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Authors

Hare, Stephanie M
Law, Alicia S
Ford, Judith M
et al.

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Disrupted Network Cross Talk, Hippocampal Dysfunction and Hallucinations in Schizophrenia

Stephanie M. Hare[a], **Alicia S. Law**[b], **Judith M. Ford**[c,d], **Daniel H. Mathalon**[c,d], **Aral Ahmadi**[b], **Eswar Damaraju**[e], **Juan Bustillo**[f], **Aysenil Belger**[g], **Hyo Jong Lee**[h], **Bryon A. Mueller**[i], **Kelvin O. Lim**[i,j], **Gregory G. Brown**[k], **Adrian Preda**[l], **Theo G.M. van Erp**[l], **Steven G. Potkin**[l], **Vince D. Calhoun**[e,m], and **Jessica A. Turner**[a,b,e]

[a]Neuroscience Institute, Georgia State University, Atlanta, GA, USA

[b]Department of Psychology, Georgia State University, Atlanta, GA, USA

[c]Psychiatry Service, San Francisco VA Medical Center, San Francisco, CA, USA

[d]Department of Psychiatry, University of California, San Francisco, CA, USA

[e]Mind Research Network, Albuquerque, NM, USA

[f]Department of Psychiatry, University of New Mexico, Albuquerque, NM, USA

[g]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

[h]Department of Computer Science and Engineering, Chonbuk National University, Jeonju, Republic of Korea

[i]Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

[j]GRECC, Minneapolis VA Medical Center, Minneapolis, MN, USA

[k]Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

[l]Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA

[m]Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, United States

Corresponding Author: Stephanie M. Hare, Neuroscience Institute, Georgia State University, PO Box 5030, Atlanta, GA 30302-5030, Phone: 262-364-7427, Fax: 404-413-5446 (Attn: Stephanie Hare), share1@student.gsu.edu.

Contributors

Ms. Hare designed and performed the FNC/ALFF analyses, and took primary responsibility for drafting and revising the manuscript. Ms. Law assisted with the FNC analyses, outlining, and writing a first draft of the manuscript. Drs. Ford, Mathalon, and Turner provided guidance with data interpretation, while Dr. Calhoun provided guidance on the group ICA methods. Drs. Ford, Mathalon, Bustillo, Mueller, van Erp, Calhoun, and Turner provided suggestions for revisions at various stages of the manuscript. Ms. Ahmadi, Mr. Damaraju and Ms. Hare assisted with data preprocessing and curation. Dr. Hyo Jong Lee collected and quality checked data. Drs. Bustillo, Belger, Mueller, Lim, Brown, Preda, van Erp, Calhoun, Turner and Potkin contributed to the FBIRN study design and implementation, data collection, and data sharing. All authors reviewed and approved the final manuscript.

Disclosures

Dr. Mathalon has served as a consultant for Boehringer Ingelheim, Alkermes, Takeda, and Upsher-Smith. All other authors declare no conflicts of interest.

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.

Keywords

hallucinations; ALFF; FNC; resting-state; fMRI

1. Introduction

An estimated 59% of patients with schizophrenia (Sz) report auditory hallucinations (AH); nearly half of those reporting AHs also report visual hallucinations (VHs) (Waters et al., 2014). To address the question of how individuals with Sz come to experience hallucinations, researchers have used non-invasive resting-state functional magnetic resonance imaging (rs-fMRI) to compare spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal in Sz reporting hallucinations relative to control subjects. Resting-state functional connectivity (rs-FC) analyses are commonly employed in hypothesis-driven investigations of Sz symptoms and provide an estimate of how correlated or “in synch” BOLD signal activation is across regions of interest. Both VH and AH are associated with abnormal sensory (Clos et al., 2014; Ford et al., 2015; Gavrilescu et al., 2010; Hoffman, Ralph et al., 2012; Shinn et al., 2013; Sommer et al., 2012), striatal (Amad, A. et al., 2014; Hoffman, Ralph et al., 2012; Rolland et al., 2015), insular (Clos et al., 2014; Rolland et al., 2015), medial frontal (Amad, A. et al., 2014; Clos et al., 2014), and parahippocampal/hippocampal (Amad, A. et al., 2014; Clos et al., 2014; Ford et al., 2015; Rolland et al., 2015; Sommer et al., 2012) rs-FC. Yet, it remains unclear how these widespread disruptions in rs-FC give rise to hallucinations.

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

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

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

The present study models the relationships between hippocampal ALFF, FNC, and targeted symptomology (AH and VH severity) in the resting-state brain. We first test the hypothesis

that altered FNC between salience and sensory networks underlies modality-specific hallucinations, predicting that Sz patients with VH will have higher FNC between visual and salience networks relative to all groups, and patients with AH will have higher FNC between auditory and salience networks relative to nonhallucinating Sz patients and HC.

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

2. Experimental materials and methods

2.1. Subjects

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

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

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

phase FBIRN project including subject characteristics, imaging parameters, and behavior assessments see Keator et al., 2016.

2.2. Grouping of Participants

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

2.3. 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 77°, 32 slices collected sequentially from superior to inferior, 3.4 × 3.4 × 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.

2.4. Data Processing

Pre-processing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox which runs with the REST software (Song et al., 2011). 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 (Power et al., 2012). To correct for confounding effects of head motion on the fMRI signal, we included mean framewise displacement as a subject-level covariate.

2.5. Group Spatial Independent Component Analysis

We performed spatial group ICA using GIFT software (Calhoun et al., 2001). 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 (Erhardt et al., 2011).

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., 2011), 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.

2.6. Statistical Analyses

2.6.1. 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.

2.6.2. 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 (de Leon and Diaz, 2005), and has been shown to significantly impact brain functional connectivity (Jasinska et al., 2014), 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 (Woods, 2003) 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 $p < 0.05$.

2.6.3 Hippocampal ALFF & FNC: Regression Analyses—Voxelwise mean ALFF maps were computed for each subject using REST software (Song et al., 2011) as described in (Hare et al., 2017) The left hippocampal cluster that showed significant ALFF variation across VH vs. AH subgroups in Hare et al., 2017, 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 (Woods, 2003) as an additional covariate. Confidence was specified as $p < 0.05$.

3. Results

3.1. FNC Group Differences

3.1.1. 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.

3.1.2. 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.

3.1.3. 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).

3.1.4. 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).

3.2. Regression Analyses of FNC

3.2.1. 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.

3.2.2. 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.

3.2.3. 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 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. 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

(Friston et al., 2016), 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 (Damaraju et al., 2014). 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. 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 (Palaniyappan et al., 2012; Palaniyappan et al., 2011). Reported AH severity correlates negatively with *FC within the SN* (between SN hubs and intrinsic FC of the right anterior insula) (Manoliu et al., 2014; Pu et al., 2012). In addition, SN hubs showed increased FC with dorsomedial prefrontal cortex in patients with AH relative to NH patients (Alonso-Solís et al., 2015). While these studies delineate links between SN dysfunction and AH, changes in SN functional communication are also linked to diverse behaviors and clinical outcomes (see Menon, 2015, Figure 14; Palaniyappan et al., 2013, Supplemental Figure S3).

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 (Menon, 2015; Palaniyappan and Liddle, 2012), and abnormal self-monitoring (forward modeling) theories (Frith, 1996). 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 (van Lutterveld et al., 2012). Slow theta oscillations are thought to play a key role in temporally coordinating local network oscillations in the faster gamma range (> 30 Hz) (Lisman and Buzsáki, 2008). 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 (Buzsaki, 2002; Lisman and Buzsáki, 2008). 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 AH (Lefebvre et al., 2016). 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 (Copolov et al., 2003).

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 (Grace and Gomes, 2018). Phasic dopaminergic signaling plays an essential role in encoding motivational/behavioral salience (Bromberg-Martin et al., 2010). The SN contains network hubs in dopamine-rich midbrain

regions (e.g. ventral tegmental area, substantia nigra) (Seeley et al., 2007), 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 (Gillespie et al., 2017; Mouchlianitis et al., 2016). 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 VH 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 (van Lutterveld et al., 2012), which are driven by voltage-dependent neural oscillations, but also by summed synaptic activities of local networks, fast action potentials, and neuron-glial interactions (Buzsáki et al., 2012). 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 (Lefebvre et al., 2016), 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 (Palaniyappan et al., 2012), while another study reported that Sz patients had abnormally high beta oscillations in the insula in response to task-irrelevant stimuli (Liddle et al., 2016). 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 (Yaesoubi et al., 2017). 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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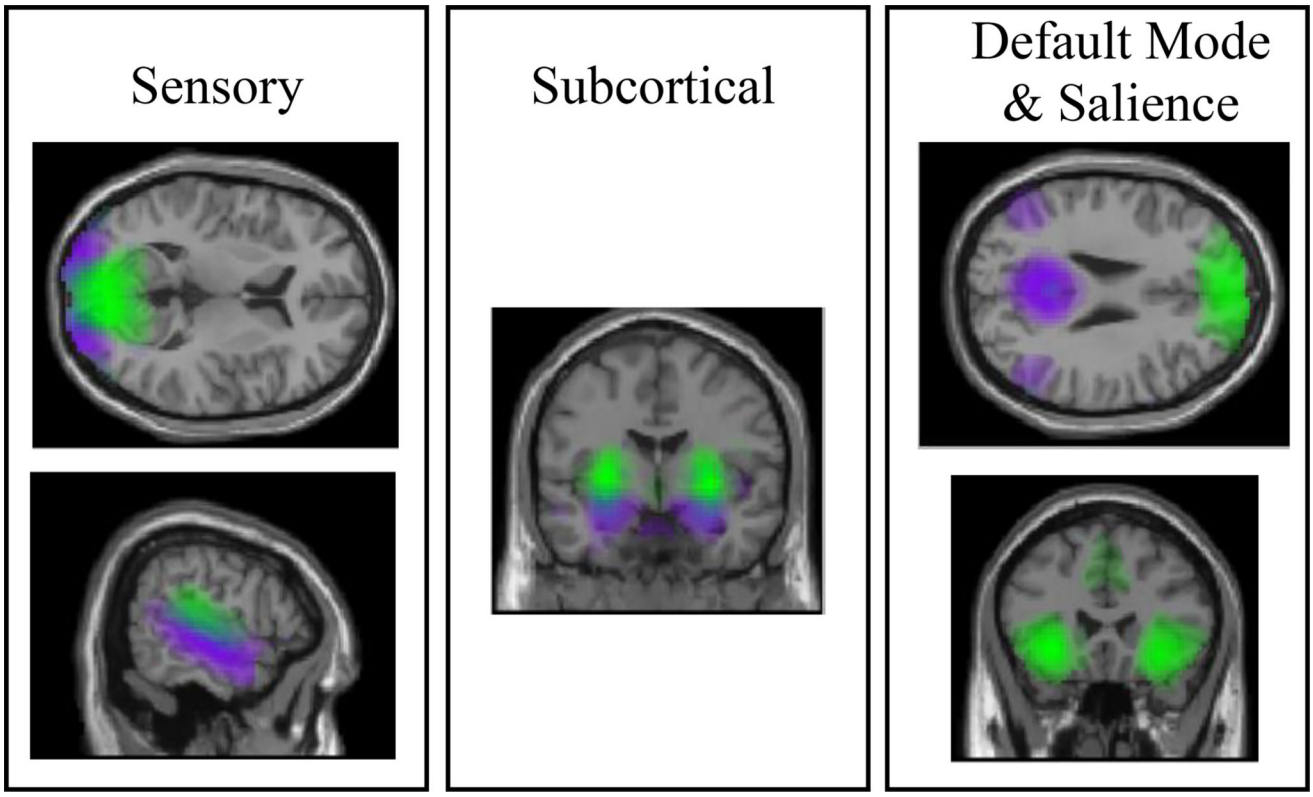

Figure 1. Networks

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 $Z > 3$.

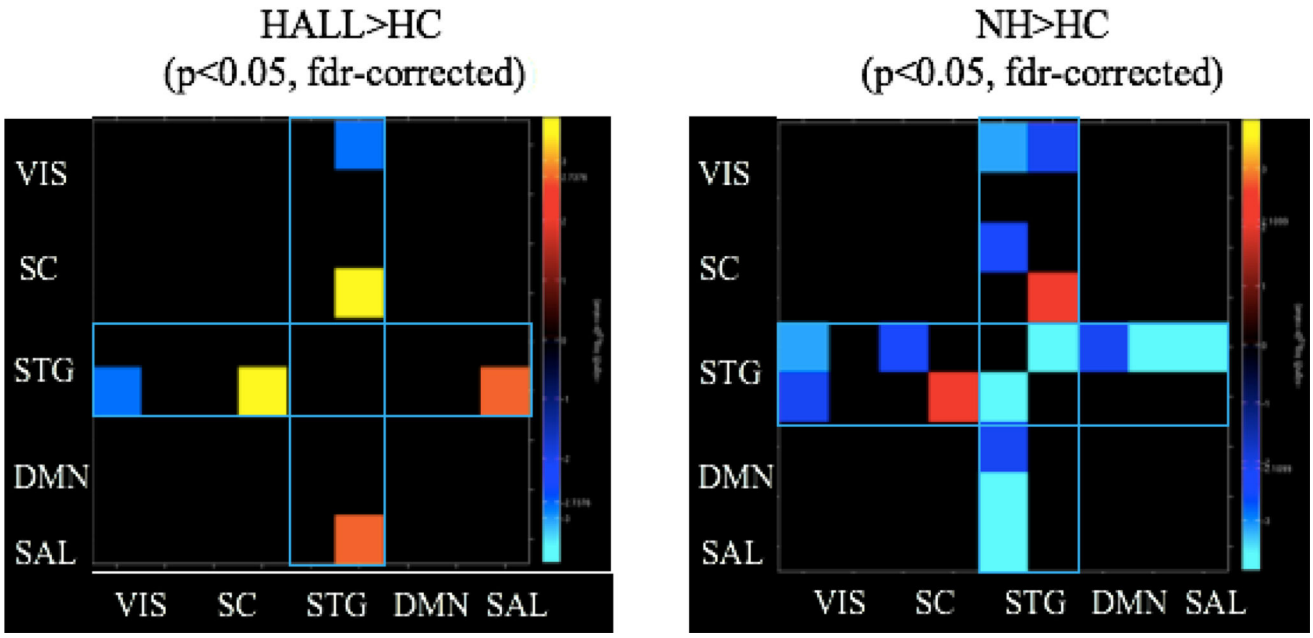

Figure 2. Altered Superior Temporal Network Connections in Hallucinating and Nonhallucinating Patients

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.

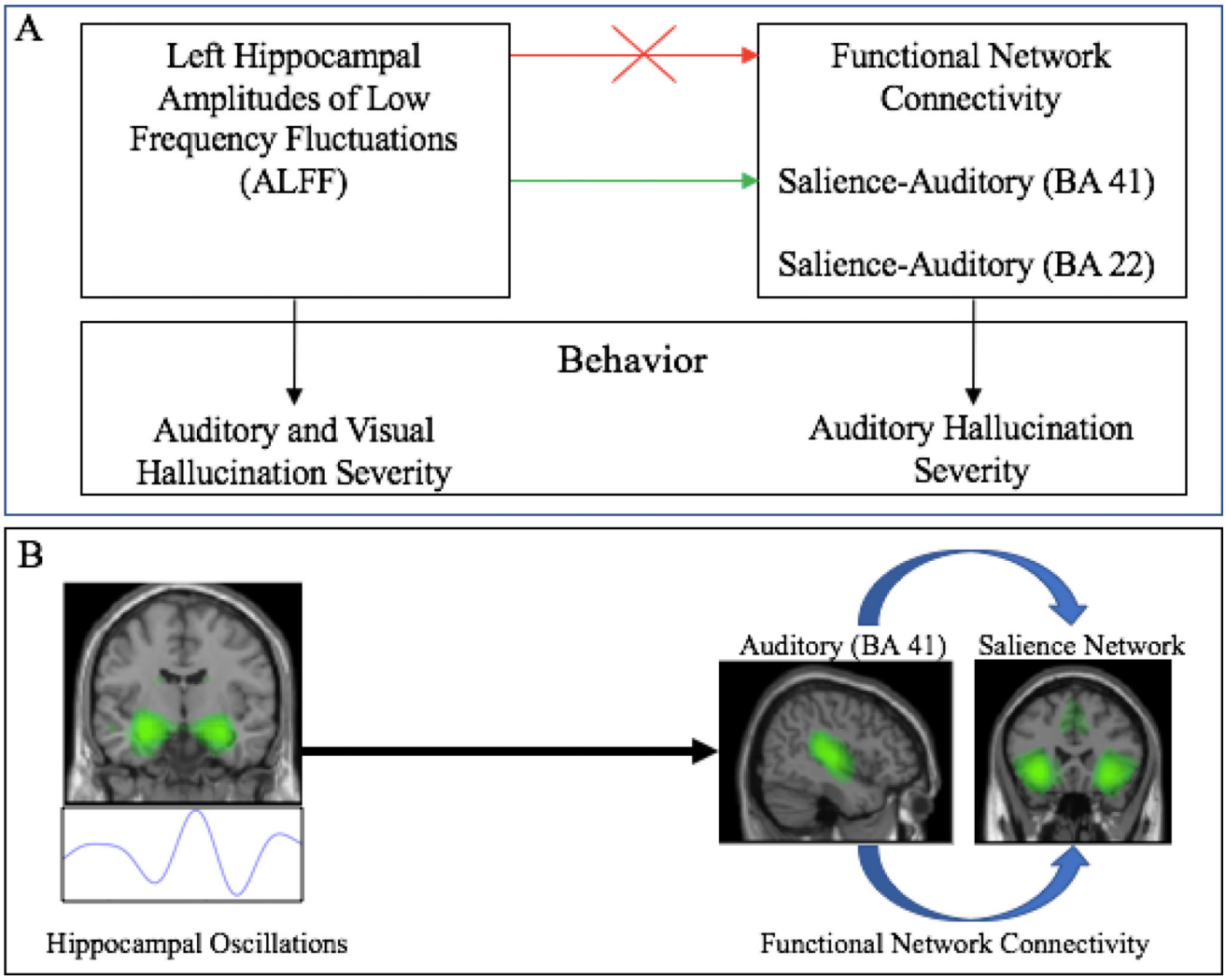

Figure 3. Abnormal Hippocampal Activity and Functional Communication Between Salience and Auditory Networks in Schizophrenia

(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

Table 1

Participant 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)	83 144 (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 *b	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

*Group ANOVA is significant at p=0.05

[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 = 87.2%

[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)

Table 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)