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Alterations in hippocampal connectivity across the psychosis dimension

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ABSTRACT

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 dysconnected 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.

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 15 O-water (Medoff et al., 2001); later, increased activity 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

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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, and 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 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, 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.

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