/deactivation.[35,36] These findings suggest that functional and structural communication between SN hubs is required for efficient switching between internally-directed and externally-directed network states.

Like those with traumatic brain injury, Sz patients have trouble deactivating DMN during task performance.[37–39] Failure to deactivate DMN during task performance has been associated with severity of both positive and negative symptoms in Sz[37], but also with impaired working memory.[37,38] It lies outside the scope of this chapter to discuss all the prior studies of DMN activation/deactivation in Sz and other mental disorders, but it is worth noting that there is considerable debate about whether abnormal DMN activation/deactivation reflects broad features of psychopathology or is a marker of more general cognitive impairment (see Whitfield-Gabrieli

& Ford[40] for a broader discussion of findings and their significance, and Anticevic et al.[41] for an overview of links between abnormal DMN function and cognitive impairments).

In addition, Sz patients show abnormal DMN functional communication during rest. Two resting-state fMRI studies found that spatial maps of DMN functional connectivity were highly variable in Sz subjects.[37,39] As predicted, activation of posterior cingulate cortex was tightly correlated with activation of DMN hubs in healthy subjects.[37] In Sz patients, however, posterior cingulate activation was correlated with activation of voxels across the entire brain.[37] These findings demonstrate that DMN hubs non-selectively communicate with hubs outside of the network during rest in Sz.

While DMN hubs are *hyperconnected to regions outside the network* during rest in Sz, *connectivity between network hubs is reduced* during rest in Sz. A small study found that rs-FC between anterior and posterior midline DMN hubs was reduced in Sz.[42] A later study[43] analyzed rs-FC between hubs of functional networks in a larger sample (100 patients with a psychotic disorder, 100 healthy controls), and found that rs-FC was reduced between DMN hubs and between SN hubs in patients with a psychotic disorder.[43] Additional studies also report reduced rs-FC between SN hubs in Sz patients.[44,45]

Schizophrenia patients' failure to deactivate DMN during task performance[37–39] may stem from failed SN regulatory control. Manoliu et al.[46] explored rs-FC between DMN and SN, and reported that Sz patients had seemingly normal rs-FC between SN and DMN. In addition to the traditional rs-FC analyses, the researchers performed *time-lag-shifted* FNC analyses exploring rs-fMRI signal coherence of SN and DMN, with fixed time lags introduced between network time series. When time lags of 1 TR (2 seconds) and 2 TRs (4 seconds) were introduced between DMN and SN time series, Sz had significantly reduced rs-FC between DMN and SN relative to

healthy controls. These findings demonstrate that traditional (zero-lag) FNC analyses may be ill-equipped to detect time-varying communication between different brain regions as well as group differences in communication between regions. Since no post-hoc correlation/regression analyses were performed on these time-lag-shifted connectivity estimates, this leaves open the questions of whether and how time-lag-shifted rs-FC between SN and DMN might relate to particular symptoms of Sz.

1.4 Dissertation Aims

The triple network theory has several advantages. Given the expansive functional roles of these networks (e.g. tracking salience, orienting attention, etc.), the triple network theory might explain diverse symptoms of Sz. As a model of hallucinations, the theory accounts for the fact that hallucinations are associated with abnormal patterns of activity across many different brain regions. In addition to the open question concerning potential links between particular Sz symptoms and time-lag-shifted network connectivity, a few questions remain unanswered.

Adopting a triple network account of hallucinations, what role might auditory and visual cortex play in the generation of hallucinations? It is plausible that improper monitoring of salient internal events (e.g. auditory-verbal imagery, visual images) generates hallucinations, but no study has tested this hypothesis by examining how sensory networks interact with the SN in the context of hallucinations. Alternatively, hallucinations may be driven by abnormal resting-state interactions between the DMN and sensory cortex[48,49], but this hypothesis has not been tested either.

This dissertation research addresses current gaps in existing knowledge by mapping time-lag-shifted rs-FC between salience and default-mode networks onto Sz symptom dimensions (Chapter 2), exploring potentially novel sites of regional variation in BOLD signal fluctuations

associated with VH and AH (Chapter 3), and testing the hypotheses that hallucinations in Sz are associated with abnormal resting-state functional communication between sensory networks and (1) the SN, and/or (2) the DMN (Chapter 4). This dissertation aims to delineate targeted relationships between abnormal SN-DMN functional communication and specific Sz symptoms. A refined understanding of these relationships is required to develop promising treatments that target particular symptoms such as auditory verbal hallucinations, which are resistant to pharmacological treatment(s) in over 25% of cases.[10]

2 SALIENCE-DEFAULT MODE FUNCTIONAL NETWORK CONNECTIVITY LINKED TO POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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2.1 Abstract

Schizophrenia is a complex, debilitating mental disorder characterized by wide-ranging symptoms including delusions, hallucinations (so-called "positive symptoms"), and impaired motor and speech/language production (so-called "negative symptoms). Salience-monitoring theorists propose that abnormal functional communication between the salience network (SN) and default mode network (DMN) begets positive and negative symptoms of schizophrenia, yet prior studies have predominately reported links between disrupted SN/DMN functional communication and positive symptoms. It remains unclear whether disrupted SN-DMN functional communication explains (1) solely positive symptoms, or (2) both positive and negative symptoms of schizophrenia.

To test these hypotheses, we incorporate a *time-lag-shifted* functional network connectivity (FNC) analyses that explored coherence of the resting-state fMRI signal of three networks (anterior DMN, posterior DMN, SN) with fixed time lags introduced between network time series (1 TR = 2 seconds; 2 TR = 4 seconds). Multivariate linear regression analysis revealed that severity of disordered thought and attentional deficits were negatively associated with 2TR-shifted FNC between anterior DMN and posterior DMN. Meanwhile, severity of flat affect, and bizarre behavior were positively associated with 1TR-shifted FNC between anterior DMN and SN. These results provide support favoring the hypothesis that lagged SN-DMN functional communication is associated with both positive and negative symptoms of schizophrenia.

2.2 Introduction

The abnormal salience monitoring theory of schizophrenia (Sz) proposes that abnormal functional communication between the salience network (SN) and default mode network (DMN) begets wide-ranging symptoms including hallucinations, disorganized thought, and psychomotor poverty.[32,50] When healthy subjects perform cognitive tasks requiring externally-focused attention, the DMN deactivates and regions essential for executive functioning (e.g. lateral prefrontal and parietal cortex) become active; DMN hubs include medial prefrontal cortex/anterior cingulate (anterior midline), posterior cingulate/precuneus (posterior midline) and angular gyri (posterior lateral).[40,51] Both anterior and posterior midline hubs have strong structural connections to limbic regions involved in emotion and memory.[52] But, studies exploring DMN function during rest and across different tasks suggest that anterior and posterior DMN hubs may play specialized functional roles. Tasks requiring explicit self-reference preferentially activate medial prefrontal cortex[53], while posterior midline hubs are thought to integrate self-referential judgments and play an important role in autobiographical memory.[53–55] Finally, two studies exploring effective (directional) connectivity within the DMN reported that the anterior prefrontal cortex acts as a sink of propagated activity (e.g. anterior prefrontal activity lags behind activity of posterior DMN hubs).[56,57]

The salience network (SN) plays a critical role in monitoring the proximal salience of cues — from startling noises to changes in homeostatic state. The anterior insular (AI) hub receives convergent input from visual and auditory cortex[58–61], while the dorsal anterior cingulate cortex (dACC) hub projects to the spinal cord.[62] These connections allow the SN to integrate incoming perceptual information, and respond quickly when confronted with salient changes to internal states of the body and external states of the environment.[62] Diminished white matter

integrity of AI-dACC tracts in individuals with traumatic brain injury disrupts normal patterns of DMN activation/deactivation[35,36], suggesting that the SN is required for regulating DMN activation.

Schizophrenia patients demonstrate an attenuated ability to deactivate DMN during task performance[37–39], and elevated DMN resting-state functional connectivity (rs-FC).[47,63,64] These abnormalities are associated with global assessments of positive symptoms (e.g. delusions, hallucinations and disorganized speech)[37], working memory deficits[65], social deficits[66] and hallucinations.[46,67] Depressed rs-FC with SN hubs in Sz is linked to hallucinations[44,46], general assessments of reality distortion (hallucinations + delusions)[45] and defective error monitoring.[68]

An innovative study by Manoliu et al.[46] first examined rs-fMRI signal coherence of DMN and SN in Sz, and reported that Sz patients had seemingly normal rs-FNC between the SN and DMN relative to healthy controls. Next, a series of *time-lag-shifted* FNC analyses[47] explored rs-fMRI signal coherence of SN and DMN, but introduced fixed time lags between network time series. When time lags of 1 TR (2 seconds) and 2 TRs (4 seconds) were introduced between network time series, Sz had abnormal rs-FNC between DMN and SN relative to HC. However, the researchers did not explore potential associations between symptom severity and time-lag-shifted FNC between DMN and SN.

Prior studies have predominately reported links between disrupted SN/DMN functional communication and positive symptoms of Sz.[37,44,46,67] Yet, we know that the SN and DMN play indispensable roles in monitoring internal and environmental states, and orienting attention. At present, it remains unclear whether disrupted SN-DMN functional communication explains exclusively positive symptoms, or, alternatively, both positive and negative symptoms. The present study explores the relationship between positive and negative symptom expression in Sz

and alterations in DMN and SN functional communication. Specifically, we explore the relation between rs-FNC (zero-lag) and time-lag-shifted (1 TR = 2 seconds; 2 TR = 4 seconds) rs-FNC between resting-state networks (RSNs: anterior DMN, posterior DMN and SN) and reported severity of nine Sz symptom dimensions: hallucinations, delusions, bizarre behavior, positive formal thought disorder, affective flattening/blunting, alogia, avolition/apathy, anhedonia/asociality, attention.

2.3 Methods

2.3.1 Subjects

The present study draws from the Functional Biomedical Informatics Research Network (FBIRN) Phase III study (see Hare et al.[69], Ford et al.[18] and Damaraju et al.[70]). For a detailed description of the multi-phase FBIRN project including subject characteristics, and imaging/behavior assessments see Keator et al.[71] For this study, we analyzed resting-state fMRI scans from a large, clinically-diverse sample of 100 Sz subjects (Table 1).

Raw imaging data were collected from seven sites; written informed consent was obtained from all participants. The consent process was approved by University of California Irvine, University of California Los Angeles, 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 subjects in this study were diagnosed with schizophrenia or schizoaffective disorder by experienced clinicians using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders.[72] Patients were either stable on antipsychotic medication or were not taking antipsychotic medication at the time of the study (only 4 unmedicated out of 100 Sz subjects). Exclusion criteria 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 a current substance abuse disorder, or an intelligence quotient less than 75.

2.3.2 Assessments of Symptoms

Symptom severity was assessed using the Scale for the Assessment of Positive Symptoms (SAPS)[73] and the Scale for the Assessment of Negative Symptoms (SANS).[74] Subscale scores for each symptom dimension were calculated by deriving the sum of individual items in each dimension: hallucinations (SAPS 1-6); delusions (SAPS 8-19); bizarre behavior (SAPS 21-24); positive formal thought disorder (SAPS 26-33); affective flattening/blunting (SANS 1-7) , alogia (SANS 9-12), avolition/apathy (SANS 14-16), anhedonia/asociality (SANS 18-21), attention (SANS 23-24) (see Table 1). Clinicians and research staff at each FBIRN site were designated to perform the symptom ratings. To successfully calibrate symptom ratings, they participated in mandatory training sessions, run by experienced clinicians.

2.3.3 Imaging

As part of the larger FBIRN Phase III study, data were acquired using six 3T Siemens TIM Trio scanners and one 3T GE MR750 scanner using an AC-PC aligned echo-planar imaging pulse sequence (TR/TE 2 s/30 ms, flip angle 77º, 32 slices collected sequentially from superior to inferior, 3.4 x 3.4 x 4 mm with mm gap, 162 frames, 5:24 mins) to obtain T2*-weighted images. Subjects were instructed to lie in the scanner with eyes closed.

2.3.4 Data Processing

Pre-processing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox which runs with the REST software.[75] The first two time frames were removed to allow for signal stabilization. Raw data underwent motion correction to the first

image, slice-timing correction to the middle slice, normalization to MNI space, and spatial smoothing with an 8 FWHM Gaussian kernel. Framewise displacement (FD) – defined as the sum of the absolute values of the derivatives of the 6 realignment parameters (3 linear + 3 rotational converted from degrees to millimeters)[76] – was calculated for each image. The FD measurement differentiates head realignment parameters across frames and generates a 6-dimensional times series that represents instantaneous head motion.[76] Mean FD was calculated for each subject by taking the average of the sum of the absolute values of the derivatives of the 6 realignment parameters (3 linear + 3 rotational). Although independent component analysis (ICA) has been shown to be resistant to motion artifacts[77], we also corrected for potentially confounding effects of head motion on the fMRI signal by including mean FD as a subject-level covariate.

2.3.5 Group Spatial Independent Component Analysis

Group spatial ICA and FNC correlation analyses were performed using GIFT software.[78] As part of a prior network analysis of hallucinations in Sz, we performed group spatial ICA on a large sample of FBIRN subjects, and analyzed FNC between nine RSNs (two auditory networks, two visual networks, 2 subcortical networks, anterior DMN, posterior DMN, and SN).[79,80] Back-reconstruction was performed using group information guided ICA (GIG-ICA) which takes the group maps and runs a spatially constrained ICA on individual subjects, producing individual subject component maps and time courses. This approach has been shown to be robust to artifacts as well as sensitive to individual and group differences.[81,82] In this work we performed a new analysis of spatial maps and time series of SN, anterior DMN, and posterior DMN in order to explore DMN-SN functional communication.

Subject time courses were detrended and despiked, then filtered with a high frequency cutoff of 0.15 Hz prior to computing FNC correlations (zero-lag) and time-lag-shifted FNC correlations; FNC correlations (zero-lag) are defined as the pairwise correlations between network time courses, and time-lag-shifted FNC correlations are defined as pairwise correlations between one network's time course and another network's time course shifted by a specified lag. In a previous analysis, Manoliu et al.[46] performed time-lag shifted FNC analyses with specified lags of 1 TR (2s), 2 TR (4s) and 3 TR (6s), and found that Sz had abnormal 1TR-shifted and 2TR-shifted FNC between DMN and SN (but normal 3TR-shifted FNC between DMN and SN) relative to healthy controls.[46] Given these findings, we explored time-lag-shifted FNC between anterior/posterior DMN and SN with specified time lags of 1TR (2s) and 2TR (4s). All FNC correlations (zero-lag and lagged) were transformed to z-scores using Fisher's transformation.

2.3.6 Statistical Analyses

We performed hierarchical linear regression analyses of FNC correlations (zero-lag and time-lag-shifted), controlling for confounding effects of nuisance variables in block 1 of the linear model (age, gender, scanning site, and mean FD). Symptom scores including the scale for the assessment of negative symptoms (SANS)[74] subscale scores (affective flattening/blunting, alogia, avolition/apathy, anhedonia/asociality, attention), and the scale for the assessment of positive symptoms (SAPS)[73] subscale scores (hallucinations, delusions, bizarre behavior, positive formal thought disorder) were entered in block 2 of the linear model. Subjects with residuals > 3 standard deviations from the mean were excluded ($N \geq 98$ subjects for each regression analysis).

To ensure that observed associations between symptom severity and FNC were not driven by confounding effects of medication, we also performed regression analyses including

total chlorpromazine equivalents[83] as an additional covariate in block 1. We lacked information to derive chlorpromazine equivalents[83] for 11 Sz subjects, so we calculated the mean value of total chloropromazine equivalents (based on the available data; n = 89 subjects), and interpolated the mean value for the 11 subjects with missing data. Results of these analyses are reported in Supplemental Table 2.

Since nicotine use is 2-3 times higher in Sz than in the healthy population[84], and has been shown to significantly impact brain functional connectivity[85], we examined Spearman correlations between FNC and smoking status (factor with three levels: "never smoker", "ex-smoker", "current smoker"). We found no significant correlations between smoking status and FNC measures, so smoking status was not included as a covariate.

Although we hypothesized that rs-FNC with DMN/SN would be linked predominately to positive symptoms, our FNC analyses were largely exploratory to test whether DMN/SN connectivity might also be linked to negative symptoms, and to determine whether FNC-symptom associations depend on the direction and/or magnitude of lag between SN/DMN time courses. For clarity of reporting the results below, lag magnitude is reported parenthetically, while lag direction is denoted with an arrow. For instance, "lagged (1TR) aDMN→SN connectivity" refers to the correlation between aDMN and SN resting-state fMRI signal when the time series of the SN lags behind the time series of the DMN by 1 TR (2 seconds). For each set of time-lag-shifted FNC analyses of a specified lag (1TR, 2TR), confidence was initially specified as $p < 0.05$, and then Bonferroni-corrected for six tests (SN→aDMN, aDMN→SN, SN→pDMN, pDMN→SN, aDMN→pDMN, pDMN→aDMN) ($p < 0.0083$).

2.4 Results

Below, we report significant associations between time-lag-shifted FNC and symptom dimension scores of the SAPS/SANS (Table 2). Results of the zero-lag FNC analyses are reported in Supplemental Table 1a; nominally significant (non-Bonferroni-corrected, $p < 0.05$) results of the time-lag-shifted FNC analyses are reported in Supplemental Table 1b. To provide estimates of effect sizes, we parenthetically report standardized regression coefficients.

Associations between Symptoms and FNC Between Anterior and Posterior DMN. Lagged (2TR) aDMN→pDMN connectivity was negatively associated with severity of attentional deficits ($b = -0.31$, $p = 0.003$), and disordered thought ($b = -0.31$, $p = 0.005$) (Table 2) (Figure 2).

Associations between Symptoms and FNC Between Anterior DMN and SN. Lagged (1TR) aDMN→SN connectivity was positively associated with severity of flat affect ($b = 0.29$, $p = 0.005$) (Table 2), and bizarre behavior (Figure 2), although the latter association did not survive Bonferroni-correction for multiple tests ($b = 0.25$, $p = 0.014$) (Supplemental Table 1b).

2.5 Discussion

The objective of this study was to ask whether functional communication between SN and DMN explains exclusively positive symptoms, or both positive and negative symptoms. Prior research suggests that traditional (zero-lag) FNC analyses may be ill-equipped to detect time-varying communication between different brain regions as well as group differences in communication between regions. We focused on functional communication between the SN and DMN and how this communication is affected by Sz.[46] Specifically, we probed the roles of lag magnitude and direction to explore the relations between SN-DMN connectivity and targeted behavioral dimensions of Sz. We hypothesized that time-lag-shifted rs-FNC across three networks (aDMN, pDMN, SN) would be linked predominately to positive symptoms.[37,44–46,67]

Instead, we found that specific patterns of time-lag-shifted rs-FNC were associated with negative symptoms (e.g. attentional deficits and flat affect) as well as positive symptoms (e.g. disordered thought and bizarre behavior).

First, the (2TR) aDMN→pDMN connectivity analysis revealed that patients with more severe thought disorder had less time-lag-shifted functional communication between DMN networks (specifically, aDMN activation preceding pDMN activation by 4 seconds). This lag might contribute to derailment and illogicality, symptoms of thought disorder.[74] It is thought that the DMN supports internal mental processes (memories, thought, etc.)[30,86], but it remains unclear how exactly the DMN supports these processes. Our findings suggest that functional communication between DMN hubs may be critical for organizing thoughts into coherent, meaningful utterances. Yet, this theory remains speculative until future research provides insight into how the DMN supports complex thought processes and addresses targeted associations between disrupted DMN function and wide-ranging formal thought disturbances in Sz — from derailment (e.g. where the patient's ideas slip off topic) to blocking (e.g. where the patient's train of thoughts is interrupted).

The same pattern of lagged aDMN→pDMN connectivity was also negatively associated with severity of attentional deficits. Put another way, patients with more severe attentional deficits had less temporally coherent (4-second-lagged) functional co-activation of aDMN and pDMN. In addition, we observed numerous nominally significant associations between attentional deficits and FNC between pDMN and SN (both pDMN→SN and SN→pDMN connectivity; see Supplemental Table 1b). A previous study found that elevated posterior cingulate activity was observed during lapses in attention when healthy research subjects performed a demanding perceptual task.[87] In another study, increased activity in posterior

midline regions predicted which words were forgotten on a memory task.[88] Thus, our results are consistent with the theory that posterior DMN functional communication plays a critical role in regulating attention.[52]

Next, we observed flat affect was more pronounced in patients to the extent that the aDMN activation preceded SN activation by 2 seconds, as reflected in lagged aDMN→SN connectivity. The aDMN contains midline structures spanning the medial prefrontal cortex (MPFC) and ACC. Whitfield-Gabrieli et al.[89] reported that *dorsal* MPFC was preferentially engaged during performance of a task that required explicit self-reference, relative to DMN activation evoked by a rest condition. Meanwhile, *ventral* MPFC plays a critical role in the regulation of amygdala activity[90]; patients with ventral MPFC damage have marked reductions in autonomic arousal to emotionally-charged stimuli.[91] These findings suggest that anterior midline DMN hubs contains functional subdivisions essential for explicit self-reference (dorsal MPFC), and tracking the salience of emotional stimuli and regulating our responses to those stimuli (ventral MPFC). It is plausible that flat affect stems from elevated aDMN-SN functional communication that manifests as disturbances in emotional salience tracking/monitoring, and/or inability to disengage with self-reflective thought and engage with surroundings. Future studies should explore these functional subdivisions of the MPFC and their potential contributions to diminution of vocal inflection, and affective gestures, as well as inappropriately elevated displays of affect in Sz.

Finally, bizarre behavior was positively associated with the same FNC pattern (2-second-lagged aDMN→SN connectivity). However, this small effect (standardized beta = 0.25) did not survive Bonferroni correction for multiple tests. Elevated functional communication between SN and DMN could result in awareness of mislabeled bursts of inner speech or thoughts. These

experiences may, in turn, affect planning, social engagement, and engagement with the environment, resulting in bizarre behavior. Future studies in patients selected to have a broader range of bizarre behaviors may further examine this relationship.

Our findings support the hypothesis that specific patterns of lagged DMN/SN functional communication are associated with both positive and negative symptoms. We observed two main trends: (2TR) lagged aDMN→pDMN connectivity was *negatively* associated with symptom severity, while (1TR) lagged aDMN→SN connectivity was *positively* associated with symptom severity (Figure 3). On the one hand, to the extent that lagged functional communication between anterior and posterior DMN hubs is reduced, patients had more severe cognitive disturbances (disordered thought and attentional deficits). On the other hand, patients had more pronounced flat affect and engaged in more bizarre behavior to the extent that aDMN activation consistently preceded SN activation (by 2 seconds).

Given Manoliu et al.'s report of a significant negative correlation between strength of functional connectivity within the right anterior insula and hallucination severity in Sz patients[46], we predicted that SN functional communication would be linked to hallucination severity. Yet, we observed no associations between hallucination severity and SN functional communication, and only a nominally significant negative association between hallucination severity and (zero-lag) aDMN-pDMN connectivity (Supplemental Table 1a). Notably, our analysis of 100 Sz patients drew from a larger sample than in Manoliu et al. (n = 18 patients), and we modeled effects of symptom severity on FNC, controlling for extraneous effects of motion, age, gender, and scanning site (versus performing bivariate correlation analyses). Thus, our null findings might be treated as evidence favoring rejection of the hypothesis that abnormal SN function underlies hallucinations in Sz. However, a targeted analysis of FNC between SN and sensory

networks by our group[79,80] revealed that elevated FNC between SN and an auditory network was positively associated with severity of auditory hallucinations. Future analyses should continue to explore and test targeted hypotheses of hallucinations by exploring potential associations between hallucination severity and disrupted SN functional communication.

Observed associations between symptom severity and FNC were dependent on lag direction. In resting-state analyses of healthy subjects, the anterior midline DMN hub acts as a *sink* of propagated activity (e.g. anterior midline activity lags behind posterior midline activity during rest).[56,57] In the present study, we observed that symptom severity was associated with atypical aDMN→pDMN connectivity, and aDMN→SN connectivity. Converging evidence from rs-FC analyses[19–21], along with a dynamic rs-FNC analysis[49] demonstrating that Sz show reduced dynamic switching of network states, suggests that patients may be stuck in DMN states associated with self-referential processing. As such, it makes sense that DMN activity might precede activity in networks such as the SN. While it remains unclear why lagged FNC with aDMN (aDMN→pDMN, aDMN→SN) was associated with reported symptom severity, this is an interesting result which requires further investigation with other modalities such as EEG/MEG which provide more precise timing information.

Associations between symptom severity and FNC were also dependent on lag magnitude. In healthy subjects, brief delays are observed between network sources of propagated activity and subsequent activation of network sinks such as the anterior frontal cortex (typically < 0.5 seconds).[57] We observed that symptom severity was associated with lagged FNC with longer, atypical delays of 2 seconds and 4 seconds. However, our methodological approach in the present study limits us in making the strong claim that symptoms are *caused* by these lags.

Future investigations must explore precise timing of activation of functional network hubs, and how this relates to behavioral task performance and Sz symptomology.

Given that the physiological basis of BOLD-fMRI remains controversial, this entails some speculation will be required when considering the significance of multi-second lags between BOLD hemodynamic responses of RSN hub regions. Lags in BOLD-fMRI signaling may be caused by vascular effects, changes in neural signaling, or a combination of factors. Prior findings suggest that changes in neural signaling contribute to observed BOLD hemodynamic lags[57], and that vascular effects alone cannot account for BOLD-signal lag structure.[92] Prior research also suggests that infra-slow neuronal oscillations (0.01-0.1 Hz) play a key role in generating the BOLD-fMRI response.[93,94] Although, direct (causal) links between BOLD fluctuations and infra-slow neuronal oscillations in humans remains unestablished, it is widely acknowledged that proper functional network communication depends on dynamic phase coupling of fast neural rhythms (e.g. gamma; > 30 Hz) to slower rhythms (e.g. delta, theta; < 8 Hz).[95,96] It is plausible that coherent BOLD signal fluctuations in RSN hubs of healthy subjects may reflect frequency-dependent coupling of network hub activation. In Sz, cross-frequency coupling of activity across DMN hubs is disrupted.[96,97] We propose that these disruptions may manifest as measurable lags between hemodynamic responses of RSNs. At the same time, we acknowledge that additional physiological factors/interactions are associated with BOLD-signal fluctuations, and that exact (causal) relationships between oscillatory coupling disturbances and measurable changes in FNC using BOLD fMRI remains unknown.

Although our study was the first to examine targeted relationships between time-lagged FNC between SN and DMN and wide-ranging Sz symptoms, we must acknowledge several limitations. While we were able to probe potential links between rs-FNC and a relatively broad

set of nine symptom dimensions, the SAPS/SANS clinical assessments limited our ability to explore links with an even more broad array of symptoms, and targeted behavioral outcomes such as working memory deficits. Next, the cross-sectional nature of this analysis limited our ability to explore how neural function changed in patients over time; it remains unclear whether observed FNC effects reflect chronic dispositions. Third, all but four of the 100 Sz subjects were taking antipsychotic medication at the time of the FBIRN study, introducing potentially confounding effects on brain FNC. We controlled for these potentially confounding effects by including total chlorpromazine equivalents[83] as a covariate in our regression analyses of FNC; including chlorpromazine equivalents as a covariate in the regression analyses had no significant impact on the results (see Supplemental Table 2). Finally, our analyses of FNC explore *correlations* between the rs-fMRI signal of DMN and SN. In our discussion of results, we use arrows to denote direction of lag. This effort to enhance clarification should not be taken to imply *causation* (e.g. that one network's activity exerts causal influence over another network's activity).

The objective of this study was to address whether disrupted functional communication between SN and DMN explains exclusively positive symptoms, or both positive and negative symptoms. To achieve this aim, we explored associations between time-lag-shifted FNC between SN and DMN and heterogeneous behavioral outcomes in Sz. We found strong associations between time-lag-shifted FNC with aDMN (specifically aDMN→SN and aDMN→pDMN) and both positive and negative symptoms of Sz (Figure 3); all other reported FNC-symptom associations did not survive Bonferroni correction for multiple tests. Our results suggest that disrupted functional communication with the anterior DMN may play a crucial role in the pathophysiology of Sz, and etiology of both positive and negative symptoms. Future studies

should build upon these findings and explore time-lag-shifted FNC between SN/DMN hubs and sensory networks, motor networks, and attention networks to gain a more complete, nuanced understanding of the neural mechanisms underlying specific symptoms.

2.6 Acknowledgments

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2.7 Chapter 2 Tables

Table 2.1 Demographic Information

	Descriptive Statistics (for continuous variables, means and standard deviations are reported)	Range
Gender	78 (male), 22 (female)	N/A
Handedness	93 (right), 5 (left), 2 (both)	N/A
Smoking Status	43 (current smoker), 26 (ex-smoker), 31 (never)	N/A
Age in Years	39.3 (12.0)	18-60
Duration Illness in Years	17.7 (11.4)	1-41
Chlorpromazine Equivalents (Woods 2003)	414.3 (407.9)*	2-1800
Scale for the Assessment of Positive Symptoms (SAPS) Total Score	18.9 (15.0)	0-63
SAPS Hallucinations Subscale Score (SAPS Items 1-6 Total Score)	3.7 (5.0)	0-22
SAPS Delusions Subscale Score (SAPS Items 8-19 Total Score)	6.0 (6.2)	0-33
SAPS Bizarre Behavior Subscale Score (SAPS Items 21-24 Total Score)	1.0 (1.6)	0-8
SAPS Thought Disorder Subscale Score (SAPS Items 26-33 Total Score)	3.1 (5.1)	0-27
Scale for the Assessment of Negative Symptoms (SANS) Total Score	28.3 (17.0)	0-80
SANS Affective Flattening Subscale Score (SANS Items 1-7 Total Score)	5.3 (6.2)	0-24
SANS Alogia Subscale Score (SANS Items 9-12 Total Score)	2.0 (2.4)	0-13
SANS Avolition/Apathy Subscale Score (SANS Items 14-16 Total Score)	4.6 (3.4)	0-14
SANS Anhedonia/Asociality Subscale Score (SANS Items 18-21 Total Score)	6.7 (5.3)	0-19
SANS Attention Subscale Score (SANS Items 23-24 Total Score)	2.4 (2.2)	0-8
*We lacked data to derive chlorpromazine equivalents for 11/100 (11%) subjects. Mean and standard deviation calculations are based on the sample of 89 subjects without missing data.		

Table 2.2 Associations Between Symptom Dimension Scores and Network Connectivity

FNC	Lag Summary	Symptom Dimension	Beta	T-stat	P
aDMN→pDMN	pDMN time series lags aDMN time series by 2 TRs	Attention	-0.31	-3.0	0.003
aDMN→pDMN	pDMN time series lags aDMN time series by 2 TRs	Thought Disorder	-0.31	-2.9	0.005
aDMN→SN	SN time series lags aDMN time series by 1 TR	Flat Affect	0.29	2.9	0.005

2.8 Chapter 2 Figures

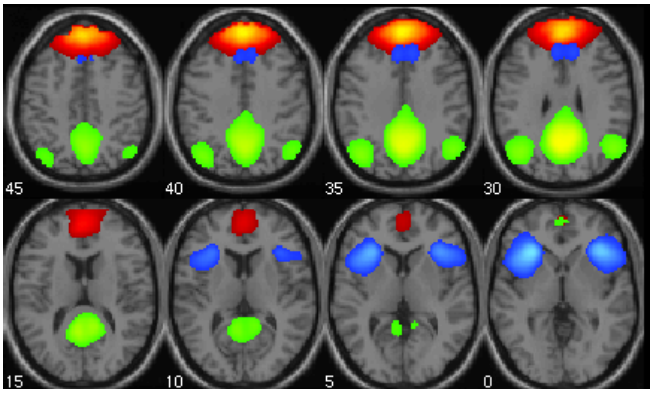

Figure 2.1 Anterior Default Mode, Posterior Default Mode, and Salience Networks.
Mean aggregate spatial maps of the three independent component networks analyzed in the functional network connectivity analysis are shown above (threshold: Z > 2): anterior default mode network (red), posterior default mode network (green), and salience network (blue).

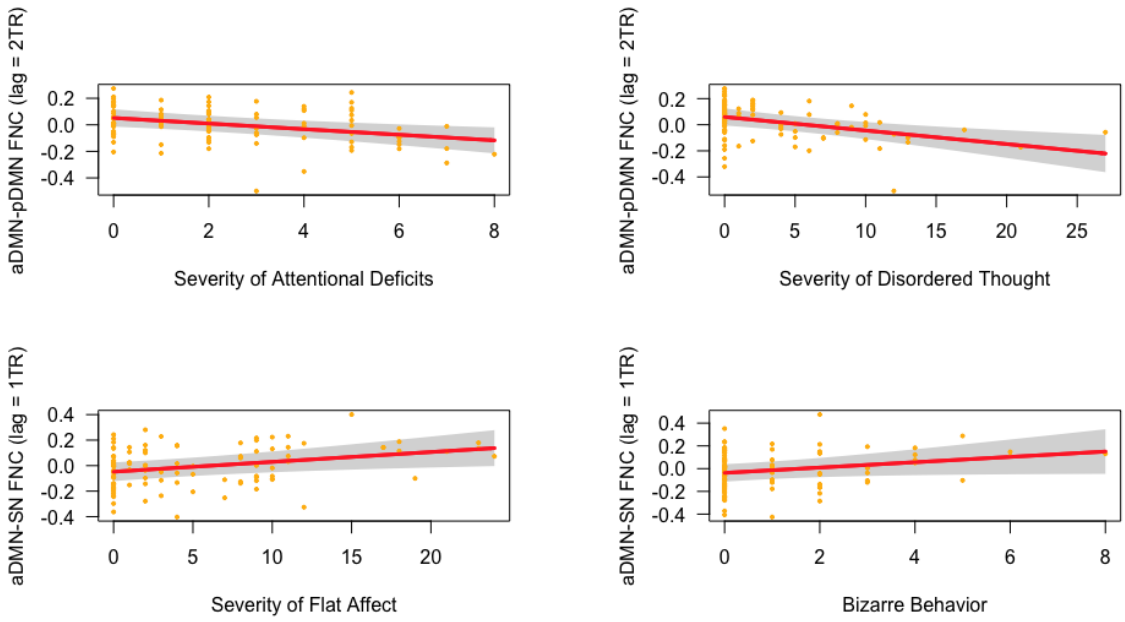

Figure 2.2 Associations Between Symptom Severity and Time-Lag-Shifted Functional Network Connectivity

Partial regression plots showing negative associations between lagged (2TR) aDMN→pDMN connectivity and reported severity of attentional deficits (top left), and thought disorder (top right), in addition to, positive associations between lagged (1TR) aDMN→SN connectivity and severity of flat affect (bottom left) and bizarre behavior (bottom right). Covariates controlled for in the linear model included age, gender, scanning site, and mean framewise displacement.

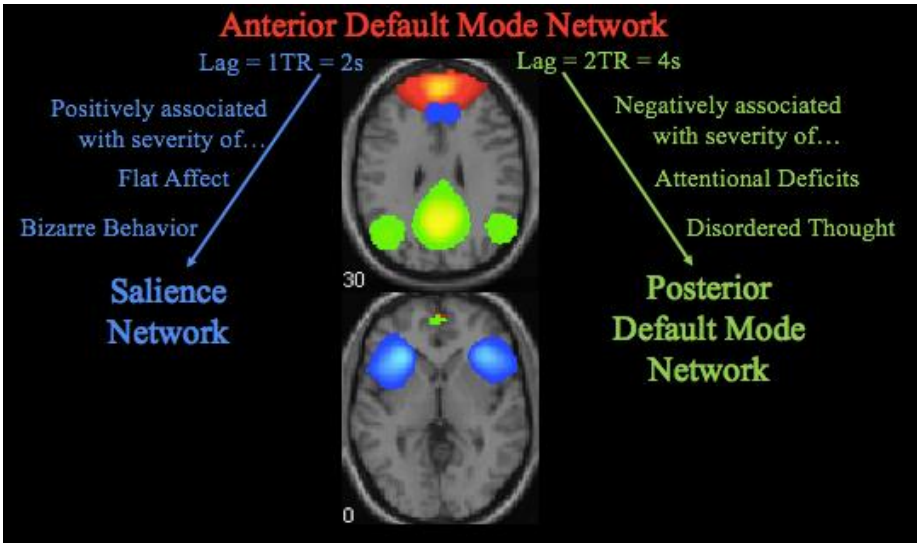

Figure 2.3 Disrupted Anterior Default Mode Network Functional Communication Linked to Positive and Negative Symptoms

Time-lag-shifted FNC between anterior default mode network (red) and salience network (blue) is positively associated with bizarre behavior and severity of flat affect. Meanwhile, time-lag-shifted FNC between anterior default mode network and posterior default mode (green) was negatively associated with attentional deficits and severity of disordered thought. Abbreviations: FNC = functional network connectivity; arrows denote direction of lag and do not imply causal relationships.

3 MODALITY-DEPENDENT IMPACT OF HALLUCINATIONS ON LOW-FREQUENCY FLUCTUATIONS IN SCHIZOPHRENIA

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3.1 Abstract

Prior resting-state functional magnetic resonance imaging (fMRI) analyses have identified patterns of functional connectivity associated with hallucinations in schizophrenia (Sz). In this study, we performed an analysis of the mean amplitude of low-frequency fluctuations (ALFF) to compare resting state spontaneous low-frequency fluctuations in patients with Sz who report experiencing hallucinations impacting different sensory modalities. By exploring dynamics across 2 low-frequency passbands (slow-4 and slow-5), we assessed the impact of hallucination modality and frequency range on spatial ALFF variation. Drawing from a sample of Sz and healthy controls studied as part of the Functional Imaging Biomedical Informatics Research Network (FBIRN), we replicated prior findings showing that patients with Sz have decreased ALFF in the posterior brain in comparison to controls. Remarkably, we found that patients that endorsed visual hallucinations did not show this pattern of reduced ALFF in the back of the brain. These patients also had elevated ALFF in the left hippocampus in comparison to patients that endorsed auditory (but not visual) hallucinations. Moreover, left hippocampal ALFF across all the cases was related to reported hallucination severity in both the auditory and visual domains, and not overall positive symptoms. This supports the hypothesis that dynamic changes in the ALFF in the hippocampus underlie severity of hallucinations that impact different sensory modalities.

3.2 Introduction

Schizophrenia (Sz) is a psychiatric disorder associated with heterogeneous symptoms that impact cognitive, affective, perceptual and motor function. While approximately 59% of Sz patients report experiencing auditory hallucinations (AH), nearly half of those report visual hallucinations (VH).[6] Despite the prevalence of these symptoms, the underlying mechanisms remain elusive.

Resting-state functional magnetic resonance imaging (rs-fMRI) analyses can probe the relation between different aspects of the blood-oxygen-level-dependent (BOLD) signal and behavioral traits. Seed-based functional connectivity (FC) analyses perform voxel-by-voxel comparisons within seed regions and rest on the assumption that voxels with similar temporal profiles (e.g. time series) are functionally *connected*. While FC analyses assess associations between BOLD time series of voxels in different regions, analyses of the amplitude of low frequency fluctuations (ALFF)[98] measure voxelwise fluctuations in the amplitude of BOLD signal in the very low frequencies (typically 0.01-0.08 Hz). ALFF is correlated with baseline cerebral blood flow[3] and is thought to reflect spontaneous, intrinsic neuronal activity.[98–100] It remains unclear how ALFF relates to FC. Di et al.[101] found that regional ALFF correlated with FC of several ROIs (e.g. anterior cingulate, medial prefrontal, precuneus, insula, basal ganglia and thalamus) to other regions. However, ALFF-FC correlations were not uniform across the whole brain, suggesting that increased ALFF does not necessarily translate to increased rs-FC.

Prior studies have investigated rs-FC in Sz patients with hallucinations, yet no studies have investigated the relation between ALFF and hallucinations in Sz. Aberrant patterns of rs-FC with superior temporal gyrus (STG)[13–17], putamen[16] and hippocampus[14,17] are associated with AH in Sz. Resting-state FC differences have also been identified in Sz patients that endorse different

types of hallucinations. Due to AH prevalence in Sz, these studies are designed to assess FC differences across patient groups that endorse both VH and AH vs. patients that endorse only AH. Relative to patients that endorsed only AH, patients that endorse VH and AH show functional hyperconnectivity with subcortical structures including caudate[20], putamen[19], amygdala[18], nucleus accumbens[19], parahippocampus[19], and hippocampus.[18,20]

We posit that Sz patients that endorse AH will have distinct, dynamic patterns of rs-activity in comparison to patients that endorse both VH and AH. To test this hypothesis, we examined the relation between resting-state ALFF and modality-dependent hallucinations in a large, multi-site dataset of Sz cases and controls studied as part of the Functional Imaging Biomedical Informatics Research Network (FBIRN). Specifically, we analyzed *mean* ALFF (e.g. the calculated power of a voxel within the very low frequencies, normalized by the subject's mean within-brain ALFF). By performing voxel-by-voxel (voxelwise) comparisons across the brain, this analysis can potentially provide insight into the link between novel sites of regional variation in patterns of dynamic activity of the BOLD signal within the very low frequencies and the experience of particular symptoms such as VH and AH. Studying hallucinations using ALFF is crucial to contextualize previous findings and to probe the relation between ALFF fluctuations and differences in FC.

Although no previous studies examine the relationship between hallucination modality and ALFF in Sz, a recent study reported that Parkinson's disease (PD) patients with VH showed elevated ALFF in the hippocampus, parahippocampus, inferior parietal lobe, and cerebellum, but decreased ALFF in the occipital lobe, when compared to a non-hallucinating PD patient control group.[102] Relative to controls, Sz patients show elevated ALFF in frontal brain regions and decreased ALFF in posterior (parietal and occipital) regions.[100,103–106] Schizophrenia patients also

show elevated ALFF in parahippocampal cortex[103,106], hippocampus[100,103,104], amygdala[104], insula[104], and medial temporal regions[105] relative to controls. McHugo et al.[100] found that patients had increased hippocampal ALFF relative to controls, but normal hippocampal FC to hubs of the default mode network. One study[105] reported a significant interaction between frequency band (slow-5 vs. slow-4) and group (Sz vs. controls) in the precuneus, inferior occipital gyrus, and thalamus suggesting that observed dynamic changes in low-frequency fluctuations are likely frequency-dependent. Taking this into account, we examined ALFF across the slow-5 [0.01-0.027 Hz] and slow-4 [0.027-0.08 Hz] frequency ranges. Drawing from the FBIRN study[18,104], we aimed to replicate previous findings using this dataset[104] and to determine whether there are frequency-dependent differences in ALFF across three hallucination subgroups with Sz: patients that endorse AH, patients that endorse VH and patients that do not endorse either type of hallucination.

3.3 Methods

3.3.1 Subjects

Data was collected from 143 patients with Sz and 155 healthy control (HC) subjects matched for age, sex, and handedness (Table 1); this is the same resting-state dataset as used in Ford et al.[18] and largely overlapping with Turner et al.[104] and Damaraju et al.[70] Raw imaging data was collected from six sites and written, informed consent was obtained from participants at all sites, including permission to share de-identified data across the centers (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).

The set of diagnostic criteria for inclusion was based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P). To be eligible for participation, Sz must have also been stable on anti-psychotic medication for at least 2 months and were excluded if they showed significant extrapyramidal symptoms. In addition, HCs were excluded if they had a current or past history of major psychiatric illness or had a first-degree relative with an Axis-I disorder.

Additional exclusion criteria for all participants included: history of major medical illness, contraindications for MRI, insufficient eyesight to see with normal acuity with MRI compatible corrective lenses, drug dependence in the last 5 years or a current substance abuse disorder, intelligence quotient < 75 as measured by the North American Adult Reading Test (NAART), and those who moved more than 4mm during scanning.

3.3.2 Grouping of Participants

Sorting of the 143 Sz into clinical subgroups was achieved by evaluating responses to the Scale for the Assessment of Positive Symptoms (SAPS)[73] Item #1 and SAPS Item #6 (Table 1). Item #1 asks if the participant "reports voices, noises, or other sounds that no one else hears", while SAPS Item #6 asks if he/she "sees shapes or people that are not actually present." Each item is scored using a 1 to 5 rating scale [0 = not present; 1 = questionable; 2 = mild; 3 = moderate; 4 = marked; 5 = severe]. The auditory (but not visual) group (AH, n=42) had SAPS Item #1 scores > 1 and SAPS Item #6 scores of zero. The non-hallucinator (NH) group scored zero for both Items, while the visual group (n=40) had SAPS Item #6 scores > 1. Due to prevalence of the symptom of AH in Sz, participants in this subgroup generally reported AH (SAPS Item #1 > 1) in addition to VH (38/40 participants); we refer to this group as the VH+AH subgroup since 95% of those in this group experienced both VH and AH.

3.3.3 Imaging

Data were acquired using five 3T Siemens TIM Trio scanners and one 3T GE MR750 scanner. We used an AC-PC aligned echo-planar imaging pulse sequence (TR/TE 2 s/30 ms, flip angle 77°, 32 slices collected sequentially from superior to inferior, 3.4 × 3.4 × 4 mm with 1 mm gap, 162 frames, 5:38 min:sec) to obtain T2*-weighted images. Subjects were instructed to lie in the scanner with eyes closed; this scan followed an object working memory task with emotional distractors.

3.3.4 Data Pre-Processing

Traditional pre-processing steps were performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox that runs off the REST software platform (http://resting-fmri.sourceforge.net).[75] The first two time frames were removed for all participants to allow for signal stabilization. The data underwent (1) motion correction to first image (2) slice-timing correction to the middle slice, and (3) normalization to MNI space using an EPI template. These normalized images were the input to our ALFF analyses. Framewise displacement (FD) was calculated for each image; FD differentiates head realignment parameters across frames and generates a six dimensional times series that represents instantaneous head motion.[76] We performed a one-way ANOVA on mean FD values for each subject and found significant differences across groups (Table 1). To correct for effects of this confounding factor, we included mean FD as a covariate in our analyses.

3.3.5 ALFF Calculation and Smoothing

ALFF images were computed using REST software.[75] Following linear detrending of the time series, the power spectra were extracted using a Fast Fourier Transform. The ALFF measure at each voxel is the averaged square root of the power across a low-frequency range, normalized

by the mean within-brain ALFF value for that subject. In this study, we analyzed ALFF across the slow-5 (0.01-0.027 Hz) and slow-4 (0.027-0.08 Hz) frequency ranges as in Yu et al.[105] Images were subsequently smoothed with an 8 mm full-width-half-maximum (FWHM) Gaussian kernel.

3.3.6 Statistical Analyses

We analyzed the smoothed ALFF images using a General Linear Model (GLM) with a group factor of four levels (AH, VH+AH, NH and HC). We included site as a dummy variable and age, gender, and mean FD as covariates.[76]

To ensure that these results were not driven by spurious motion and physiological artifacts, we performed an additional analysis using images that underwent standard pre-processing described above followed by regression of 6-motion parameters and mean physiological (white matter and cerebrospinal fluid) signals. Then the ALFF images were calculated followed by smoothing (8 FWHM). We analyzed these smoothed images using an identical GLM to that described above. Thus, in this second analysis, we modeled the impact of motion artifacts on the BOLD signal *prior to* performing group-level analysis in which mean FD was modeled as a nuisance regressor.

Post-hoc t-test contrasts were performed to explore the effect of group on frequency-specific alterations in ALFF. Confidence was a-priori specified at $p < 0.05$, family-wise-error (FWE) corrected, for all comparisons with HC. All t-contrasts were masked with the main effect of group ($p=0.001$, uncorrected).

For the clinical subgroup comparisons (AH vs. AH+VH vs. NH), we also set our confidence at $p < 0.05$, but corrected for multiple (voxel-by-voxel) comparisons by performing a simulation using AFNI 3dClustSim

(http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). This program allows the user to obtain a minimum cluster size threshold for a given alpha significance level. We opted to use this approach for correcting for multiple comparisons (vs. FWE-correction) due to the reduced statistical power associated with these clinical subgroup comparisons. All reported cluster-wise-corrected results are masked with the main-effect of group (p=0.001, uncorrected).

To assess the relation between modality-specific hallucination severity and ALFF, we extracted the eigenvalues for each subject from clusters that were significantly different across the clinical subgroups with hallucinations (AH vs. VH+AH). We performed a multi-level linear regression to assess the respective impact of nuisance covariates (e.g. age, gender, scanning site) (Level 1), positive symptom severity adjusted for the two hallucination (auditory and visual) items (Level 2), VH severity (Level 3), and AH severity (Level 4) on ALFF.

3.4 Results

In this study, we were interested in exploring the effect of hallucination modality on ALFF. The results of our one-way ANCOVA (4-group-levels) revealed a main effect of group (Supplemental Figure 1). First, we summarize the significant results obtained when we compared the pooled Sz group to the HC group. Next, we explore regional ALFF differences between each of the hallucination subgroups and HC to assess if these differences were similar to those found in the HC vs. pooled Sz group comparisons. Finally, we report significant differences in regional ALFF variation across hallucination subgroups.

3.4.1 Patients with Schizophrenia vs. Healthy Controls

Relative to controls, Sz had decreased ALFF in the lingual region, cuneus (BA 17, 18, 19), and right thalamus (Figure 1a), but elevated ALFF in bilateral inferior frontal gyri (IFG)

(BA 45, 47) (Figure 2a). Specifically, across the slow-5 band, patients showed elevated ALFF in the left hippocampus. Full results are summarized in Supplementary Table 1.

3.4.2 Hallucination Modality Subgroups vs. Healthy Controls

Decreased ALFF in hallucination-modality subgroups vs. HC. Similar to the pooled Sz group, both AH and NH groups had decreased ALFF across posterior regions of the brain such as the cuneus and lingual regions (BA 17, 18, 19) relative to HC. The decreased ALFF in the AH group was only seen in the slow-4 passband. These striking differences in anterior-posterior spatial variation of ALFF were not seen in the VH+AH group; VH+AH only showed decreased ALFF in two very small clusters in the occipital lobe when compared to HC. Full results are summarized in Supplementary Tables 2a, 3, and 4a.

Increased ALFF in hallucination-modality subgroups vs. HC. Across the slow-4 passband, the AH group showed significantly elevated ALFF in the right IFG (BA 45, 47) and a small cluster in the inferior temporal lobe in comparison to HC (Figure 2b). VH+AH predominately showed increases in ALFF in Brodmann Area 20 including the left hippocampus and left inferior temporal region in comparison to HC (Figure 3a). The NH group showed no significant increases in ALFF relative to HC. Full results are provided in Supplementary Tables 2b and 4b.

3.4.3 Comparisons Between Hallucination Modality Subgroups

NH vs. hallucination-modality subgroups (AH and VH+AH). Neither VH+AH nor AH groups showed any significant regional ALFF differences across either frequency range, relative to NH.

VH+AH group vs. AH group. The VH+AH group had significantly elevated ALFF in the left hippocampus and left inferior temporal lobe (Table 2a, Figure 3b) relative to AH across both

low-frequency passbands. Across slow-4, VH+AH had decreased ALFF in the right inferior frontal gyrus (BA 45, 46) relative to AH (Table 2b).

3.4.4 Relation to Symptoms

To examine the relationship between left hippocampal ALFF and symptom severity, we extracted ALFF beta-values for each subject within the left hippocampus cluster shown in Figure 3b (cluster-wise corrected results at p=0.05 uncorrected, minimum cluster size = 147 voxels, k =10 voxels) and performed a multi-level linear regression. Reported VH severity (Block 3) and AH severity (Block 4) significantly predicted variability in subject-specific estimates of left hippocampal ALFF, accounting for 7.9% and 5.5% of the observed change in variance respectively (p=0.001 Block 3; p=0.005 Block 4). Nuisance covariates (age, gender, scanning site; Block 1) and positive symptom severity (adjusted for the two hallucination items) (Block 2) did not significantly predict left hippocampal ALFF.

3.5 Discussion

In this first investigation of resting state ALFF and hallucinations in Sz, we identified spatial variations of ALFF in two hallucination-modality subgroups with Sz. Patients in the VH+AH group showed left hippocampal elevations in ALFF when compared to HC and AH groups. Reduced ALFF in the posterior brain relative to HC is strongest in the NH and AH groups, while this reduction is very weak in the VH+AH group.

Yu et al.[105] reported a significant interaction between frequency band (slow-5 vs. slow-4) and group (Sz vs. HC), suggesting that observed changes in the amplitude of low-frequency fluctuations are frequency-dependent. For this reason, we analyzed group differences in ALFF across the slow-5 (0.01-0.027 Hz) and slow-4 (0.027-0.08 Hz) ranges. Consistent with previous findings, Sz had increased ALFF in frontal regions (primarily inferior frontal), but decreased

ALFF in posterior regions (precuneus, cuneus, lingual and other occipital regions) relative to controls. These effects were seen across both slow-5 and slow-4 passbands, although the effect was more robust across slow-4 frequencies. Relative to controls, Sz had elevated ALFF in the left hippocampus; the VH+AH group showed the same pattern of increased hippocampal ALFF relative to controls and the AH group. For the case vs. control comparisons, the observed effects in hippocampus were more robust across the lowest frequencies (i.e. slow-5 passband).

The observed alterations in low-frequency BOLD signal dynamics in the VH+AH group were linked to the general (non-modality-specific) tendency to hallucinate, rather than overall positive symptoms, or VH in particular. The results of a multi-level linear regression showed that reported hallucination severity in both the auditory and visual domains explained a significant amount of the variance, while nuisance regressors (age, gender, and scanning site) and positive symptoms adjusted for these two hallucination items did not significantly account for the observed variability.

Hippocampal/parahippocampal dysfunction has consistently been shown to be associated with the experience of hallucinations. Yao et al. previously reported that Parkinson's disease patients with a history of VH had significantly increased ALFF in the right hippocampus and parahippocampus.[102] Ford et al. reported that Sz patients with VH and AH had hippocampal-occipital hyperconnectivity in comparison to HC and AH groups.[18] Relative to controls, Sz patients with AH show patterns of left STG-left hippocampus hypoconnectivity at rest.[14] A second line of evidence implicating hippocampal/parahippocampal *hypofunction* in the experience of AH comes from symptom-capture studies, which ask the subject to report when he/she is actively experiencing a hallucination during an fMRI scan. Schizophrenia patients showed left parahippocampal *deactivation* directly prior to their reported experience of AH.[107]

Yet, after performing a coordinate-based meta-analysis of 10 AH-symptom-capture studies, Jardri et al. found that the hippocampus showed an elevated likelihood of *increased activation* during the experience of AH.[11]

The oscillation dynamics of the hippocampus and its crucial role in generating theta rhythm underlie its unique ability to coordinate and synchronize activity generated by different neuronal ensembles across the brain.[108] Findings from our study suggest that aberrant hippocampal low frequency fluctuations are linked to hallucinations in Sz. If our findings are generalizable to a broader population, then this might explain why rs-FC studies find evidence favoring both hippocampal *hypo*connectivity and *hyper*connectivity hypotheses of AVH in Sz. Altered amplitudes of hippocampal low-frequency fluctuations may beget *dysregulated* patterns of functional connectivity (e.g. observed patterns of hyperconnectivity observed in some instances and patterns of hypoconnectivity observed in others).

In Sz patients, altered amplitudes of low-frequency fluctuations in the hippocampus may be related to the escalating sensory complexity of the hallucinations (e.g. how many sensory modalities are involved).[19] Rolland et al.[19] found that mesolimbic connectivity patterns changed with escalating sensory complexity of the experiences (e.g. 0, 1, or 2 modalities). Relative to patients that did not endorse hallucinations in any sensory domain and those that endorsed hallucinations solely in the auditory domain, Sz patients that endorsed both VH and AH had significantly elevated parahippocampal, insular and striatal connectivity with the nucleus accumbens, while significant differences in hippocampal connectivity were not found between the pure AH group and NH. The authors took these results to suggest that aberrant hippocampal FC may be related to VH in particular. The results of our regression analyses suggest that observed changes in hippocampal low-frequency fluctuations relate to both VH and AH.

The chosen design features of the present analysis preclude us from directly testing this "escalating complexity" hypothesis; we are unable to assign subjects to "escalating sensory complexity subgroups" with the same rigor as Rolland et al. Notably, the subjects in the Rolland et al. study were more clinically severe than those in the present study (e.g. the researchers required a minimum reported hallucination severity of "marked" or "severe"), and many of the subjects in our study have complex hallucination profiles that preclude us from assigning them to an "escalating complexity" hallucination subgroup (e.g. scoring "questionable" on tactile/olfactory hallucination SAPS items, etc.). Future analyses should gear their experimental design to directly test this novel "escalating sensory complexity" hypothesis. Our current analysis and these proposed future analyses would be in line with proposed initiatives of the 2015 International Consortium on Hallucination Research, which called for progression in research beyond the auditory modality and to analyze hallucinations impacting various different sensory modalities.[109]

To ensure that spurious motion and physiological artifacts did not drive these observed effects, we performed an additional analysis using an identical GLM and data that underwent regression of 6-motion parameters and physiological (white matter and cerebrospinal fluid) signals prior to the ALFF calculation and smoothing. Regressing out these signals prior to group-level analysis (while retaining subject-specific mean FD as a covariate in the GLM) had no significant impact on the major results of this study (Supplementary Figure 2).

There are several limitations of this study. The first relates to potential confounding effects of divergent anti-psychotic treatment trajectories. Duration of illness and the derived standardized chlorpromazine equivalents were variable across Sz patients in this study. To control for these confounding factors, we ensured that hallucination subgroups did not differ

significantly with respect to these two factors (See Table 1). We were also unable to study a clinical group that endorsed exclusively VH. We adopted a research design that made comparisons between a patient group that endorsed AH but not VH and a group that endorsed VH. Due to the prevalence of AH as a symptom of Sz, 95% (38/40) of the patients in the VH group also reported experiencing AH. Notably, the term "VH+AH" is purely reflective of a naming strategy and should not be taken to suggest that we find linear (additive) effects with respect to VH.

A final limitation is the paucity of phenomenological information regarding hallucinatory symptoms; we were only able to work with two questions from a single scale (SAPS). There is heterogeneity associated with phenomenology of the hallucinations, leading some researchers to suggest that there should be subtypes of AH such as *hypervigilance-AH*.[110,111] To date, only two studies with large sample sizes ($n \geq 100$) investigating this phenomenological heterogeneity have been published.[9,112] This limitation highlights the importance of developing and utilizing more in-depth, nuanced assessments that capture phenomenological diversity associated with the experience of hallucinations.

In conclusion, we identified unique spatial patterns of ALFF in two hallucination-modality subgroups with Sz. Our results suggest that altered dynamics in two low-frequency ranges in the left hippocampus may play a crucial role in the development and sustained propensity to hallucinate. To build upon these current findings and more fully elucidate the link between functional dysregulation in regions like the left hippocampus and the experience of hallucinations, future analyses should test novel hypotheses such as the escalating sensory complexity hypothesis[19] and make use of more fine-scaled assessments of VH and AH phenomenology.

3.6 Acknowledgments

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3.7 Chapter 3 Tables

Table 3.1 Demographic and Clinical Information

	AH (n=42)	VH+AH (n=40)	NH (n=61)	HC (n=155)
Demographic Info				
Age	37.8 (11.9)	37.2 (11.3)	40.2 (11.8)	37.8 (11.3)
Gender	32 (m), 10 (f)	30 (m), 10 (f)	44 (m), 17 (f)	110 (m), 45 (f)
Handedness (r/l/a)	36 (r), 5 (l), 1 (a)	33 (r), 5 (l), 2 (a)	61 (r), 0 (l), 0 (a)	146 (r), 7 (l), 2 (a)
Smoking Status	19 (s), 23 (n)	20 (s), 20 (n)	24 (s), 37 (n)	14 (s), 141 (n)
Socioeconomic Status Subject*[a]	50.8 (13.1)	50.7 (13.7)	50.2 (12.7)	33.5 (12.8)
Socioeconomic Status caregiver*[b]	33.8 (14.8)	35.0 (14.2)	37.8 (14.5)	30.51 (14.7)
Subject Motion				
Mean Framewise Displacement[c]	0.44 (0.3)	0.42 (0.3)	0.35 (0.2)	0.30 (0.2)
Patient Population				
Duration of Illness	18.0 (11.0)	17.0 (12.4)	17.3 (11.5)	n/a
Chlorpromazine equiv.(CPZ Woods)[d]	401.1 (443.1)	335.4 (294.6)	367.9 (356.2)	n/a
Total PANSS*[e]	57.7 (12.6)	63.3 (13.4)	54.0 (13.1)	n/a
PANSS-positive*[e]	16.6 (4.5)	17.6 (4.1)	12.9 (4.1)	n/a
PANSS-negative	13.7 (5.3)	15.2 (6.1)	13.9 (4.7)	n/a
Total SAPS*[f]	25.1 (13.3)	40.0 (17.4)	12.1 (12.3)	n/a
Total SAPS adjusted for 2 hallucination items*[g]	21.8 (12.8)	33.9 (16.5)	12.1 (12.3)	n/a

Note: HC, healthy control; AH, auditory hallucinations; NH, non-hallucinator; VH, visual hallucinations; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms

[a]AH, VH+AH, and NH groups all significantly different than HC (Bonferroni post-hoc, $p<0.01$)

[b]NH vs. HC significantly different (Bonferroni post-hoc, $p<0.01$)

[c]AH vs. HC significantly different (Bonferroni post-hoc, $p<0.01$); VH vs. HC significantly different (Bonferroni post-hoc, $p = 0.018$).

[d]We only had this information for a subset of patients; percent reporting = 80.4%

[e]VH+AH vs. NH significantly different (Bonferroni post-hoc, $p<0.01$)

[f]AH vs. NH and VH+AH vs. NH both significantly different (Bonferroni post-hoc, $p<0.01$)

[g]all post-hoc comparisons are significantly different (Bonferroni post-hoc, $p<0.01$)

*Group ANOVA is significant at $p=0.05$

Table 3.2 Visual+Auditory Hallucination Patient Group Increased Relative to Auditory Hallucination Patient Group (VH+AH > AH)

	Cluster Size	MNI coord.	T	Z-score	Hemisphere	Region	BA
Slow-5	174	[-33, -12, -21]	3.99	3.93	Left	Hippocampus	20
		[-42, -30, -27]	2.54	2.52	Left	Inferior Temporal	20
Slow-4	196	[-30, -18, -12]	3.84	3.79	Left	Hippocampus	20
		[-42, -27, -24]	1.98	1.97	Left	Inferior Temporal	20

Table 3.3 Auditory Hallucination Patient Group Increased Relative to Visual+Auditory Hallucination Patient Group (AH > VH+AH)

	Cluster Size	MNI coord.	T	Z-score	Hemisphere	Region	BA
Slow-5	No results pass significance						
Slow-4	179	[51, 45, -3]	3.21	3.18	Right	Inferior Frontal (Pars Orbitalis)	46
		[42, 36, 0]	2.63	2.61	Right	Inferior Frontal (Pars Triangularis)	45
		[57, 33, -9]	2.40	2.39	Right	Inferior Frontal (Pars Orbitalis)	n/a

3.8 Chapter 3 Figures

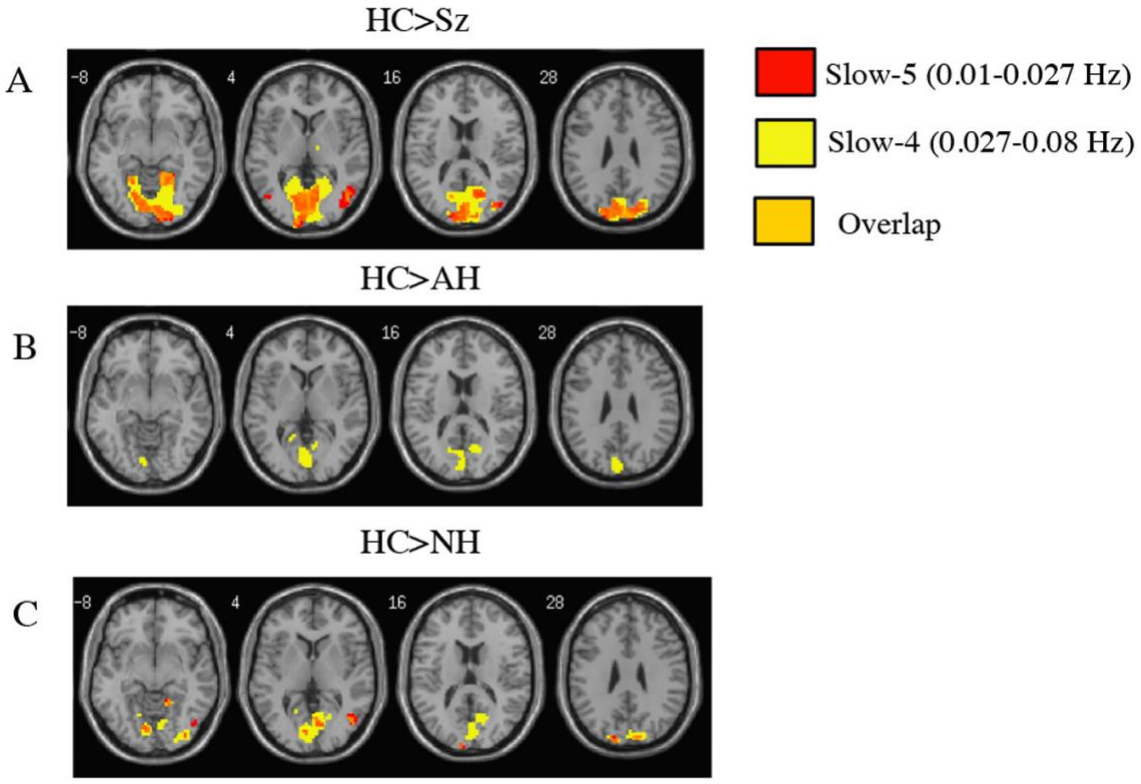

Figure 3.1 Patients with Auditory Hallucinations and Non-Hallucinators Show Similar Decreases in ALFF in the Back of the Brain in Comparison to Healthy Subjects
(A) t-contrast (HC>Sz) (B) t-contrast (HC>AH) (C) t-contrast (HC>NH). This same pattern of reduced ALFF in the posterior brain was not seen in the HC>VH+AH contrasts. All contrasts are thresholded at $p<0.05$, FWE-corrected, masked with the main effect of group ($p=0.001$ uncorrected) with an extent threshold of $k=10$ voxels.

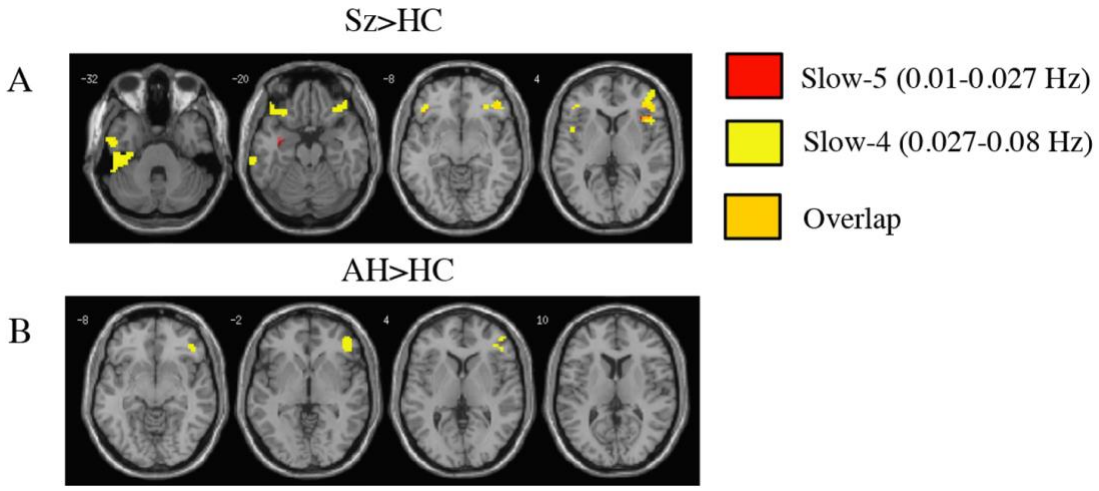

Figure 3.2 The Pooled Sz Group and Patients in the AH group Both Have Increased ALFF in the Right Inferior Frontal Gyrus

(A) t-contrast (Sz>HC) (B) t-contrast (AH>HC). All contrasts are thresholded at $p<0.05$, FWE-corrected, masked with the main effect of group ($p=0.001$ uncorrected) with an extent threshold of $k=10$ voxels.

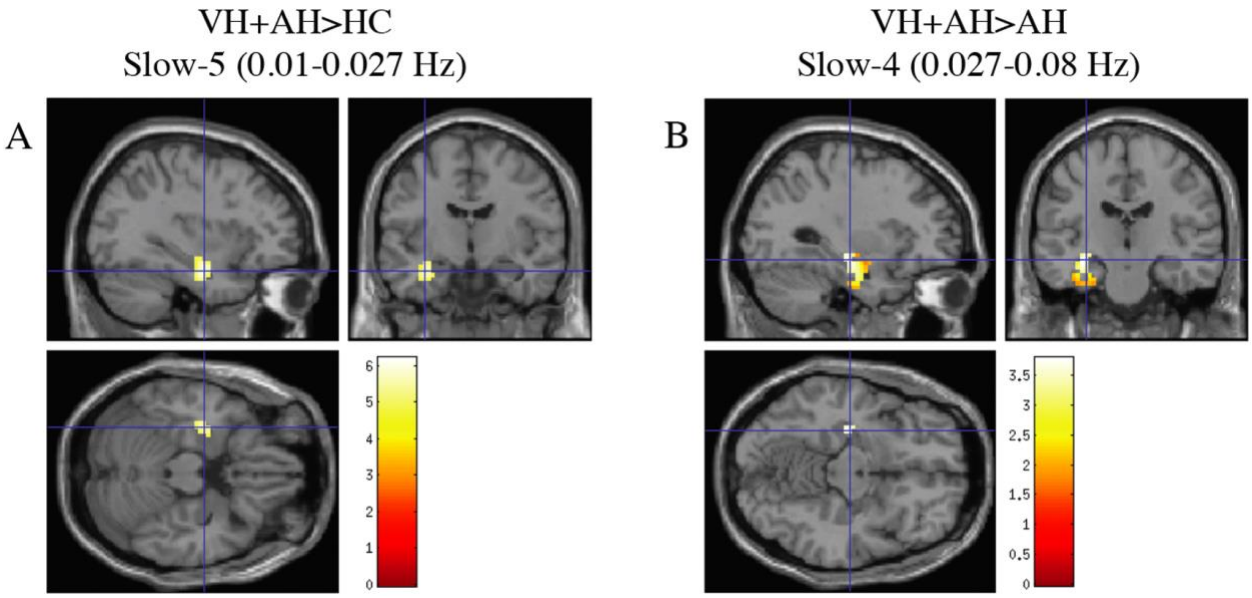

Figure 3.3 Visual Hallucinators Have Significantly Increased ALFF in the Left Hippocampus
(A) t-contrast (VH+AH>HC) across slow-5 passband; $p<0.05$, FWE-corrected, masked with the main effect of group ($p=0.001$ uncorrected) with an extent threshold of $k=10$ voxels. Crosshairs are at global maximum [-33, -9, -21]. (B) t-contrast (VH+AH>AH) across slow-4 frequency band depicting cluster-wise corrected results thresholded at $p=0.05$ (uncorrected) with a minimum cluster size of 147 voxels. Crosshairs are at global maximum [-30, -18, -12].

4 DISRUPTED NETWORK CROSS TALK, HIPPOCAMPAL DYSFUNCTION AND HALLUCINATIONS IN SCHIZOPHRENIA

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4.1 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.

4.2 Introduction

An estimated 59% of patients with schizophrenia (Sz) report auditory hallucinations (AH); nearly half of those reporting AHs also report visual hallucinations (VHs).[6] 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 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[13–18], striatal[16,19,20], insular[17,19], medial frontal[17,20], and parahippocampal/hippocampal[14,17–20] 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).[113,114] 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.[31,32] Dynamic causal modeling and Granger causality analyses suggest the right anterior insula regulates activation/deactivation of the default-mode network (DMN).[33,34] The DMN is associated with internally-directed attention and self-referential processing[51]; 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[37,39,70], 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.[11] 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.[69]

In a magnetoencephalography (MEG) symptom-capture study of AH, transient decreases in hippocampal theta band power (4-10 Hz) preceded reported AHs.[115] Hippocampal theta oscillations are measured in local field potentials of humans[116], and all other mammals studied to date.[117–120] 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).[121–124] 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).[95,108] 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[69]) 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.

4.3 Experimental Materials and Methods

4.3.1 Subjects

We analyzed 294 resting-state fMRI scans from the Functional Biomedical Informatics Research Network (FBIRN) dataset.[71] 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.[69]; Ford et al.[18]; Damaraju et al.[70]). Multiple behavioral/symptom assessments were performed as part of the FBIRN Phase III study including the Scale for the Assessment of Positive Symptoms (SAPS)[73] and the Scale for the Assessment of Negative Symptoms (SANS).[74] 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.

4.3.2 Grouping of Participants

We used the same clinical subgroup sorting strategy used previously in Hare et al.[69] and Ford et al.[18] Sorting of the 141 Sz into clinical subgroups was achieved by evaluating responses to two SAPS items.[73] Item #1 asks if the participant "reports voices, noises, or other sounds that no one else hears," while Item #6 asks if he/she "sees shapes or people that are not actually

present." Each item is scored using a 1 to 5 rating scale (0 = not present; 1 = questionable; 2 = mild; 3 = moderate; 4 = marked; 5 = severe). The AH (but not VH) group (n = 42) had SAPS Item #1 scores > 1 and SAPS Item #6 scores of zero. The non-hallucinator group (NH, n = 60) scored zero for both items, while the VH group (n = 39) had SAPS Item #6 scores > 1. Due to prevalence of AH in Sz, all but two of the participants in the VH subgroup also reported AH (95%). For a subset of analyses, the VH and AH subgroups were pooled to form a hallucinating (HALL) subgroup reporting AH, VH or both.

4.3.3 Imaging

Data were acquired using five 3T Siemens TIM Trio scanners and one 3T GE MR750 scanner using an AC-PC aligned echo-planar imaging pulse sequence (TR/TE 2 s/30 ms, flip angle 77º, 32 slices collected sequentially from superior to inferior, 3.4 x 3.4 x 4 mm with mm gap, 162 frames, 5:24 mins) to obtain T2*-weighted images. Subjects were instructed to lie in the scanner with eyes closed.

4.3.4 Data Processing

Pre-processing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox which runs with the REST software.[75] The first two time frames were removed to allow for signal stabilization. Raw data underwent motion correction to the first image, slice-timing correction to the middle slice, normalization to MNI space, and spatial smoothing with an 8 FWHM Gaussian kernel. Framewise displacement was calculated for each image; framewise displacement differentiates head realignment parameters across frames and generates a 6-dimensional times series that represents instantaneous head motion.[76] To correct for confounding effects of head motion on the fMRI signal, we included mean framewise displacement as a subject-level covariate.

4.3.5 Group Spatial Independent Component Analysis

We performed spatial group ICA using GIFT software.[78] One hundred independent component networks were obtained from the group principal component analysis matrix using the *Infomax* algorithm. The ICA algorithm was repeated twenty times in ICASSO and the most central result was used to ensure stability of estimation. Subject-specific spatial maps and time courses were obtained using back reconstruction implemented in GIFT.[125]

We examined z-transformed spatial maps thresholded at $z > 3$ to identify artifactual RSNs (e.g. "ringing" motion artifacts, spatial maps with peak signal arising from CSF/white matter). Using the method proposed by Allen et al.[126], we discarded components with poor low frequency/high frequency power ratios, and those with stability quotients < 0.85. From the remaining RSNs, nine networks of interest were selected: two visual RSNS, two auditory RSNs, SN, anterior DMN, posterior DMN, bilateral putamen, and bilateral hippocampus (Figure 1, Table 2).

Subject timecourses were detrended and despiked, then filtered with a high frequency cutoff of 0.15 Hz prior to computing FNC correlations; FNC correlations are defined as the pairwise correlations between network time courses. For all FNC analyses, FNC correlations were transformed to z-scores using Fisher's transformation.

4.3.6 Statistical Analyses

Group differences. We performed a two-sample t-test (HC vs. Sz) to explore FNC correlations associated with Sz diagnosis. We examined changes in FNC associated with the general trait to experience hallucinations (AH, VH or both) with a three-group level ANCOVA (HALL, NH, HC); FNC associated with modality-specific hallucinations was explored using a four-group level ANCOVA (VH, AH, NH, HC). Age, scanning site, gender, and mean

framewise displacement were included as covariates. Statistical significance was a priori specified as $p < 0.05$ using a false discovery rate (FDR) correction for multiple comparisons.

Symptom severity & FNC: regression analyses. To test the hypothesis that abnormal FNC between salience and sensory networks underlies modality-specific hallucinations, we performed linear regression analyses of FNC. To ensure that observed associations between AH/VH severity and FNC were not driven or influenced by confounding factors, we modeled effects of nuisance covariates (age, gender, and mean framewise displacement; scanning site was dummy coded and modeled as a random effect). Since nicotine use is 2-3 times higher in Sz than in the healthy population[84], and has been shown to significantly impact brain functional connectivity[85], we examined Spearman correlations between FNC and smoking status (factor with three levels: "never smoker", "ex-smoker", "current smoker") in our sample of 294 subjects. These analyses revealed a significant association between smoking status and SN-STG (BA 22) FNC ($rho = -0.244$, $p < 0.01$), so smoking status was included as an additional covariate.

To confirm that observed effects of VH/AH severity on FNC were not driven by confounding effects of antipsychotic medication, we performed post-hoc regression analyses of FNC, including total chlorpromazine equivalents[83] as an additional covariate. We lacked information to derive chlorpromazine equivalents for 18 Sz subjects, so the mean value of total chlorpromazine equivalents was calculated (based on the available data) and interpolated for those subjects with missing data. For all analyses, confidence was specified as $p < 0.05$.

Hippocampal ALFF & FNC: regression analyses. Voxelwise mean ALFF maps were computed for each subject using REST software[75] as described in Hare et al.[69] The left hippocampal cluster that showed significant ALFF variation across VH vs. AH subgroups in

Hare et al. was saved as a binary mask. Subject-specific weighted ALFF averages within this cluster were derived from the 294 ALFF maps using SPM's MARSBAR utility.

We calculated the relationship between these subject-specific hippocampal ALFF averages and FNC to explore whether the nature and/or strength of ALFF-FNC relationships are different in Sz vs. HC. Only FNC correlations that were significantly different across Sz and HC in the group analysis were examined in these ALFF-FNC regression analyses. First, we examined potential ALFF x diagnosis interactions in a linear regression analysis. Age, gender, mean framewise displacement, and smoking status were included as covariates; scanning site was modeled as a random effect.

To further probe whether the nature and/or strength of ALFF-FNC relationships are different in Sz vs. HC, we explored ALFF-FNC associations in separate analyses of HC and Sz. We modeled effects of hippocampal ALFF on FNC, controlling for confounding influences on FNC (age, gender, mean framewise displacement, smoking status, and random effects of scanning site) in the linear model. Separate regression analyses were performed in HALL and NH to address the question of whether abnormal ALFF-FNC associations are observed in Sz reporting hallucinations exclusively or were also observed in NH patients. We confirmed that observed associations between hippocampal ALFF and FNC were not driven by confounding effects of antipsychotic medication by performing post-hoc regression analyses, including total chlorpromazine equivalents[83] as an additional covariate. Confidence was specified as $p < 0.05$.

4.4 Results

4.4.1 FNC Group Differences

FNC differences between Sz patients and HC. Relative to HC, Sz had higher FNC between STG (BA 22) and hippocampus, and lower FNC between (1) the two STG networks (BA 21, BA 41), (2) STG (BA 22) and visual cortex (BA 17), and (3) STG (BA 41) and SN (see Supplemental Figure 1). For clarity, locations of peak voxels of sensory networks are reported parenthetically.

FNC differences between subgroups of Sz. No significant changes in FNC across hallucination subgroups (NH vs. HALL, NH vs. AH, NH vs. VH, VH vs. AH) survived FDR-correction.

FNC differences between NH and HC. Relative to HC, NH patients showed higher FNC between hippocampus and STG (BA 22), but lower FNC between (1) the two STG networks (BA 22, BA 41), (2) STG (BA 22) and visual cortex (BA 17), (3) STG (BA 41) and visual cortex (BA 17), (4) STG (BA 41) and putamen, (5) STG (BA 41) and SN, and (6) STG (BA 41) and both anterior DMN and posterior DMN (Figure 2).

FNC differences between HALL and HC. Relative to HC, HALL showed higher FNC between STG (BA 22) and hippocampus and between STG (BA 22) and SN, but lower FNC between STG (BA 22) and visual cortex (BA 17) (Figure 2).

4.4.2 Regression Analyses of FNC

Symptom severity & FNC. We observed a significant association between AH severity and FNC between STG (BA 22) and SN ($t = 2.3$, $p < 0.05$); SN-STG (BA 22) FNC was not associated with VH severity, nor total positive/negative symptoms. This association between AH severity and SN-STG (BA 22) FNC remained significant when we included total chlorpromazine

equivalents as an additional regressor in the model ($t = 2.0$, $p < 0.05$). There were no other significant associations between FNC correlations and symptom scores.

Hippocampal ALFF & FNC: HC vs. Sz. We observed significant diagnosis x ALFF interactions on (1) FNC between STG networks (BA 41 and BA 22) ($t = -2.9$, $p < 0.01$) and (2) SN-STG (BA 41) FNC ($t = -3.0$, $p < 0.01$). To ensure that observed effects were not driven by outliers, we re-ran regression analyses after omitting four subjects that had weighted hippocampal ALFF averages exceeding 4 standard deviations from the mean. The diagnosis x ALFF interaction on SN-STG (BA 41) FNC remained significant ($t = -3.0$, $p < 0.01$) while the diagnosis x ALFF interaction on FNC between STG networks (BA 41 and BA 22) did not remain significant ($t = -1.8$, $p = 0.08$).

In HC, hippocampal ALFF was positively associated with FNC between (1) STG (BA 22) and hippocampus ($t = 4.2$, $p < 0.001$), and negatively associated with FNC between (2) the two STG networks (BA 41, BA 22) ($t = -3.1$, $p < 0.01$), and (3) STG (BA 41) and SN ($t = -2.4$, $p < 0.05$). In Sz, hippocampal ALFF was positively associated with SN-STG (BA 41) FNC ($t = 2.2$, $p < 0.05$). This observed association between left hippocampal ALFF and SN-STG (BA 41) connectivity remained significant ($t = 2.2$, $p < 0.05$) when total chlorpromazine equivalents were introduced as an additional covariate in the model.

Hippocampal ALFF & FNC: HALL vs. NH. There were no associations between hippocampal ALFF and FNC in NH patients. In HALL patients ($n = 81$), hippocampal ALFF was positively associated with FNC between the STG (BA 41) and SN ($t = 2.1$, $p < 0.05$). When we included chlorpromazine equivalents as an additional covariate in the regression analysis, the observed association between hippocampal ALFF and SN-STG (BA 41) connectivity remained significant ($t = 2.1$, $p < 0.05$).

4.5 Discussion

This analysis shows higher STG-SN FNC in Sz linked to the trait of experiencing AH. Furthermore, it identifies disrupted patterns of auditory network FNC in Sz and suggests a potential mechanism that may drive these FNC disturbances: hippocampal ALFF. To contextualize these results, we highlight FNC differences in Sz vs. HC before discussing the results of our targeted investigations of AH/VH.

Since convergent evidence from studies examining rs-FC, brain structure, genetics, and neurotransmitters support the hypothesis that Sz is a disorder of brain dysconnectivity[127], we anticipated that Sz would show widespread differences in cross-network communication. Significant increases and decreases in FNC were observed in Sz patients (Supplemental Figure 1), consistent with results from a prior analysis using this dataset.[70] In both studies, Sz had lower FNC between sensory networks, and higher FNC between subcortical and sensory networks. In the present analysis, we observed STG-*hippocampal hyperconnectivity* in patients (Supplemental Figure 1); Damaraju et al.[70] did not include a hippocampal network and observed sensory-*thalamic hyperconnectivity* in Sz patients. While Damaraju et al. investigated FNC linked to Sz diagnosis, a central aim of this study was to identify targeted markers of hallucinations in Sz.

Prior findings support the hypothesis that abnormal salience monitoring underlies AH.[113,114] Reported AH severity correlates negatively with *FC within the SN* (between SN hubs and intrinsic FC of the right anterior insula).[44,46] In addition, SN hubs showed increased FC with dorsomedial prefrontal cortex in patients with AH relative to NH patients.[67] While these studies delineate links between SN dysfunction and AH, changes in SN functional communication are also linked to diverse behaviors and clinical outcomes.[32,128]

In this study, we find that hallucinating patients (98% reporting AH, 48% reporting VH), but not NH patients, had higher FNC between STG (BA 22) and SN relative to HC. Regression analysis revealed that SN-STG (BA 22) FNC was associated with AH severity (and not VH severity nor global assessments of positive/negative symptoms). This targeted association between AH severity and SN-STG (BA 22) FNC provides support favoring the hypothesis that disrupted FNC between SN and associative-auditory cortex underlies AH in Sz.

We predicted that patients with VH would have higher FNC between visual and salience networks relative to all groups. Our failure to detect this anticipated effect could be driven by low statistical power (i.e. only 39 Sz patients reported VH), but might also be interpreted as evidence favoring rejection of the hypothesis that abnormal SN-visual FNC underlies VH in Sz.

Our analyses exploring the relation between hippocampal ALFF and FNC were motivated by theoretical and methodological shortcomings of prior analyses. First, although numerous studies report links between abnormal hippocampal function and hallucinations, the hippocampus remains absent from dominant models of hallucinations including abnormal salience monitoring theories[32,50], and abnormal self-monitoring (forward modeling) theories.[129] Second, while many fMRI studies have examined the neural basis of hallucinations in Sz, fewer studies have used MEG/EEG to examine neurophysiological changes that occur on a millisecond scale.

A rare MEG symptom-capture study found that transient decreases in hippocampal theta band power (4-10 Hz) preceded reported AHs.[115] Slow theta oscillations are thought to play a key role in temporally coordinating local network oscillations in the faster gamma range (> 30 Hz).[95] Fast gamma cycles in local networks can couple to the same theta phase, providing a means for cross-network functional communication. The precise phase and timing information

provided by slow theta rhythms may be essential for coordinating and synchronizing activity across distributed networks.[95,108] In line with this view, we hypothesized that abnormal hippocampal theta oscillations in Sz disrupt normal brain FNC.

Due to fMRI's poor temporal resolution, we were unable to directly test the hypothesis that abnormal hippocampal *theta oscillations* beget changes in brain FNC. Our finding that hippocampal ALFF was associated with different FNC correlations in Sz and HC provides preliminary, indirect support favoring this hypothesis. In HC, hippocampal ALFF was positively associated with FNC between (1) hippocampus and STG (BA 22), and negatively associated with FNC between (2) BA 41 and BA 22 auditory networks, and (3) STG (BA 41) and SN. These findings suggest that the hippocampus may regulate auditory FNC in healthy subjects. In Sz, we observed an abnormal *positive* association between hippocampal ALFF and SN-STG (BA 41) FNC; this association was observed only in Sz reporting AH and/or VH (no significant association was observed in NH). Our findings (summarized in Figure 3a) support a hippocampal binding model of FNC in which abnormal hippocampal oscillations in Sz disrupt normal auditory FNC and beget abnormal functional communication between salience and primary-auditory networks (Figure 3b).

A recent dynamic causal modeling study examined interactions between the left hippocampus, DMN, SN and an executive network in Sz actively experiencing AHs.[130] Hallucination transition periods (e.g. periods of transition from no reported AH to reported AH) were associated with disruptions to all network connections, while active AH periods were associated with left hippocampal input to the SN. The authors speculate that AH are the result of misattributing salience to auditory memory fragments that are brought into consciousness.[131]

Our findings are consistent with this hypothesis, but allow us to glean further insight into the mechanisms that drive salience misattribution. Proper functional communication between hippocampal, salience and auditory networks facilitates our ability to recall auditory memories, tag them as salient, and bring them into consciousness at will. In the case of volitional recall, one anticipates bringing an auditory memory into consciousness, and recognizes it as self-generated. We would expect the phenomenology associated with this type of event to be different from the phenomenology associated with SN-auditory (BA 22) hyperconnectivity that drives abnormal attribution of salience to auditory images, which are brought into consciousness at random. The Sz patient would not anticipate the auditory image(s) being brought into consciousness, and might conclude that the conscious percept was generated by an alien source. In this respect, our SN-auditory hyperconnectivity theory of AH may provide an account of why AHs feel alien.

Finally, our findings link up with neurochemical hypotheses of Sz. One model proposes that hyperactive phasic midbrain dopaminergic responses stem from a loss of inhibitory regulation of hippocampal pyramidal neurons.[132] Phasic dopaminergic signaling plays an essential role in encoding motivational/behavioral salience.[133] The SN contains network hubs in dopamine-rich midbrain regions (e.g. ventral tegmental area, substantia nigra)[31], and may rely on these phasic signals to orient our attention to threats, rewards, and other salient cues. This neurochemical hypothesis predicts that abnormal hippocampal activity may lead to abnormal tracking and monitoring of salient stimuli in Sz, which is consistent with our findings.

There are several limitations of this cross-sectional analysis. We scanned subjects at one point in time, and don't know how neural function changed in patients over the course of the disorder, and whether observed FNC effects reflect chronic dispositions. In this study, we were interested in identifying trait markers of AH/VH, but, we expect that symptoms fluctuate over

the course of the illness; those in the NH group reported neither VH nor AH at the time of the scan, but they might have reported VH and/or AH at earlier time(s). These realities should be considered when developing inferences from these data. Second, patients had chronic schizophrenia; all but eight patients were taking antipsychotic medication at the time of the study. This precluded our ability to control for extraneous effects of antipsychotic medication on FNC by performing separate analyses of patients on medication and those not taking medication. Post-hoc analyses of FNC showed that observed associations with FNC (e.g. symptom-FNC, ALFF-FNC) remained significant after modeling effects of total chlorpromazine equivalents. Particular antipsychotic treatments such as clozapine have been shown to influence brain areas related to default mode.[134,135] We lacked detailed drug information to explore these targeted effects, so this limitation must be acknowledged.

Due to AH prevalence in Sz, we were unable to study VH independent of AH (95% of patients reporting VH also reported AH). However, our results allow us to glean insight into why AHs are roughly twice as prevalent as VHs in Sz. Patients reporting neither AH nor VH show widespread decreases in STG network connectivity relative to HC (Figure 2), suggesting that STG network connectivity is especially vulnerable to disruption in all Sz patients (including those that do not report hallucinations). Future studies should explore the mechanisms that underlie normal STG functional network communication in healthy subjects to better understand how functional communication with STG networks becomes disrupted in Sz.

Finally, low frequency BOLD signal fluctuations (<0.1 Hz) are associated with changes in local field potentials[115], which are driven by voltage-dependent neural oscillations, but also by summed synaptic activities of local networks, fast action potentials, and neuron-glial interactions.[136] Thus, our findings suggest important links between altered *hippocampal activity*

and abnormal FNC in Sz. We speculate that disrupted hippocampal theta oscillations may disrupt functional communication between auditory and salience networks in Sz patients reporting hallucinations, but alternative hypotheses of AH could be proposed. In line with the dynamic causal modeling analysis findings[130], abnormal coupling between hippocampal oscillations and SN oscillations may give rise to the active AH state. Our findings suggest that disturbed oscillatory coupling between salience and auditory networks may play a role in the generation of AHs.

To date, these hypotheses have not been tested. In general, very little is known regarding SN oscillations and their functional/behavioral significance. One study found that reduced insular thickness in Sz was associated with inefficient resetting of frontal theta oscillations[137], while another study reported that Sz patients had abnormally high beta oscillations in the insula in response to task-irrelevant stimuli.[138] Future studies of SN oscillations need to be performed to refine our understanding of how the SN communicates with other functional networks in healthy subjects, and how disrupted SN oscillations may give rise to various symptoms such as hallucinations.

In sum, our findings raise a number of interesting hypotheses and provide *indirect* support favoring our proposed hippocampal binding hypothesis of AH. Innovative fMRI methods are currently being developed that explore FNC dependence on different spectral frequency modes of the BOLD signal.[139] Future studies should use a combination of methodological approaches (including combined EEG/MEG + fMRI approaches) to explore frequency-dependent coupling between salience, hippocampal and sensory networks, and directly test the hypothesis that disrupted *hippocampal theta oscillations* beget changes in functional network communication in Sz.

4.6 Acknowledgments

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4.7 Chapter 4 Tables

Table 4.1 Demographic and Clinical Information

	AH (n=42)	VH (n=39)	NH (n=60)	HC (n=153)
Demographic Info				
Age	37.8 (11.9)	37.1 (11.4)	40.0 (11.8)	37.8 (11.4)
Gender	32 (m), 10 (f)	30 (m), 9 (f)	43 (m), 17 (f)	108 (m), 45 (f)
Handedness (r/l/a)	36 (r), 5 (l), 1 (a)	32 (r), 5 (l), 2 (a)	60 (r), 0 (l), 0 (a)	144 (r), 7 (l), 2 (a)
Smoking Status	19 (s), 23 (n)	19 (s), 20 (n)	24 (s), 36 (n)	14 (s), 139 (n)
Socioeconomic Status Subject* [a]	50.8 (13.1)	51.2 (13.6)	50.2 (12.7)	33.5 (12.7)
Socioeconomic Status caregiver*	33.8 (14.8)	35.4 (14.1)	37.6 (14.6)	30.4 (14.7)
Subject Motion				
Mean Framewise Displacement[c]	0.44 (0.3)	0.42 (0.3)	0.35 (0.2)	0.29 (0.2)
Patient Population				
Duration of Illness	18.0 (11.0)	16.9 (12.5)	17.0 (11.4)	n/a
Chlorpromazine equiv.(CPZ Woods)[d]	401.1 (443.1)	335.4 (294.6)	367.9 (356.2)	n/a
Total PANSS*[e]	57.7 (12.6)	63.6 (13.5)	54.2 (13.1)	n/a
PANSS-positive*[e]	16.6 (4.5)	17.8 (4.1)	13.0 (4.1)	n/a
PANSS-negative	13.7 (5.3)	15.3 (6.1)	13.9 (4.8)	n/a
Total SAPS*[f]	25.1 (13.3)	40.0 (17.4)	12.1 (12.3)	n/a
Total SAPS adjusted for 2 hallucination items*[g]	21.8 (12.8)	33.9 (16.5)	12.1 (12.3)	n/a

Note: HC, healthy control; AH, auditory hallucinations; NH, non-hallucinator; VH, visual hallucinations; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms

[a]AH, VH, and NH groups all significantly different than HC (Bonferroni post-hoc, $p<0.01$)

[b]NH vs. HC significantly different (Bonferroni post-hoc, $p<0.01$)

[c]AH vs. HC significantly different (Bonferroni post-hoc, $p<0.01$); VH vs. HC significantly different (Bonferroni post-hoc, $p = 0.018$).

[d]We only had this information for a subset of patients; percent reporting = 80.4%

[e]VH vs. NH significantly different (Bonferroni post-hoc, $p<0.01$)

[f]AH vs. NH and VH vs. NH both significantly different (Bonferroni post-hoc, $p<0.01$)

[g]all post-hoc comparisons are significantly different (Bonferroni post-hoc, $p<0.01$)

*Group ANOVA is significant at $p=0.05$

Table 4.2 Nine Networks: Characteristics of Spatial Maps

	Location of Peak Voxel in Group Aggregate Spatial Map	**MNI coordinates of peak voxel**	**Other Regions Included in Z-thresholded Aggregate Spatial Map (Z > 3)**
Network 1	Right Calcarine/Cuneus (BA 17)	[9, -84, 9]	Superior/Middle Occipital (BA 18), Precuneus/PCC (BA 30)
Network 2	Middle Occipital (BA 18)	[27, -96, 0]	Precuneus, Calcarine (BA 17)
Network 3	Right Putamen	[30, -3, 0]	Cerebellum, Anterior Lobe/Vermis
Network 4	Left Hippocampus (BA 20)	[-30, -9, -18]	Parahippocampal Gyri, Left/Right Amygdala, Anterior Cerebellum (Dentate)
Network 5	Left Superior Temporal (BA 41)	[-42, -33, 15]	Opercular/Insular Cortex; Superior Temporal (BA 22)
Network 6	Right Superior Temporal (BA 22)	[60, -18, -6]	Middle Temporal (BA 6, 21)
Network 7	Medial Frontal (Interhemispheric) (BA 9)	[0, 51, 39]	Superior Frontal (BA 32)
Network 8	Left Precuneus (BA 23)	[-6, -54, 27]	Left/Right Angular Gyrus (BA 39); Medial Frontal (BA 10)
Network 9	Left Insula	[-30, 24, -6]	Dorsal Anterior Cingulate, Middle Cingulate (BA 32); Medial Frontal (BA 9)

4.8 Chapter 4 Figures

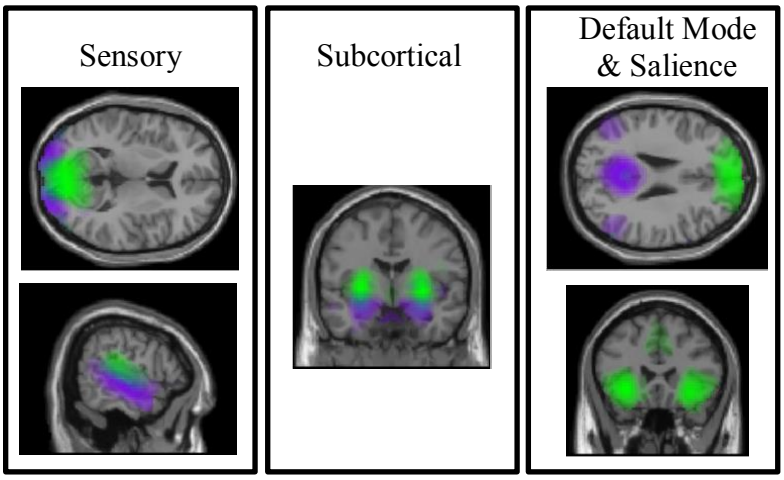

Figure 4.1 Networks

Nine networks were selected based on their putative involvement in the generation of auditory and visual hallucinations. Different colors (green/purple) depict distinct resting-state networks. Top left: two visual networks; bottom left: two auditory networks; middle: subcortical networks (hippocampus in purple, putamen in green); top right: default mode network (anterior shown in green and posterior shown in purple); bottom right: salience network. All spatial maps were thresholded at $Z > 3$.

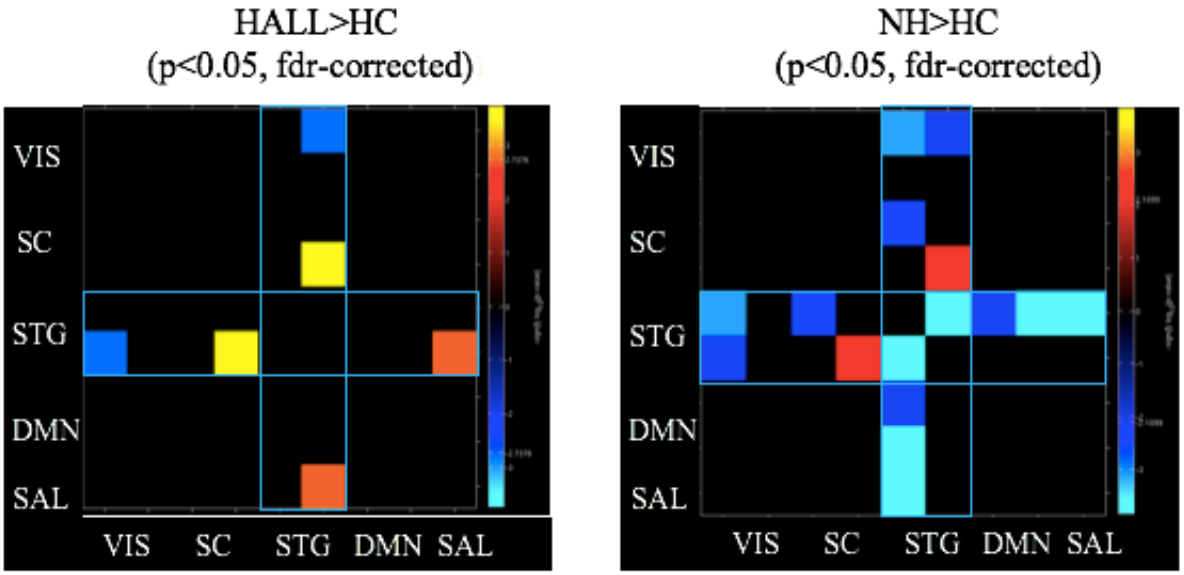

Figure 4.2 Altered Superior Temporal Network Connections in Hallucinating and Nonhallucinating Patients

Warm (yellow/red) colors depict areas of increased network connectivity in patients while cool (blue) colors depict network connectivity that is decreased in patients relative to controls. Relative to healthy subjects, both patient groups show significantly increased connectivity between the STG and hippocampus; hallucinators show elevated connectivity between STG and salience network, while nonhallucinating patients show widespread decreases in STG network connectivity. All significant group differences occur with STG networks (outlined in blue rectangles). VIS: visual networks; SC: subcortical networks; STG: superior temporal gyri; DMN: default mode network; SN: salience network.

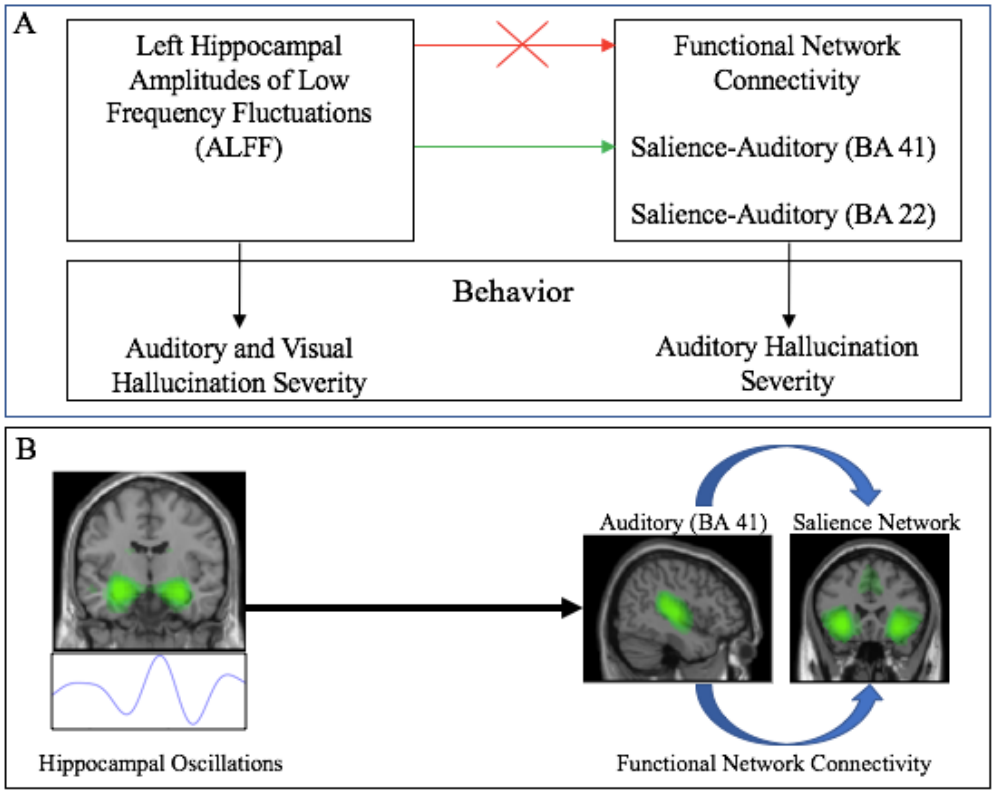

Figure 4.3 Abnormal Hippocampal Activity and Functional Communication Between Salience and Auditory Networks in Schizophrenia

(A) Reported VH and AH severity are associated with left hippocampal ALFF (Hare et al. 2017), while AH severity is associated with salience-auditory (BA 22) FNC. In schizophrenia, there is a loss of normal relationships between hippocampal ALFF and FNC found in healthy subjects (red arrow). In hallucinating (HALL) patients, there is an abnormal positive association between hippocampal ALFF and FNC between salience and auditory (BA 41) networks (green arrow). (B) These results favor an abnormal hippocampal binding model in which disrupted hippocampal oscillations beget a loss of normal FNC in schizophrenia patients, and may drive abnormal FNC between salience and auditory networks. ALFF: amplitudes of low frequency fluctuations; AH = auditory hallucination; FNC = functional network connectivity; VH = visual hallucination

5 GENERAL DISCUSSION

5.1 Summary

My dissertation research combined resting-state fMRI approaches to identify underlying mechanisms of Sz symptoms, with a central focus on delineating functional biomarkers of hallucinations in Sz. Here, I discuss the results and significance of two exploratory analyses (Sections 5.2, 5.3), followed by a hypothesis-driven analysis of hallucinations in Sz (Section 5.4). My findings suggest there are three key players in the generation of AH: auditory cortex, the salience network (SN), and hippocampus. Drawing on this research, I propose novel theories of AH grounded in abnormal salience monitoring (Sections 5.5, 5.6), while reflecting on translational applications of this research (Section 5.8).

5.2 Time-Lag Shifted Network Connectivity & Symptoms

Prior findings suggest that traditional (zero-lag) FNC analyses may be ill-equipped to detect time-varying communication between different brain regions as well as group differences in communication between regions.[46] My first analysis explored whether and how FNC between SN and DMN might relate to specific Sz symptoms. The study revealed that Sz patients had more severe cognitive disturbances (attentional deficits and disordered thought) to the extent that (4-second) lagged functional communication between DMN hubs was reduced. Attentional deficits were predominately associated with posterior DMN functional communication, which is consistent with prior studies that implicate posterior cingulate cortex in attentional processing.[140] These results also suggest that proper functional communication between DMN hubs may be critical for organizing and combining individual thoughts into coherent, meaningful utterances. Yet, precise links between DMN hub functional communication and specific symptoms such as derailment (e.g. where the patient's ideas slip off topic) remain unknown.

A major goal of my dissertation research was to identify links between Sz symptoms and SN dysfunction. The SN acts like the brain's spotlight, helping us monitor what is important (e.g. a broad range of biologically-salient, motivationally-salient, and socially-salient stimuli). Through its interactions with the DMN and fronto-parietal networks, the SN can quickly shift our attention to what matters most. Since prior studies predominately reported links between SN function and positive symptoms[44,46,67], I hypothesized that time-lag-shifted functional communication between SN and DMN would be associated with positive symptoms. Running counter to this hypothesis, I found that flat affect was more pronounced in patients to the extent that anterior DMN activation preceded SN activation. Also running counter to this hypothesis, no significant associations were observed between SN connectivity and hallucination severity. However, this null finding may be due to the fact that key networks implicated in hallucinations (e.g. sensory cortex, hippocampus, putamen, etc.) were not included in the FNC analysis.

5.3 Hypothesis I: Abnormal Resting-State Hippocampal Activity is Associated with Hallucinations

Prior analyses of hallucinations explored the degree of coherence of BOLD activity in different regions or networks of interest. My second analysis explored potentially novel sites of variation in BOLD low-frequency power (< 0.08 Hz) associated with hallucinations. Rather than identifying novel brain regions associated with hallucinations, the results confirmed that the hippocampus is a key player in the generation of hallucinations. Resting-state ALFF in the left hippocampus was elevated in patients reporting VHs relative to clinical and healthy control groups. Further, left hippocampal ALFF was *positively* associated with VH severity in a post-hoc regression analysis (and was not associated with overall positive/negative symptoms). Based on the results of the group analysis, I predicted that left hippocampal ALFF would be associated

with VH severity, but not AH severity. Unexpectedly, left hippocampal ALFF was *negatively* associated with AH severity. These results suggest that modality-dependent hallucinations may be driven by dysregulated hippocampal activity; excessive activity may produce VHs, while diminished activity may produce AHs.

Hippocampal structure and function is abnormal in Sz.[141] In the context of studies of hallucinations, the left hippocampus shows the highest likelihood of activation during the active AH state.[11] A recent dynamic causal modeling study examined interactions between the left hippocampus, DMN, SN and a fronto-parietal network in Sz actively experiencing AHs.[130] In the study, active AHs were associated with left hippocampal input to the SN.

A major shortcoming of this study was that it failed to incorporate the auditory cortex into the network model of the active AH state. Another recent symptom-capture study found that activity in a bilateral auditory/posterior language network was positively correlated with active AH periods.[142] To successfully explain AHs, critical contributions of the auditory cortex must be incorporated into causal models.

5.4 Hypothesis II: Auditory Hallucinations Arise from Elevated Resting-State Communication Between Salience and Auditory Networks

Of the three theories of AHs discussed in Chapter 1, only predictive coding theories incorporate auditory cortex into causal models of AHs. Individuals with Sz may hear voices and other sounds, because the SN signals that internal stimuli (e.g. memories of voices, and/or inner speech) are salient. In line with this view, I hypothesized that resting hyperconnectivity between auditory and salience networks may be associated with AHs. The results of the final analysis (Chapter 4), are consistent with this hypothesis. Relative to healthy subjects, Sz reporting AHs had elevated connectivity between the SN and associative auditory cortex. Functional

connectivity between these networks was exclusively associated with AH severity (and not VH severity nor global positive/negative symptom severity), suggesting that hyperconnectivity between SN and auditory cortex during rest may be a targeted biomarker of the AH trait.

Northoff (2014) theorized that AHs may arise from elevated rs-FC between DMN and auditory networks.[49] Elevated DMN-auditory FNC was not observed in either Sz subgroup (HALL, NH), providing initial support favoring rejection of this hypothesis. In addition, I predicted that patients reporting VHs would have elevated SN-visual FNC relative to patients reporting AH (but not VH) and healthy controls, but did not observe the anticipated effect. This null finding provides preliminary support favoring rejection of the hypothesis that abnormal SN-visual FNC underlies VH in Sz.

5.5 Linking Hippocampal, Auditory, and Salience Dysfunction: A Hippocampal Binding Model

My findings suggest that the hippocampus, auditory cortex, and SN are all key players in the generation of AHs. But, what role do each of these networks play in the generation of AHs? Answering this question requires critical reflection on the functional and behavioral significance of activity in each of these networks. The hippocampus is widely recognized for its contributions to learning and memory processes. On this view, hippocampal dysfunction in Sz may be linked to abnormal learning and memory in Sz patients. But development of compelling multi-networks models of hallucinations may require us to think outside the box when it comes to the hippocampus. To build a multi-network model of AHs, we must consider underlying mechanisms that facilitate hippocampal functional communication with other networks.

My proposed hippocampal binding model of hallucinations (Chapter 4) draws on what is currently known about the function(s) of frequency-dependent hippocampal oscillations.

Hippocampal theta oscillations provide essential phase and timing information for synchronizing activity across distributed networks.[95,108] An appropriate balance of hippocampal activity may be required to regulate cross-network functional communication. In line with this view, I hypothesized that abnormal hippocampal theta oscillations in Sz – measured indirectly as hippocampal ALFF – disrupt brain FNC. As predicted, hippocampal ALFF was associated with cross-network connectivity in healthy subjects, but not in NH patients. Further, hippocampal ALFF was positively associated with FNC between salience and auditory networks in HALL patients, but negatively associated with FNC between these networks in healthy control subjects. This interesting interaction led me to propose a novel hippocampal binding model in which disrupted hippocampal oscillations beget a loss of normal FNC in Sz and may drive abnormal salience-auditory FNC in Sz patients reporting AHs (Chapter 4, Figure 3b).

Notably, hippocampal ALFF does not measure neural oscillations on a millisecond scale; spontaneous BOLD signal fluctuations serve as an indirect measure of hippocampal activity. While the hippocampal binding model is an interesting hypothesis, the present findings can only provide preliminary, indirect support favoring the hypothesis. Future investigations should directly test this hypothesis using EEG/MEG methods with improved temporal precision.

5.6 Linking Hippocampal, Auditory, and Salience Network Function: Alternative Explanations

Regardless of whether the hippocampal binding model is validated (or refuted) by future testing, alternative theories and hypotheses should be developed that explain why hippocampal, auditory, and salience networks are all implicated in the generation of hallucinations. Development of a robust, multi-network model of AHs requires a foundational understanding of

individual network function(s), but also an understanding of the shared functional roles that these three networks play in signaling prediction error and salience monitoring.

5.6.1 Prediction Error: Auditory and Hippocampal Networks

The auditory cortex and hippocampus both play essential roles in monitoring and signaling prediction errors. Self-monitoring theorists emphasize the role that the auditory cortex plays in signaling prediction errors.[27] Predictions (conveyed by efference copies) are weighed against actual sensory feedback; this allows us to develop models about ourselves and the world, and to update those models when we receive new or unexpected information.

These predictions are powerful for at least two reasons. First, efference copies tag self-generated actions, and convey a sense of agency (e.g. the unshakeable sense that *I am* walking, talking, etc.). Second, predictions regulate activity in sensory systems. Activity in the primary auditory cortex is attenuated when healthy adult human subjects hear themselves speak.[23] A later EEG study manipulated the feedback subjects received during the speech task, and confirmed that the auditory dampening effect is maximal when the auditory feedback is unaltered (e.g. when subjects hear their own unaltered voice and not a pitch-shifted or alien voice).[24] This is thought to occur because an efference copy conveys a prediction that attenuates auditory responses to sounds predicted by the model (e.g. one's own speech).

Activity in the human auditory cortex is also attenuated when subjects manually generate non-speech sounds (via button press).[143,144] The cellular correlates of these auditory attenuation effects in human EEG/MEG studies were recently explored in mice that were trained to generate noise bursts by pressing a lever.[145] As expected, responses of auditory cortical neurons were attenuated on self-generated trials relative to trials where noise bursts were played at random, unpredictable intervals.

In the same study, similar effects were observed in hippocampal neurons. On self-generated trials, hippocampal neurons were nearly silent, but there was a spike in activity on unpredictable trials. These findings are consistent with the hypothesis that the hippocampus detects (mis)matches between sensory input and predictions generated from associative retrieval of past experiences.[146] Functional MRI studies provide additional support favoring this hypothesis.[147,148] In one study[147], subjects were first presented with a string of four objects, followed by a second presentation of the stimuli either (1) in a completely different order, or (2) maintaining the order of the first two objects, and reversing the last two objects. The left hippocampus responded maximally in the second case (e.g. when predictions about the next object in the sequence were violated), suggesting that the hippocampus may detect mismatches between associative representations and sensory input.[147] A more recent fMRI study also reported that the hippocampus was responsive to perceptual prediction errors.[148]

Consideration of the shared contributions of hippocampal and auditory networks in predictive coding many shed light on a seemingly puzzling finding. Regardless of whether Sz patients endorsed hallucinations as a symptom, they had elevated FNC between auditory and hippocampal networks relative to healthy controls (Figure 5.1B). Resting-state hyperactivity in hippocampal and auditory networks may stem from prediction failures in Sz (e.g. failures to generate, monitor or convey predictive signals). Spikes in auditory and hippocampal activity during rest may reflect hyperactive prediction error signals stemming from prediction failures in Sz. This may explain why Sz patients (regardless of hallucination status) have elevated functional communication between hippocampal and auditory networks during rest.

5.6.2 Multiple Levels of Salience Monitoring: Neurochemistry to Networks

Salience monitoring relies on coordinated signaling and functional communication of multiple networks, with an essential contribution from midbrain dopamine neurons. Active dopamine neurons have two firing modes: tonic (ongoing) firing or phasic (burst) firing. Until recently, phasic firing of midbrain dopamine neurons was thought to encode expected rewards and reward prediction errors exclusively.[149] But a recent non-human primate study found that some subpopulations of midbrain dopamine neurons responded selectively to reward-predicting stimuli, while others were excited by both reward-predicting and aversive-predicting events (e.g. air puffs).[150] These findings are consistent with the hypothesis that midbrain phasic dopamine signaling plays an all-purpose functional role in encoding motivational/behavioral salience.[133]

The hippocampus regulates phasic dopamine signaling. In rats, neonatal lesions to the ventral hippocampus (corresponding to anterior hippocampus in humans) produces Sz-like symptoms and a midbrain hyperdominergic state that emerges later in adulthood.[132,151] Researchers were initially puzzled by the observed association between early hippocampal damage and hyperdopaminergia, but the circuits regulating phasic dopamine neurons are now better understood. Phasic responses of VTA dopamine neurons are held under tight regulation by GABAergic inputs from the ventral pallidum in the basal ganglia.[132] Hippocampal glutamatergic projections activate neurons in the ventral striatum (e.g. nucleus accumbens), which inhibit neurons in the ventral pallidum. On this model, activity in the hippocampus is required to release midbrain dopamine neurons from inhibition (Figure 5.1A).[132] The model predicts that hippocampal hyperactivity begets hyperactive phasic midbrain dopamine signaling. But lesion studies show that a lack of hippocampal activity during development also produces a midbrain

hyperdopaminergic state.[151] Together, these findings demonstrate that the right balance of hippocampal signaling is required to regulate phasic responses of midbrain dopamine neurons.

Compelling salience-monitoring models must bridge levels of analysis. The SN contains hubs in dopamine-rich midbrain regions (VTA; substantia nigra).[31,32] This finding suggests that the SN relies on phasic midbrain dopamine signals to detect salient stimuli, and raises a number of interesting questions: How are midbrain signals conveyed to the more expansive SN? How do central SN hubs (anterior insula and dorsal anterior cingulate) integrate these signals that carry important information about proximal salience? Future studies should bridge neurochemical and functional-network levels of analysis to address these important questions. For example, future studies of rodent models should explore the effects of targeted pharmacological interventions designed to selectively alter activity of specific subcortical neuron (e.g. hippocampal, striatal, and midbrain) populations. In addition, future positron emission tomography (PET) imaging studies of (midbrain and striatal) dopamine signaling in human subjects will be needed to address the basic question of how dopaminergic signals are conveyed to the expansive SN.

5.7 Advantages of Proposed Models of AH

In patients reporting AHs, the SN was hyperconnected to an associative auditory network, which is consistent with an abnormal salience monitoring model of AHs in Sz (Figure 5.1C). There are several advantages of adopting this model. First, this model may help us bridge levels of analysis. My proposed model (Figure 5.1C) provides an account of how changes in neurochemical signaling (e.g. phasic midbrain dopamine signaling) might relate to observed changes in functional network communication (e.g. aberrant SN activation and functional communication).

Second, an aberrant salience monitoring model of AH is compatible with aberrant prediction error models of AH. Prior research suggests that SN hubs are responsive to rewarding and aversive prediction errors.[152] If we assume that *one of the functions of the SN* is to monitor prediction errors, then SN hyperactivity might be driven by hyperactive prediction error signaling (in regions like the hippocampus, auditory cortex, etc.). But the SN monitors more than prediction errors; this network responds to wide-ranging stimuli — from states of metabolic stress and hunger[153] to viewing pictures of loved ones.[154] Rather than treating a predictive coding account of AHs as a mutually-exclusive theory, my theory accounts for predictive coding deficits, considers their impact on network signaling and functional communication, and builds all of this into a compelling, multi-network model of AHs.

A final attractive feature of abnormal salience monitoring theories more generally is their explanatory depth. As a general theory of psychopathology, abnormal salience monitoring theories explain wide-ranging symptoms including delusions, disorganized thought/behavior and psychomotor poverty.[32,128] For instance, SN hyperactivity while watching TV might beget the delusional thought that a news anchor is sending personal messages. On the other hand, SN hypoactivity may explain symptoms such as apathy, diminished emotional responses, and social withdrawal. Thus, there are several advantages of adopting an aberrant salience monitoring model of AHs.

5.8 Future Treatments

In over 25% of cases, AHs remain resistant to antipsychotic treatments.[10] Antipsychotic drugs competitively bind to dopamine receptor subtypes (D2, D3, D4) with varying affinities to block binding of endogeneous dopamine in the striatum. There are several reasons that antipsychotics may be ineffective at treating Sz symptoms. Prolonged exposure may lead to

decreased sensitivity of targeted circuits over time, and relapse of symptoms. In addition, side effects of the drugs often lead to non-compliance.

Researchers have used non-invasive techniques such as transcranial magnetic stimulation (TMS) to stimulate cortical structures just underneath the scalp. Early studies exploring TMS effects on cortical excitability consistently found that low frequency (1 Hz) TMS applied for extended durations (> 15 minutes) reduced cortical excitability.[155] A small pilot study[156] applied 1 Hz stimulation to left temporoparietal cortices of three Sz patients. Following extended (16 minute) stimulation, AH severity was significantly reduced in all three patients relative to the sham condition; two out of the three patients reported that the voices had disappeared completely. Since this pilot study, subsequent TMS studies have targeted regions essential for speech perception which span the left posterior portion of the superior temporal gyrus (e.g. Wernicke's area), extending into the left inferior parietal cortex. Recent reviews conclude that 1 Hz TMS applied to the left temporoparietal cortex is generally successful at treating verbal hallucinations in Sz.[157,158]

The results of my dissertation analyses may elucidate novel sites for TMS treatment of AHs. Functional communication between the associative auditory cortex (containing Wernicke's area) and the SN was elevated in Sz patients reporting AHs (Figure 5.1C). Prior neuroanatomical analyses reveal that the auditory cortex (including Wernicke's area) and anterior insular hub of the SN are directly connected by white matter pathways.[59,61] Given these findings, researchers might consider applying low-frequency TMS to auditory-anterior insular white matter pathways to reduce excitability. However, important caveats must be considered. Traditional TMS coils can only stimulate surface cortical structures. Deep TMS has been developed to stimulate deeper structures, but deeper stimulation comes at the cost of more diffuse (e.g. less targeted)

stimulation. This trade-off must be kept in mind, as advancing research informs potentially novel treatment sites.

Finally, we might consider novel strategies to restore appropriate hippocampal signaling in Sz patients reporting hallucinations, but there are various challenges. Given the limitations of deep TMS discussed above, it is not likely that deep TMS will be able to selectively target hippocampal activity. Taylor et al.[158] recently discussed promises and challenges of more invasive strategies such as deep brain stimulation (DBS), which might restore the right balance of hippocampal activity. However, several caveats must be considered. First, as an invasive technique, DBS introduces various ethical and safety concerns.[158] Second, restoration of appropriate hippocampal signaling hinges on a variety of factors including prior drug exposure. The alpha-5 GABA receptor subunit is selectively expressed and concentrated within dendrites of hippocampal pyramidal cells.[159] Drugs developed to target this system have been ineffective at treating symptoms in the clinic.[160–162] This failure may stem from long-term effects of anti-psychotic treatment, including increased trafficking of dopamine receptors and associated dopamine hypersensitivity.[132]

Traditional (open-loop) DBS technologies allow physicians to enter a fixed set of stimulation parameters, but closed-loop DBS allows for dynamic updating of stimulation parameters based on evolving neurophysiological states of individuals.[163] Closed-loop DBS of the hippocampus for Sz patients with AHs may be a promising avenue for future research. For instance, phasic midbrain dopamine responses could inform dynamic updating of hippocampal stimulation parameters, circumventing certain limitations associated with static pharmacologic and stimulation approaches.

5.9 Future Directions

While these research findings advanced our understanding of the neural mechanisms underlying hallucinations in Sz, several questions remain unanswered. First, why are auditory hallucinations so common in Sz? The final analysis (Chapter 4) revealed that both patients reporting AHs and nonhallucinating patients had altered functional communication with auditory networks relative to healthy controls. Patients reporting AHs had elevated functional connectivity between salience and auditory networks, but nonhallucinating patients showed widespread decreases in auditory cortex functional connectivity. Future studies should explore why auditory cortex functional communication is especially vulnerable to disruption in Sz.

No significant alterations in functional connectivity were observed between salience and visual networks in Sz patients reporting AH. Visual hallucinations are reported by patients with Parkinson's disease, a neurodegenerative disorder that impacts striatal dopamine neurons. In addition, two resting-state fMRI studies of Sz patients reported links between VHs and striatal hyperconnectivity.[19,20] These results provide preliminary support favoring the hypothesis that a predominate cause of VH is abnormal striatal function. Future research must address the questions of whether there are distinct biological underpinnings of VHs, and whether stand-alone causal models of VHs need to be developed.

Finally, we need to improve our understanding of how the SN functionally communicates with functional networks including sensory networks. Preliminary studies have explored the anterior insula's role(s) in multi-sensory attention[164], and auditory processing[59], but future research is needed to develop a comprehensive understanding of how the SN integrates information and directs attention. This knowledge can be applied to better understand how disrupted SN functional communication may give rise to Sz symptoms such as hallucinations.

5.10 Chapter 5 Figures

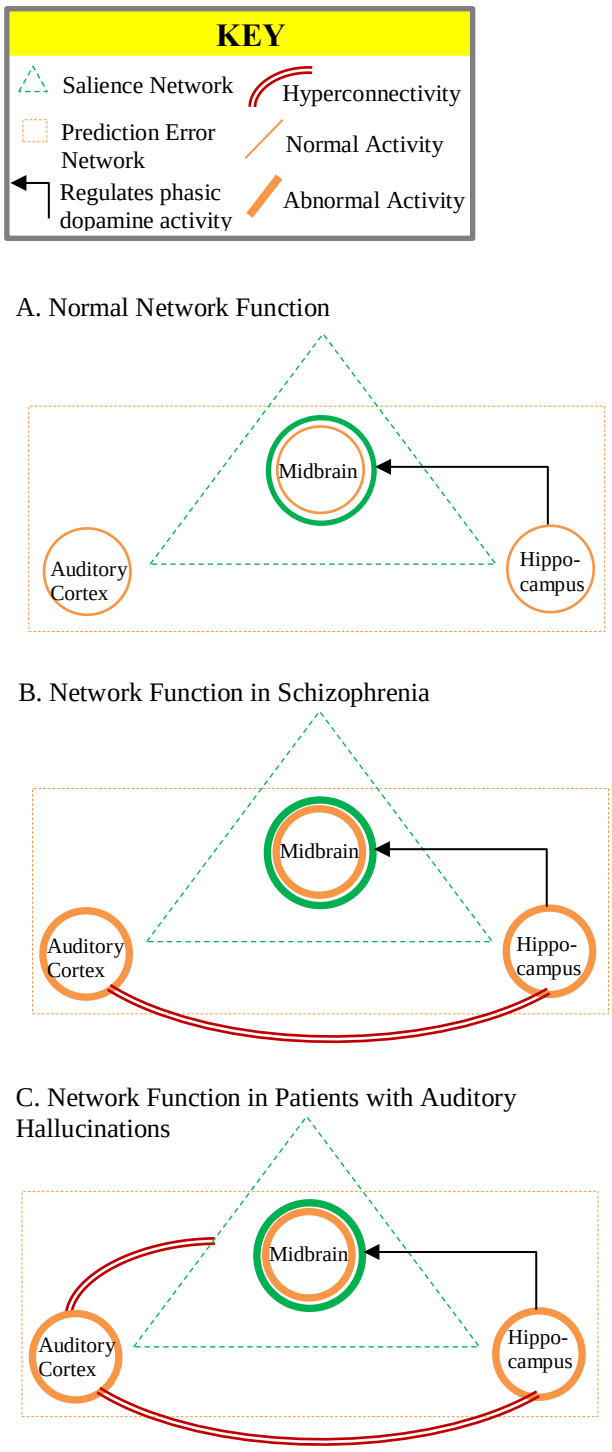

Figure 5.1 Salience and Prediction Error Monitoring: A Multi-Network Model

(A) Hippocampus, midbrain, and auditory cortex are all part of a larger network that tracks prediction errors (orange). The salience network (green) contains multiple network hubs including dopamine-rich midbrain regions (ventral tegmental area, substantia nigra). Hippocampal activity regulates phasic midbrain dopamine neuron activity by releasing midbrain dopamine neurons from inhibition (arrow). (B) Regardless of whether schizophrenia patients endorse auditory hallucinations as a symptom, resting-state functional connectivity between hippocampal and auditory networks is elevated (red) (C) Patients with auditory hallucinations may have abnormal functional connectivity along a salience-hippocampal-auditory network loop (red). Elevated resting-state functional connectivity was observed between auditory and hippocampal networks (as in nonhallucinating patients) and between auditory and salience networks in patients reporting auditory hallucinations.

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164. Chen T, Michels L, Supekar K, Kochalka J, Ryali S, Menon V. Role of the anterior insular cortex in integrative causal signaling during multisensory auditory-visual attention. *Eur J Neurosci*. 2015;41(September 2014):264-274. doi:10.1111/ejn.12764

APPENDIX

Curriculum Vitae

Stephanie M. Hare
Georgia State University
Neuroscience Institute
P.O. Box 5030
Atlanta, GA 30303

EDUCATION

2013-2018 Ph.D., Neuroscience, Georgia State University
with a concentration in Neuroethics

2010-2012 M.A., Philosophy, Loyola University Chicago

2006-2009 B.S., Neurobiology, University of Wisconsin – Madison

GRANTS & FELLOWSHIPS

2017-2018 *Provost's Dissertation Fellowship,* Georgia State University

2016-2018 *Kenneth W. and Georganne F. Honeycutt Fellowship*, Georgia State University

2013-2017 *2CI Neuroethics Fellowship*, Georgia State University

AWARDS

2017 Awarded Travel Stipend (Airfare & Hotel)
Winter School on the Neuroscience of Consciousness
Canadian Institute for Advanced Research (CIFAR)

2017 Finalist for Public Communication Essay Contest
Hearing Voices: First-Person Perspectives & Combatting Social Stigma
International Neuroethics Society

2011 *Travel Stipend for Best Abstract*
International Neuroethics Society

PEER REVIEWED PUBLICATIONS

Hare, S., Ford, J.M., Mathalon, D.H., Ahmadi, A., Damaraju, E., Bustillo, J., Belger, A., Lee, H.J., Mueller, B.A., Lim, K.O., Brown, G.G., Preda, A., van Erp, T.G.M., Potkin, S.G., Calhoun, V.D., Turner, J.A. (under review). Salience-Default Mode Functional Network Connectivity

Linked to Positive and Negative Symptoms of Schizophrenia. *Schizophrenia Bulletin*.

Hare, S., Law, A., Ford, J.M., Mathalon, D.H., Ahmadi, A., Damaraju, E., Bustillo, J., Belger, A., Lee, H.J., Mueller, B.A., Lim, K.O., Brown, G.G., Preda, A., van Erp, T.G.M., Potkin, S.G., Calhoun, V.D., Turner, J.A. (2018). Disrupted Network Cross Talk, Hippocampal Dysfunction and Hallucinations in Schizophrenia. *Schizophrenia Research.* Published online ahead of print March 2018. doi: 10.1016/j.schres.2018.03.004

Hare, S., Ford, J.M., Ahmadi, A., Damaraju, E., Belger, A., Bustillo, J., Lee, H.J., Mathalon, D.H., Mueller, B.A., Preda, A., van Erp, T.G.M., Potkin, S.G., Calhoun, V.D., Turner, J.A. 2017. Modality-Dependent Impact of Hallucinations on Low-Frequency Fluctuations in Schizophrenia. *Schizophrenia Bulletin*, 43(2), 389-396.

Hare, S., Vincent, N.A. 2016. Happiness, Cerebroscopes and Incorrigibility: Prospects for Neuroeudaimonia. *Neuroethics*, 9(1), 69-84.

Hare, S. (2012). Making Room for Neuroscience in Normative Theory (abstract). *American Journal of Bioethics: Neuroscience* 3:2

PRESENTATIONS

(a) Oral Presentations

2018. Hare, S. *Monitoring Self & World: A Novel Network Model of Hallucinations in Schizophrenia*. Hard Data Café Series, Georgia State University, Atlanta, GA.

2017. **Hare, S.,** Turner, J.A. *Stigma and the Medicalization of Hearing Voices*. Neuroethics in the News Series, Emory University, Atlanta, GA.

2017. Hare, S. *Disrupted Network Cross Talk, Hippocampal Dysfunction and Hallucinations in Schizophrenia*. International Congress on Schizophrenia Research. San Diego, CA.

2017. Hare, S. *Disrupted Network Cross Talk, Hippocampal Dysfunction and Hallucinations in Schizophrenia*. Neuroscience Institute Breakfast Lecture Series. Georgia State University, Atlanta, GA.

2016. Hare, S. *Hallucinations in Schizophrenia: Current Projects and Future Directions*. Invited Talk, Center for Music in the Brain, Aarhus, Denmark.

2015. **Hare, S.,** Vincent, N. Happiness, Cerebroscopes and Incorrigibility: Prospects for Neuroeudaimonia. Center for Advanced Brain Imaging Colloquium. Atlanta, GA.

2014. Vincent, N., **Hare, S**. *I'm Gonna Kill the Duck Rabbit. Discerning Madness from Badness*. Law and Neuroscience: Revising the Legal Standard for Insanity Conference. Florence, Italy. (co-author on project; did not present at conference).

2011. Hare, S. *Making Room for Neuroscience in Normative Theory*. International Neuroethics Society Annual Meeting, Washington D.C.
2011. Hare, S. *Philosophy of Neuroscience and Complexity: An Alternative Methodology to Studying Inter-Level Relations*. Loyola University Chicago's 4th Annual Graduate School Interdisciplinary Research Symposium. Chicago, IL.

2011. Hare, S. *Philosophy of Neuroscience and Complexity: An Alternative Methodology to Studying Inter-Level Relations*. 6th Annual Gateway Graduate Conference in Philosophy, St. Louis, MO.

(b) Poster Presentations

2018. **Hare, S.**, Ford, J.M., Mathalon, D.H., Ahmadi, A., Damaraju, E., Bustillo, J., Belger, A., Lee, H.J., Mueller, B.A., Lim, K.O., Brown, G.G., Preda, A., van Erp, T.G.M., Potkin, S.G., Calhoun, V.D., Turner, J.A. *Salience-Default Mode Functional Network Connectivity Linked to Positive and Negative Symptoms of Schizophrenia*. Organization for Human Brain Mapping Conference. Singapore.

2016. **Hare, S.M.,** Ford, J.M., Law, A., Ahmadi, A., Damaraju, E., Belger, A., Bustillo, J., Lee, H.J., Mathalon, D.H., Mueller, B.A., Preda, A., van Erp, T.G.M., Potkin, S.G., Calhoun, V.D., Turner, J.A., Function Biomedical Informatics Research Network (FBIRN). Hallucinations & the Resting-State Brain: A Review of Findings in the FBIRN Dataset. International Consortium for Hallucinations Research North American Satellite. Chicago, IL.

2016. **Hare, S.,** Schuite-Koops, S., Sommer, I.E., Turner, J.A. Hearing Voices Without Psychosis: An Analysis of Functional Network Connectivity. Organization for Human Brain Mapping Conference. Geneva, Switzerland.

2016. Persichetti, E., Aral Ahmadi, **Hare, S.,** Turner, J.A. Seed to Voxel Connectivity in Relation to Hallucinations in Schizophrenia. Georgia Psychological Society Annual Meeting. Atlanta, GA.

2015. Law, A., **Hare, S.,** Ahmadi, A., Turner, J.A. *Functional Network Connectivity in Hallucinating Patients with Schizophrenia*. BrainModes Conference, Atlanta, GA.

2015. **Hare, S.,** Pasquerello, D., Damaraju, E., Belger, A., Ford, J., Mathalon, D., Mueller, B., Preda, A., van Erp, T., Calhoun, V., Turner, J. *The Impact of Hallucination Profile on Resting-State Low-Frequency Fluctuations in Schizophrenia.* The International Congress on Schizophrenia Research. Colorado Springs, CO.

2014. **Hare, S.,** Turner, J.A., Vincent, N.A. *The Research Domain Criteria and Biomarkers of Auditory Hallucinations in Criminal Responsibility Assessments*. Neuro-Interventions and the Law: Regulating Human Mental Capacity Conference. Atlanta, GA.

2013. Hare, S. *Can Modern-Day Cerebroscopes Undermine Incorrigibility of Happiness Claims? The Application and Limitations of Neuroimaging Technology.* International Neuroethics Society Annual Meeting. San Diego, CA.

2012. Hare, S. *Studying Human Morality in the Magnet: An Attempt to Reconcile the Complexity of the Moral Life with the Constraints of Neuroimaging Methods*. International Neuroethics Society Annual Meeting, New Orleans, LA.

2012. **Hare, S**., Molony, J., McCarthy, S., Brandstatt, K., Skiadopoulos, L., Bharani, K.L., Morrison, R.G. *Insight follows Incubation in the Remote Associates Test.* Cognitive Neuroscience Society Annual Meeting. Chicago, IL.

TEACHING

2017. Module on Positive Symptoms of Psychosis
Responsibilities/Skills: I taught four class periods about different theories of hallucinations in schizophrenia (introductory/background lecture, two lectures discussing neuroimaging papers/findings, final class focusing on integration of findings, critical thinking, and class discussion)
Course: Cognitive Neuroscience of Psychosis (Instructor: Dr. Jessica Turner)
Georgia State University

2017. Guest Lecture, Happiness and the Brain: Perspectives from Cognitive and Computational Neuroscience
Course: Brain, Self, and Society (Instructor: Dr. Eddy Nahmias)
Georgia State University

2015. Guest Lecture, Improper Argumentative Form: Fallacies of Relevance
Course: Critical Thinking (Instructor: Dr. Sandy Dwyer)
Georgia State University

2015. Guest Lecture, Happiness and the Brain: Prospects for Enhancing Happiness and Limitations, Paideia High School, Atlanta, GA

SERVICE TO PROFESSION: REFEREE WORK

Schizophrenia Bulletin
Schizophrenia Research
Journal of Ethics in Mental Health
Journal of Radiology and Diagnostic Methods

SERVICE: VOLUNTEER/OUTREACH

2018. Classroom Visit (6^{th} and 7^{th} Grade) for Atlanta Science Festival. Demonstration: Touch-a-Brain & Concussion Googles. Centennial Academy, Atlanta, GA.

2018. Atlanta Brain Bee Exhibitor. Exhibit Title: Wacky Sensory Perception. Atlanta, GA.

2017. Atlanta Brain Bee Exhibitor. Exhibit Title: Wacky Sensory Perception. Atlanta, GA.

2016. Panelist, Ethics-In-Film: *Ex Machina*, Georgia State University, Atlanta, GA.

2016. Assistant Instructor, Sheep Brain Dissection, Brain Camp at Georgia State University, Atlanta, GA.

2016. Station Leader, Build-A-Brain Activity, Trip Elementary School, Grayson, GA.

2016. Station Leader, Build-A-Brain Activity, Mary Lin Elementary Science Night, Atlanta, GA.

2015. Speaker at Collegiate Neuroscience Society Meeting, Georgia State University.

2015. Volunteer at Decatur Book Festival, Georgia State University Booth. Decatur, GA.

2015. Volunteer at STEM Science Night. International Community School – Dekalb. Decatur, GA.

2015. Station Assistant, Discovery Day 2015. Georgia State University.

2014. Graduate Student Volunteer, Build-A-Brain Activity, Science-at-Hand Day at the Fernbank Museum of Natural History, Atlanta, GA.

2014. Student Presenter, Atlanta Science Festival Exposition. Presentation Title: "My Brain Does What? The Neuroimage and Unsolved Mysteries from 400 years of Philosophical Thought." Georgia Congress Center, Atlanta, GA.

2014. Student Presenter and Station Designer, Discovery Day 2014. Presentation Title: "My Brain Does What? The Neuroimage and Unsolved Mysteries from 400 years of Philosophical Thought." Georgia State University, Atlanta, GA.

2011-2012. Mentor to First-Year Undergraduates in the Achieving College Excellence (ACE) Program, Loyola University Chicago, Chicago, IL.

PROFESSIONAL MEMBERSHIPS

American Association for the Advancement of Science
International Consortium on Hallucinations Research
Organization for Human Brain Mapping
American Philosophical Association
Neuroethics Women (NEW) Leaders
International Neuroethics Society