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Alterations in Hippocampal Connectivity Across the Psychosis Dimension

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Abstract

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Recent evidence demonstrates that hippocampal hyperactivity helps mediate psychosis. Using resting state functional magnetic resonance imaging (rsfMRI), we examined hippocampal connectivity alterations in individuals with psychosis (PS) versus healthy controls (HC). Because of its putative greater involvement in psychiatric disorders, we hypothesized that the anterior hippocampus network would show greater dysconnectivity in psychosis. We tested rsfMRI connectivity in 88 PS (including 21 with schizophrenia; 40 with schizoaffective disorder; 27 with psychotic bipolar I disorder) and 65 HC. Seed-based voxel-wise connectivity analyses were carried out using whole, anterior, and posterior hippocampal seeds. No significant differences in functional hippocampal connectivity were found across the three conventional diagnoses. PS were then contrasted with HC, showing strong reductions in anterior hippocampal connectivity to anterior neocortical regions, including medial frontal and anterior cingulate cortices, as well as superior temporal gyrus, precuneus, thalamus and cerebellum. Posterior hippocampal seeds also demonstrated decreased connectivity in PS, with fewer disconnected regions and a posterior/cerebellar distribution. Whole hippocampal outcomes were consistent with anterior/posterior hippocampal connectivity changes. Connectivity alterations did not correlate with cognition, clinical symptoms, or medication effect variables. Our results suggest a psychosis network of decreased hippocampal connectivity with limbic and frontal contributions, independent of diagnostic categories.

Keywords

resting-state functional connectivity; hippocampus; psychosis

1. Introduction

Previous scholarship suggests an important and unique involvement of hippocampus with psychosis pathology (Tamminga et al., 2010). Increased hippocampal perfusion in schizophrenia (SZ) has been reported using various *in vivo* imaging methodologies (Heckers et al., 1998; Medoff et al., 2001; Malaspina et al., 2004; Schobel et al., 2013; Talati et al., 2014; Lui et al., 2014). This increase in perfusion is an outcome associated with psychosis (Heckers et al., 1998; Medoff et al., 2001; Heckers and Konradi, 2010; Small et al., 2011). Initial reports of increased hippocampal activity were based on positron emission tomography 15O-water (Medoff et al., 2001); later, it was noted via magnetic resonance (MR) approaches, including arterial spin labeling (Pinkham et al., 2011), Vascular Space Occupancy (Schobel et al., 2013; Talati et al., 2014) and resting state functional MR (Lui et al., 2014). An increase in hippocampal activity has been shown to be reflected in perfusion increases using high resolution techniques (Schobel et al., 2013; Talati et al., 2014).

Increased hippocampal perfusion manifests alongside activity reductions in frontal, temporal, parietal, as well as subcortical brain regions in SZ (Lui et al., 2014). Subfield-specific tissue pathology also accompanies and could mediate the increase in *in vivo* hippocampal activity (Tamminga et al., 2010). Specifically, the dentate gyrus shows *reduced* GluN1 protein in postmortem SZ tissue, among other molecular lesions (Gao et al., 2000; Knable et al., 2004; Kobayashi, 2009; Stan et al., 2014). CA3, in turn, shows *increased* glutamate-related synaptic proteins (GluN2B and PSD95) as well as increased spine number

on CA3 pyramidal neuron apical dendrites, suggesting an increase in synaptic strength and whole cell sensitivity in SZ hippocampus, or increased cellular activity in psychosis (Li et al., 2015). This increased plasticity could underlie the increase in *in vivo* hippocampal perfusion in SZ, as previously modeled (Tamminga et al., 2010). Cellular and molecular alterations and the concomitant increase in hippocampal subfield activity should be reflected in network alterations that affect resting-state physiology (Xiong et al., 1998; Biswal et al., 2010). Persistently increased, psychosis-linked hippocampal activity could disrupt cerebral network connectivity and potentially define hippocampal-driven functional alterations in psychosis.

Defective hippocampal function in SZ psychosis has an anterior predominance, as well as the subfield specificity noted above. Anterior predominance is supported by perfusion data (Medoff et al., 2001; Schobel et al., 2013; Talati et al., 2014) and basic neuroscience observations regarding memory. Animal studies show distinctive structural connectivity (Fanselow and Dong, 2010) and functions (Ropireddy and Ascoli, 2011) along the long axis of hippocampus for learning and memory, findings which have also been demonstrated in studies of human learning and memory (Poppenk et al., 2013).

Newer work on hippocampal connectivity has elucidated evidence for separate anterior and posterior hippocampal networks. Kahn et al., 2008 has specifically examined intrinsic hippocampal functional connectivity with human posterior parahippocampal cortex and perirhinal cortex. Posterior hippocampus and parahippocampal cortex showed significant functional connectivity with retrosplenial cortex and medial and ventrolateral parietal areas. By contrast, anterior hippocampus showed significant functional connectivity with anterior and ventrolateral temporal cortex. Libby et al., 2012 confirms these findings regarding differential anterior and posterior hippocampal connectivity. They also find preferential perirhinal connectivity with an anterior temporal and frontal cortical network, and preferential parahippocampal connectivity with a posterior medial temporal, parietal, and occipital network. This body of work demonstrates different anterior/posterior functional connectivity with the whole brain, shown by others to be associated with differential anterior and posterior structural connectivity (Fanselow and Dong, 2010; Preston et al., 2010; Poppenk et al., 2013). Anterior hippocampus may, additionally, serve different cognitive functions than posterior hippocampus, being more associated with familiarity or decreased novelty, as well as object encoding, while posterior hippocampus activation may associate with recollection, or with scene encoding (Amaral and Witter, 1989; Strange et al., 1999; Davachi, 2006; Eichenbaum et al., 2007; Ranganath, 2010; Montaldi and Mayes, 2010; Greve et al., 2011).

Localization of pathology along the long axis of the hippocampus could impact symptom presentation in psychiatric disease. Resting-state fMRI connectivity differences in anterior and posterior hippocampal connectivity in other disorders involving hippocampus (e.g., post-traumatic stress disorder and anxiety) have been implicated in their pathophysiology (Chen and Etkin, 2013). To extend these ideas to psychosis, we hypothesized that regional dysconnectivity in SZ psychosis would be more disrupted in anterior relative to posterior regions (Medoff et al., 2001; Schobel et al., 2013; Talati et al., 2014).

Psychosis is a clinical dimension of psychopathology characterized by delusions, hallucinations and thought disorder (Carpenter, Jr. and Buchanan, 1994; Freedman et al., 2005; Koutsouleris et al., 2012; Karbasforoushan and Woodward, 2012). It is expressed in conventional diagnoses like SZ, schizoaffective disorder (SAD), and psychotic bipolar disorder (BD-P). Individuals with these psychotic diagnoses share overlapping clinical manifestations and cognitive deficits in the domains of declarative and working memory, executive function, and attention (Seidman et al., 2002; Badner and Gershon, 2002; Thaker, 2008; Ivleva et al., 2010; Ivleva et al., 2012; Hill et al., 2013; Tamminga et al., 2013). Moreover, the diagnoses share similar patterns of aberrant resting state- and event related potential-based EEG activity, oculomotor abnormalities, and shared genetic susceptibility markers, albeit of varying severity (Bramon and Sham, 2001; Badner and Gershon, 2002; Harris et al., 2009; Ivleva et al., 2010; Narayanan et al., 2013; Ethridge et al., 2014). In addition, they share similar pathological characteristics of whole brain fMRI resting-state networks across SZ and BD-P (Karbasforoushan and Woodward, 2012; Khadka et al., 2013).

Driven by recent literature that challenges a biological basis for conventional psychosis diagnoses (Badner and Gershon, 2002; Freedman et al., 2005; Tamminga et al., 2013), we looked at diagnostic boundaries within the psychosis dimension for hippocampal connectivity differences within and across conventional diagnoses. We asked whether this brain dysconnectivity was diagnostically specific or whether it spanned Diagnostic and Statistical Manual of Mental Disorders (DSM) categories.

To examine this question, we assessed the extent to which hippocampal connectivity patterns differed between SZ, SAD, BD-P; as well as between these groups and healthy controls (HC). Seed regions for connectivity analysis included whole hippocampus as well as its anterior and posterior extents. We hypothesized that hippocampal-cortical connectivity would be decreased in individuals with psychosis compared to HC. Moreover, we predicted reduction in regional connectivity to more limbic and frontal regions with respect to anterior hippocampus, compared to posterior hippocampus. Exploratory analyses to examine associations between connectivity outcomes and clinical and cognitive disease characteristics, as well as active medication status, were also conducted.

2. Methods

2.1 Participants

The study sample included 153 participants, 88 individuals with psychosis (PS) (21 SZ; 40 SAD; 27 BD-P) and 65 HC from the B-SNIP sample (Bipolar-Schizophrenia Network on Intermediate Phenotypes) from the University of Texas Southwestern Medical Center site. All participants provided written informed consent after study procedures had been fully explained. Detailed characteristics of the whole B-SNIP clinical population are described elsewhere (Tamminga et al., 2013). Participants were stable medicated outpatients, with diagnoses established by the Structured Clinical Interview for DSM-IV-TR Diagnosis (SCID-I/P) (First et al., 1996). Healthy subjects had no personal history of psychosis or recurrent mood disorder, or a family history of psychotic disorder in first-degree relatives. Active symptom severity in PS was assessed using the Positive and Negative Syndrome

Scale (PANSS) (Kay et al., 1987), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and Young Mania Research Scale (YMRS) (Young et al., 1978). The Reading Subtest scores from the Wide Range Achievement Test 4 (WRAT 4) were used to estimate premorbid intellectual functioning; the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004) composite and verbal memory subscale scores were obtained in both PS and HC. The verbal memory subscale of BACS was of interest due to the hippocampal focus of this work. The demographic and clinical characteristics of the study sample are outlined in Table 1, with details in the legend.

2.2 Scan parameters

MR images were collected on a 3 Tesla Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands). A T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) structural image used the following parameters: Sagittal slab direction, shot interval 3000 ms, inversion time 846 ms, repetition time (TR) 6.8 ms, echo time (TE) 3.1 ms, flip angle 8°, FOV 256 (foot-to-head) × 240 (anterior-to-posterior) mm², matrix 256 × 240, in-plane resolution 1 × 1 mm², 170 slices (left-to-right), slice thickness 1.2 mm, voxel size 1 × 1 × 1.2 mm³, with a total scan duration of 9 min 19 sec. Resting fMRI data were obtained by a single-shot gradient-recalled T2-weighted echo planar imaging (EPI) pulse sequence, using the following parameters: TR 1400 ms; flip angle 70°; slice thickness 5 mm; matrix 64 × 64; FOV 220 × 220 mm; voxel size 3.4 × 3.4 × 5 mm, with a total scan duration of 5 minutes.

2.3 Image processing

Images were processed to define bilateral hippocampal networks in the Analysis of Functional NeuroImaging (AFNI) fMRI analysis package, available from the National Institutes of Health (Cox, 1996). We used a seed-based voxel-wise analysis, with pre-processing techniques modeled on previous studies (Zhou et al., 2008; Hutchison et al., 2014). The preprocessing occurred using AFNI's `align_epi_anat.py` command. Functional data were time-shifted. Each subject's MPRAGE was aligned to a corresponding functional image. Functional data were corrected for motion using a rigid-body (6 degrees of freedom), least squares transformation via AFNI's `3dvolreg` command, which assured linear co-registration of all voxels in each volume to the third functional volume of each subjects' resting-state EPI (e.g., (Hutchison et al., 2014). This process ensured that possible movements did not affect the spatial organization of voxels within the EPI matrices. Functional data were band-pass filtered (0.01–0.1 Hz) and spatially smoothed (Full Width at Half Maximum smoothing kernel size = 3 mm). Following image registration, data were warped into Colin (Talarach-Tournoux) virtual space.

A whole hippocampal seed was defined in AFNI's Talarach-Tournoux atlas, and anterior and posterior hippocampal masks were hand-drawn by an experienced imaging analyst (NS). This was accomplished by bisection of the left and right whole hippocampal regions along anterior-posterior axis on every sagittal slice in Talarach-Tournoux standard space, checking axial and coronal views for concordance, similar to a technique utilized in previous studies (e.g., (Greicius et al., 2003). Anatomical boundaries for the whole hippocampus used were in accordance with the Talairach-Tournoux atlas. Individual images were transformed

into this atlas, and the whole hippocampus mask from AFNI was applied based on the Talairach Daemon associated with this atlas. Sagittal bisection of this mask to create an anterior and posterior hippocampus mask was done as described, and applied to each individual image. Voxels within the whole hippocampus mask were selected such that the anterior hippocampus was bounded, starting at slice 46 and ending at slice 59, anteriorly by the boundaries of the whole hippocampus mask, and posteriorly by the bisection line. The posterior hippocampus was bounded, starting at slice 46 and ending at slice 55, anteriorly by the bisection line and posteriorly by the boundaries of the whole hippocampus mask.

An average time series was extracted from the 6 seed regions of interest (ROIs) outlined above (three right and left hippocampal ROIs—whole, anterior, posterior hippocampus). Voxel-wise correlations with these time series were obtained using Pearson product-moment correlations, generating *r*-values which were transformed to *z*-scores using Fisher's *r*-to-*z*-transformation (Fisher, 1915). This yielded connectivity *z*-scores for each voxel with the three right and left hippocampal ROIs (whole, anterior, posterior hippocampus).

2.4 Statistical analyses

To test our *a priori* hypothesis, a one-way analysis of variance (ANOVA) on individual bilateral anterior, posterior and whole hippocampal *z*-scores was initially performed across the three diagnostic groups (SZ, SAD, and BD-P). Since no significant differences were detected across the psychosis groups, they were subsequently combined into a single PS group ($n = 88$) and contrasted with HC ($n = 65$) on right and left, anterior, posterior and whole hippocampal connectivity *z*-scores using independent sample *t*-tests in AFNI.

Significance of these independent sample *t*-tests were designated at a threshold of $p < 0.01$, $k = 32$ contiguous voxels. These values were derived from AFNI's 3dClustSim program for cluster-extent based thresholding and provided a family-wise error rate of $p < .05$. Voxels retained after thresholding demarcated statistically significant group disparate nodes, for PS and HC groups, in connectivity with the respective ROIs. Average individual *z*-connectivity scores with respective seed ROIs were acquired in these group disparate nodes (i.e., areas shown to have significantly different connectivity with hippocampus in PS compared to HC; see Table 2 for details). Thus, each PS had six “group-disparate network” individual *z*-connectivity scores: three *z*-scores quantifying connectivity with left anterior, posterior, and whole hippocampus, and three *z*-scores quantifying connectivity with right anterior, posterior, and whole hippocampus.

One-way ANOVA with a subsequent *post hoc* Tukey honest significant difference (HSD) test or Yates corrected chi-square test were used, as appropriate, for demographic and clinical variables. Spearman rank correlations between individual *z*-scores and measures of symptom severity (PANSS total and all subscales, MADRS, YMRS), cognitive function (BACS total and verbal memory subscale, WRAT-4 IQ), and concomitant medication use (antipsychotic daily dose chlorpromazine equivalents), were also computed.

3. Results

3.1 Hippocampal connectivity outcomes across DSM diagnoses: schizophrenia vs. schizoaffective disorder vs. psychotic bipolar I disorder

A three-group one-way ANOVA of individual connectivity z-scores across DSM categories (SZ vs SAD vs BD-P) showed no significant differences in hippocampal connectivity based on the whole hippocampal seed ROI (Left: $F(2, 85) = 1.40, p = 0.25$; Right: $F(2, 85) = 1.31, p = 0.27$), suggesting similar hippocampal-cortical alterations across the DSM diagnoses of psychotic illness.

Because connectivity is known to vary across the long axis of hippocampus, we also examined anterior vs. posterior seed dysconnectivity networks, based on the experimental evidence that anterior hippocampus is more dominantly involved in psychosis than the posterior hippocampus (Medoff et al., 2001). A three-group (SZ, SAD, BD-P) one-way ANOVA revealed no significant differences between diagnostic groups in anterior hippocampus (Left: $F(2, 85) = 1.82, p = 0.17$; Right: $F(2, 85) = 2.98, p = 0.06$) or in posterior hippocampus (Left: $F(2, 85) = 0.47, p = 0.63$; Right: $F(2, 85) = 0.40, p = 0.67$); albeit, a statistical trend emerged in the anterior but not the posterior seed network (see Figure 1 for graphical depiction the distribution of anterior hippocampal z-scores, demonstrating lack of statistical difference in z-score means across categorical diagnoses).

3.2 Hippocampal connectivity outcomes in psychosis vs. healthy controls

Since no differences in hippocampal connectivity across DSM diagnoses were detected, all psychosis subjects were combined into a single psychosis group (PS) for subsequent analyses. Whole hippocampal seed-based analyses showed broadly distributed cerebral connectivity changes, all with reduced connectivity in PS compared to HC. Results are expressed as k (voxel number) and t (t-stat), indicating strength of association. Target brain regions with reduced hippocampal connectivity in PS included posterior cingulate (left; $k = 73; t = -3.90$), superior temporal gyrus (right; $k = 39; t = -3.98$), thalamus (left; $k = 569; t = -5.83$; right, $k = 46; t = -4.22$) as well as several cerebellar regions (Table 2A; Figure 2A). Overall, there were slightly more left-sided hippocampal dysconnectivities with cerebral targets than right-sided.

Anterior and posterior hippocampal ROI analyses showed significant reductions in connectivity in PS as a whole compared to HC between the anterior hippocampal seed and anterior cingulate cortex (right ACC; $k = 72; t = -4.49$), medial frontal gyrus (left MFG; $k = 512; t = -4.64$), superior temporal gyrus (right STG; $k = 46; t = -3.98$), and thalamus (left; $k = 175; t = -5.11$) (Table 2B; Figure 2B; Figure 3). Anterior hippocampus also showed reduced connectivity with cerebellum (right; $k = 59; t = -3.78$) and parietal lobe/precuneus (right; $k = 54; t = -3.90$) in PS vs. HC. Likewise, posterior hippocampal seeds demonstrated decreased connectivity in the psychosis group compared to HC, but with fewer ROIs (i.e., 6 posterior ROIs compared to 12 anterior) and a predominantly posterior/cerebellar distribution (i.e., 3 left-sided cerebellar ROIs). In addition, the posterior hippocampal seed showed reduced connectivity with ACC (left; $k = 51; t = -4.69$) and thalamus (left; $k = 53; t = -4.91$) in PS compared to HC (Table 2C; Figure 2C).

3.3 Associations between hippocampal connectivity outcomes and clinical measures

No significant correlations were found in psychosis participants as a whole or in DSM groups (SZ, SAD, BD-P) between subject connectivity z-scores and clinical symptom severity (PANSS, MADRS, YMRS scores), cognitive measures (WRAT-4, BACS total or verbal memory subscale scores), or daily antipsychotic dose chlorpromazine equivalents. In addition, because a proportion of participants were off antipsychotic medications ($n=10$: 3 SZ, 4 SAD, and 3 BD-P), we carried out direct comparisons between these 10 off-antipsychotic PS and a group of on-antipsychotic PS ($n=10$) matched by diagnosis, age, sex, and other concomitant active medications. No significant connectivity differences in whole, anterior, or posterior hippocampal seeds were noted between these on- vs. off-antipsychotic PS subgroups.

4. Discussion

Overall, these data show a decrease in voxel-wise connectivity with hippocampus across the schizophrenia-bipolar psychosis dimension, consistent with the presence of aberrant hippocampal activity in psychosis. Target areas of dysconnectivity with whole hippocampus included the cingulate cortex, superior temporal gyrus and thalamus. When we restricted the hippocampal seed to anterior hippocampus, disconnected regions shifted more anteriorly, including anterior cingulate and the medial prefrontal cortex, as well as the superior temporal gyrus, thalamus and precuneus. Results illustrate dysconnectivity patterns with regions that are primarily impacted by previously reported alterations in hippocampal structure and activity (Shergill et al., 2000; Kircher et al., 2001; Shergill et al., 2003; Seiferth et al., 2008; Wolf et al., 2009; Cronenwett and Csernansky, 2010; Preston et al., 2010; Faget-Agius et al., 2012; Arnold et al., 2014; Unschuld et al., 2014; Anticevic et al., 2014; van Tol et al., 2014; Lui et al., 2014; Mathew et al., 2014). These present results lend support to the hypothesis that cerebral dysfunction in psychotic illnesses derives from hippocampal dysfunction.

Hippocampal hyperactivity has been demonstrated at the level of gene, protein, synapse, and functional connectivity. This study is the first examination of the effects of hippocampal hyperactivity on the neocortex, using seed-based resting state fMRI methodology. Uniquely, this study applies a dimensional approach to psychotic illness. It specifically examines hippocampal connectivity across the three major psychotic disorders (schizophrenia, schizoaffective disorder, bipolar disorder), evaluated concurrently with the same experimental paradigm. By contrast, the majority of other studies to date have looked at whole brain connectivity in the context of a single DSM diagnosis (e.g., schizophrenia). Previous studies have shown both increases and decreases in whole brain connectivity in the context of various DSM diagnoses. Within a large psychosis dimension sample, this study elucidates that there are only decreases in connectivity to the whole brain with respect to the hippocampus, with connectivity not being significantly different across specific DSM diagnoses. Furthermore, we specifically examined the cerebral representation of anterior and posterior hippocampal hyperactivity. We found that the regions affected by disruptions in anterior and posterior hippocampal activity are in line with regions shown to be functionally connected with each in previous studies. Therefore, we add here to previous work by testing

a specific hypothesis about hippocampal hyperactivity and the consequences to neocortical connectivity across the psychosis dimension.

We showed a diffuse network of group disparate dysconnectivity for PS compared to HC. Consistent with the outcome that no significant hippocampal connectivity differences were found across individual DSM diagnostic categories, previous literature has demonstrated that biological differences across conventional phenomenological diagnoses are difficult to establish with any traditional biomarkers (Badner and Gershon, 2002; Freedman et al., 2005; Ivleva et al., 2010; Tamminga et al., 2013; Mathew et al., 2014; Arnold et al., 2014; Liu et al., 2014). However, once connectivity was segmented into anterior vs. posterior seeds, anterior hippocampal seed outcomes were close to statistical significance with respect to the effect of categorical diagnosis. Therefore, the possibility that characteristics of conventional diagnoses could affect anterior hippocampal connectivity patterns needs to be explored further. Pathology in different regions across the long axis of hippocampus may determine, to some extent, the clinical presentation of psychotic and affective symptoms.

The disrupted psychosis network presented here is also consistent with some previous literature demonstrating reduced functional rsfMRI connectivity in psychosis (Karbassforoushan and Woodward, 2012; Anderson and Cohen, 2013). Previous studies show a mix of increased and decreased connectivity in schizophrenia and other DSM psychosis diagnoses. Decreased connectivity across the whole brain, including decreased network small-worldness and efficiency, and decreased interhemispheric connectivity, as well as decreased anatomic and functional connectivity between numerous brain regions, has been noted in schizophrenia (Karbassforoushan and Woodward, 2012; Anderson and Cohen, 2013). Altered functional and structural connectivity has been reported for the hippocampus and middle temporal gyrus (Zhou et al., 2008; Skudlarski et al., 2010; Guo et al., 2014). While most studies report decreased medial temporal lobe connectivity as part of a larger network analysis, Zhou et al. (Zhou et al., 2008) specifically examined hippocampus as a seed region in a small sample of individuals with SZ. They suggested that anterior hippocampal connectivity is decreased in schizophrenia, similar our findings in a large sample throughout the psychosis dimension.

No correlations were found between connectivity alterations and clinical and cognitive measures, including BACS and active symptoms severity scores. This may suggest that hippocampus-driven functional connectivity changes represent a stable trait-like biomarker for psychotic illness independent of active symptom severity. Likewise, we found no associations between individual hippocampal connectivity scores and daily antipsychotic dose. Moreover, in comparing an off-antipsychotic subgroup with a matched medicated PS group, we saw no changes in connectivity attributable to active antipsychotic treatment, though the sample size in this comparison was small. A few studies have shown variable effects of medication on resting-state networks, some dissimilar to ours, e.g., an increase in amplitude of low frequency fluctuations (ALFF) in frontal/parietal neocortex in antipsychotic-naïve schizophrenia patients (Lui et al., 2010; Turner et al., 2012). Disambiguating primary disease effects on functional connectivity from disease-associated factors (e.g., long-term use of various psychotropic medications) will require further investigation. Longitudinal designs focusing on brain connectivity phenotypes in

medication-naïve psychosis individuals and/or at-risk populations (such as unmedicated biological relatives with propensity for psychosis) may shed light on these complex issues.

In summary, we identify differences in hippocampal connectivity with selected brain regions within a broad psychosis population, providing a framework for future investigation of molecular and anatomic mechanisms and potential targets for treatments. These findings highlight the usefulness of relying on a dimensional approach to identify disease characteristics and, possibly, novel treatment targets (Cuthbert and Insel, 2010; Insel, 2012). The strengths of our study include a dimensional, relatively large sample of individuals with psychosis spanning several DSM diagnoses, as well as a detailed examination of hippocampal-cortical connectivity along the long axis. Limitations include the cross-sectional nature of the study and potential confounds related to chronic medication effects and other disease associated factors (e.g., lifetime medical comorbidities). Future studies will investigate hippocampal functional and structural connectivity characteristics, coupling imaging with genetic and molecular approaches and focusing on disease dimensions beyond psychosis (e.g., affect, cognition). These will clarify the role of hippocampus in severe mental illness and explicate disease biomarkers for diagnosis and treatment.

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HIGHLIGHTS

- We examine resting state fMRI data from the large-scale multisite B-SNIP consortium using a hippocampal seed-based functional connectivity approach
- We contrast 88 individuals with psychosis (including the three DSM diagnoses: schizophrenia, schizoaffective disorder, and psychotic bipolar I disorder), vs 65 healthy controls
- We find no differences in hippocampal connectivity across DSM psychosis diagnoses
- Psychosis subjects as a whole have lower connectivity between hippocampus and a broad network of frontal/limbic regions
- There are differential anterior and posterior hippocampal contributions to the dysconnectivity network

Figure 1. Anterior hippocampus connectivity scores across DSM diagnostic categories
The above box-and-whisker plots graphically detail median, 25th and 75th percentiles, and standard deviation for left and right anterior hippocampal z-scores.

(A) Whole hippocampus seed (L/R)

(B) Anterior hippocampus seed (L/R)

(C) Posterior hippocampus seed (L/R)

Figure 2. Whole, anterior, and posterior hippocampal-neocortical connectivity in psychosis vs. healthy controls

All ROIs depicted at alpha at 32 voxels; $P < 0.009$. Single hippocampus-centered sagittal slices shown for the left (L) and right (R) hemispheres. Color denotes connectivity correlation strength (strength of difference between psychosis subjects and healthy controls in synchronous hippocampal-whole brain frequency), with darker blue colors indicating higher negative t-values.

Figure 3. Alterations in the anterior hippocampus connectivity network in psychosis

Anterior hippocampus (AHPC) denoted as gray ovals. All regions with decreased connectivity ($p < 0.01$, 32 voxel threshold) are labeled, and dysconnection of anterior hippocampus network in psychosis subjects compared to healthy controls shown in blue. A continuum of reduced connectivity is demonstrated: darker blue color depicts more reduced connectivity with anterior hippocampus (higher negative t-values). *R* right; *L* left; *(A)CC* (anterior) cingulate cortex; *Cb* cerebellum, *LG* lingual gyrus, *MFG* medial frontal gyrus, *SPL* superior parietal lobule, *STG* superior temporal gyrus, *thal* thalamus, *PCG* postcentral gyrus, *PCun* precuneus

Table 1

Clinical, cognitive, and socio-demographic characteristics of the study sample

	SZ (n=21)	SAD (n=40)	BD-P (n=27)	HC (n=65)	Test statistic	p value
Socio-demographic characteristics						
Age, years; Mean (SD)	38.1 (11.2)	39.0 (11.4)	39.7 (10.9)	40.0 (11.7)	$F(3, 149) = 0.18$	0.91
Sex/Male; n (%)	14 (66.7)	18 (45.0)	8 (29.6)	29 (44.6)	$\chi^2(3) = 6.31$	0.10
Handedness; n (%)					$\chi^2(6) = 4.58$	0.60
Right-handed	17 (81.0)	36 (90.0)	25 (92.6)	56 (86.2)		
Left-handed	4 (19.0)	2 (5.0)	2 (7.4)	6 (9.2)		
Ambidextrous	0 (0.0)	2 (5.0)	0 (0.0)	1 (1.5)		
Ethnicity/Hispanic; n (%)					$\chi^2(3) = 3.59$	0.31
Race; n (%)					$\chi^2(6) = 10.82$	0.09
Caucasian	12 (57.1)	17 (42.5)	18 (66.7)	47 (72.3)		
African-American	9 (42.9)	21 (52.5)	8 (29.6)	15 (23.1)		
Other	0 (0.0)	2 (5.0)	1 (3.7)	3 (4.6)		
Education, years; Mean (SD)	12.3 (2.3)	12.9 (2.1)	14.1 (2.1)	13.9 (1.9)	$F(3, 146) = 5.18$	0.002 ^a
Clinical characteristics; Mean (SD)						
Age at illness onset, years	22.2 (12.1)	18.4 (9.6)	24.4 (11.1)	-	$F(2, 85) = 2.73$	0.07
Age at first hospitalization, years	26.0 (10.1)	24.0 (8.7)	31.0 (10.5)	-	$F(2, 70) = 3.63$	0.03 ^b
Number of lifetime hospitalizations	5.6 (5.5)	6.8 (7.6)	3.5 (4.5)	-	$F(2, 69) = 1.85$	0.17
PANSS						
Total	77.3 (10.3)	76.7 (13.1)	59.4 (12.8)	-	$F(2, 85) = 18.69$	<0.001 ^c
Positive	20.8 (3.1)	20.9 (3.8)	15.7 (3.8)	-	$F(2, 85) = 18.43$	<0.001
Negative	17.7 (2.7)	16.3 (3.6)	11.9 (3.5)	-	$F(2, 85) = 20.28$	<0.001
General	38.9 (7.0)	39.5 (7.0)	31.7 (7.3)	-	$F(2, 85) = 10.66$	<0.001
YMRS	7.1 (4.9)	8.4 (5.3)	7.4 (6.8)	-	$F(2, 84) = 0.43$	0.65
MADRS	12.2 (8.9)	14.2 (9.2)	11.4 (8.7)	-	$F(2, 84) = 0.83$	0.44
GAF	42.3 (11.9)	46.5 (11.2)	57.8 (9.4)	88.1 (3.2)	$F(3, 149) = 282.25$	<0.001 ^d

Cognitive function; Mean (SD)	SZ (n=21)	SAD (n=40)	BD-P (n=27)	HC (n=65)	Test statistic	p value
WRAT IQ (standardized scores)	91.5 (15.5)	95.1 (13.5)	99.4 (11.9)	100.2 (14.6)	$F(3, 149) = 2.68$	0.049 ^e
BACS (z-scores)						
Composite	-1.7 (1.3)	-1.6 (1.3)	-1.2 (1.3)	-0.2 (1.2)	$F(3, 127) = 11.51$	<0.001 ^f
Verbal Memory	-1.1 (1.3)	-0.9 (1.5)	-0.6 (1.3)	-0.3 (1.3)	$F(3, 127) = 2.15$	0.098
Concomitant medications; n (%)						
Off psychotropic medications	3 (14.3)	3 (7.5)	1 (3.7)	-	-	-
Antipsychotics	18 (85.7)	36 (90)	24 (88.9)	-	-	-
Daily chlorpromazine equivalent dose; mg, Mean (SD)	483.9 (375.8)	589.2 (612.1)	404.1 (462.6)	-	$F(2, 54) = 0.65$	0.53
Mood stabilizers	4 (19.0)	19 (47.5)	16 (59.3)	-	-	-
Lithium	3 (14.3)	5 (12.5)	3 (11.1)	-	-	-
Anticonvulsants	1 (4.8)	14 (35)	13 (32.5)	-	-	-
Antidepressants	9 (42.8)	19 (47.5)	15 (37.5)	-	-	-
Anxiolytics/hypnotics	5 (23.8)	14 (35)	7 (25.9)	-	-	-
Other	7 (33.3)	8 (20)	5 (18.5)	-	-	-
Combined medications	15 (71.4)	33 (82.5)	24 (88.9)	-	-	-

SZ – patients with schizophrenia, SAD – patients with schizoaffective disorder, BD-P – patients with psychotic bipolar I disorder, HC – healthy comparison subjects, SD – standard deviation, WRAT – Wide Range Achievement Test IQ estimate, PANSS – the Positive and Negative Syndrome Scale, YMRS – the Young Mania Rating Scale, MADRS – the Montgomery-Asberg Depression Rating Scale, GAF – the Global Assessment of Functioning, BACS – the Brief Assessment of Cognition in Schizophrenia

Missing demographic data: Handedness (2 HC), Education (2 SAD, 1 HC); Chlorpromazine equivalents data are available in 11 SZ, 30 SAD, and 16 BD-P

^a Education: SZ had lower education than HC ($p = 0.008$) and BDP ($p = 0.01$).

^b Age at first psychiatric hospitalization: BDP were first hospitalized at older age than SAD ($p = 0.03$).

^c PANSS total: BDP had lower scores than SZ ($p < 0.001$) and SAD ($p < 0.001$). PANSS positive symptoms subscale: BDP had lower scores than SZ ($p < 0.001$) and SAD ($p < 0.001$). PANSS negative symptoms subscale: BDP had lower scores than SZ ($p < 0.001$) and SAD ($p < 0.001$). PANSS general symptoms subscale: BDP had lower scores than SZ ($p = 0.003$) and SAD ($p < 0.001$).

^d GAF: All patient groups had lower functioning compared to HC: HC vs. SZ, $p < 0.001$; HC vs. SAD, $p < 0.001$; HC vs. BDP, $p < 0.001$. BDP had higher scores than SZ ($p < 0.001$) and SAD ($p < 0.001$). No differences were found between SZ vs. SAD ($p = 0.26$).

^e WRAT: SZ had lower IQ scores than HC ($p = 0.06$, trend).

^f BACS composite: All patient groups had lower BACS composite scores than HC: HC vs. SZ, $p < 0.001$; HC vs. SAD, $p < 0.001$; HC vs. BDP, $p = 0.005$.

Whole, anterior, and posterior hippocampal connectivity ROIs by hemisphere in psychosis participants vs. healthy controls

Table 2

2A) Whole hippocampal seed					
Left whole hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Left thalamus/medial dorsal nucleus	569	+1.7	+8.1	+10.0	-5.83
Right declive/pyramis	313	-8.6	+76.9	-19.8	-4.65
Right declive/tuber	311	-36.1	+63.1	-19.8	-4.49
Left posterior cingulate	73	+1.7	+45.9	+10.0	-3.90
Left inferior occipital gyrus/BA 18	54	+29.2	+83.8	-9.9	-4.31
Right parahipp gyrus/BA 34	32	-15.5	+1.2	-14.8	-3.64
Right whole hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Left inferior occipital gyrus/BA 18	142	+29.2	+83.8	-9.9	-4.31
Right tuber	160	-39.5	+66.6	-24.8	-5.06
Left cerebellum	57	+1.7	+76.9	-14.8	-4.55
Left cerebellum	55	+29.2	+49.4	-34.7	-4.06
Left uvula/pyramis	49	+22.3	+76.9	-24.8	-4.28
Right thalamus/pulvinar	46	-1.7	+25.3	+5.0	-4.22
Right superior temporal gyrus	39	-49.9	+1.2	-4.9	-3.98
2B) Anterior hippocampal seed					
Left anterior hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Left lingual gyrus/inferior occipital gyrus	881	+29.2	+76.9	-4.9	-4.52
Left medial frontal gyrus/BA 10	512	+5.2	-53.8	-4.9	-4.64
Left thalamus/medial dorsal nucleus	175	+1.7	+8.1	+10.0	-5.11
Left inferior semilunar lobule	61	+22.3	+66.6	-39.7	-5.30
Right cingulate/BA 24	45	-1.7	+15.0	+34.8	-4.79
Right cingulate/BA 32	32	-5.2	-15.9	+29.9	-3.82

2B) Anterior hippocampal seed

Right anterior hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Left lingual gyrus/inferior occipital gyrus	495	-39.5	+66.6	-24.8	-2.13
Right anterior cingulate/BA 9	72	-1.7	-22.8	+0.1	-4.49
Left cerebellum	59	+29.2	+59.7	-49.6	-3.78
Right postcentral gyrus/BA40	59	-29.2	+35.6	+54.7	-3.74
Left superior parietal lobule/precuneus	54	+25.8	+52.8	+54.7	-3.90
Right superior temporal gyrus	46	-49.9	+1.2	-4.9	-3.98

2C) Posterior hippocampal seed

Left posterior hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Right declive/cerebellar vermis	143	-5.2	+70.0	-14.8	-4.17
Right thalamus/medial dorsal nucleus	53	-1.7	+18.4	+10.0	-4.91
Left anterior cingulate/caudate	51	+8.6	-26.3	+0.1	-4.69
Right declive/fusiform gyrus	47	-36.1	+80.3	-14.8	-4.00
Left cerebellum	32	+29.2	+52.8	-34.7	-3.39
Right posterior hippocampal seed					
Anatomical region	Voxel number	X	Y	Z	Connectivity t-statistic
Right thalamus/medial dorsal nucleus	65	-39.5	+66.6	-24.8	-3.25

All alpha at 32 voxels; $P < 0.009$; coordinates reported in Talairach brain space. Correlation strength given as t-stat (strength of difference between psychosis subjects (SZ, SAD, BD-P) and healthy controls in synchronous hippocampal-whole brain frequency), with + denoting hyperconnectivity and - denoting hypoconnectivity.