Journal of Affective Disorders 150 (2013) 601–609

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia

Daniel Mamah [a,*], Deanna M. Barch [a,b], Grega Repovš [c]

[a] Department of Psychiatry, Washington University in Saint Louis, 660 South Euclid Avenue, Box 8134, Saint Louis, Missouri 63110, USA
[b] Departments of Psychology & Radiology, Washington University in Saint Louis, One Brookings Drive, Campus box 1125, Saint Louis, Missouri 63130, USA
[c] Department of Psychology, University of Ljubljana, Askerčeva 2, SI-1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 19 December 2012
Accepted 30 January 2013
Available online 13 March 2013

Keywords:
Schizophrenia
Bipolar
Functional connectivity
Networks
Resting state

ABSTRACT

Background: Bipolar disorder (BPD) and schizophrenia (SCZ) share clinical characteristics and genetic contributions. Functional dysconnectivity across various brain networks has been reported to contribute to the pathophysiology of both SCZ and BPD. However, research examining resting-state neural network dysfunction across multiple networks to understand the relationship between these two disorders is lacking.

Methods: We conducted a resting-state functional connectivity fMRI study of 35 BPD and 25 SCZ patients, and 33 controls. Using previously defined regions-of-interest, we computed the mean connectivity within and between five neural networks: default mode (DM), fronto-parietal (FP), cingulo-opercular (CO), cerebellar (CER), and salience (SAL). Repeated measures ANOVAs were used to compare groups, adjusting false discovery rate to control for multiple comparisons. The relationship of connectivity with the SANS/SAPS, vocabulary and matrix reasoning was investigated using hierarchical linear regression analyses.

Results: Decreased within-network connectivity was only found for the CO network in BPD. Across groups, connectivity was decreased between CO-CER ($p < 0.001$), to a larger degree in SCZ than in BPD. In SCZ, there was also decreased connectivity in CO-SAL, FP-CO, and FP-CER, while BPD showed decreased CER-SAL connectivity. Disorganization symptoms were predicted by connectivity between CO-CER and CER-SAL.

Discussion: Our findings indicate dysfunction in the connections between networks involved in cognitive and emotional processing in the pathophysiology of BPD and SCZ. Both similarities and differences in connectivity were observed across disorders. Further studies are required to investigate relationships of neural networks to more diverse clinical and cognitive domains underlying psychiatric disorders.

1. Introduction

Resting state functional connectivity MRI (rs-fcMRI) is based on the premise that spontaneous low-frequency (< 0.1 Hz) blood oxygen level dependent (BOLD) signal fluctuations in functionally-related gray matter regions show strong correlations at rest (Biswal et al., 1995). These low frequency BOLD fluctuations appear to relate to spontaneous neural activity (Biswal et al., 1995; Anand et al., 2009; Nir et al., 2006; Leopold et al., 2003). Studies employing rs-fcMRI using graph theory and hierarchical clustering (Anticevic et al., 2012; Dosenbach et al., 2007) or independent component analysis (ICA) (Ongür and Lundy, 2010; Seeley et al., 2007) have shown that the control regions of the brain separate into distinct networks. These networks show high concordance with other measures of structural and functional connectivity in healthy populations (Calhoun et al., 2011; Greicius et al., 2009) and provide an opportunity to characterize distributed circuit abnormalities in neuropsychiatric illnesses (Chai et al., 2011; Fox and Greicius, 2010). In addition, because rs-fcMRI does not require active engagement in a behavioral task, it unburdens experimental design, subject compliance, and training demands.

Several distinct, functionally connected resting state networks have been identified, generally reproducible across different study populations and methodologies. These networks include the default mode, cingulo-opercular, fronto-parietal, dorsal attention, ventral attention, cerebellar, salience, sensorimotor, visual, and auditory networks (Meda et al., 2012; Raichle, 2011; Power et al., 2011). Our previous work (Dosenbach et al., 2007; Repovs et al., 2011; Dosenbach et al., 2008; Repovs and Barch, 2012; Fair et al., 2009) has examined connectivity within and between

* Corresponding author.
E-mail address: mamahd@psychiatry.wustl.edu (D. Mamah).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.01.051

four of these brain networks thought to be critical for cognitive function: the default mode (DM), the fronto-parietal (FP), the cingulo-opercular (CO), and a cerebellar (CER) network. The DM network is hypothesized to support functions such as self-inspection, future planning, task-independent thought, and attention to internal emotional states; the role of which diminishes during traditional cognitive tasks (Raichle et al., 2001; Broyd et al., 2009; Buckner et al., 2008). The CO network is thought to instantiate and maintain set during task performance, and is believed to detect errors in behavior, thereby signaling the possible need for cognitive strategy adjustment (Dosenbach et al., 2007; Dosenbach et al., 2008; Dosenbach et al., 2006; Fair et al., 2007; Becerril et al., 2011). Regions in the FP network have been referred to as the executive control (Seeley et al., 2007; Xie et al., 2012) network, and this network is thought to incorporate feedback from other networks to make adjustments in processing on later cognitive tasks (Dosenbach et al., 2007; Dosenbach et al., 2008). The CER network shows error related activity in many different types of tasks (Dosenbach et al., 2008; Fair et al., 2007; Becerril et al., 2011). It has been suggested that the cerebellum sends error codes to the CO and FP networks or receives error information from one or both of the these networks (Dosenbach et al., 2008). This role of the CER network is consistent with the view that the cerebellum processes error information to optimize performance (Fornito et al., 2011; Fiez, 1996; Woodward et al., 2011; Fiez et al., 1992).

In addition to these networks, the salience network (SAL), which includes regions of the anterior cingulate (aCC), anterior prefrontal cortex (aPFC), and anterior insula (aI), is thought to play a role in recruiting relevant brain regions for the processing of sensory information (Seeley et al., 2007; Palaniyappan and Liddle, 2012). In schizophrenia, aberrant salience has been proposed as an important mechanism in the production of psychotic symptoms such as delusions and hallucinations (White et al., 2010; Palaniyappan et al., 2011). While appearing to overlap with regions in the CO network, the SAL regions have been described as lying anterior and ventral in aCC, lateral in aPFC and dorsal in aI; although evidence for these differentiations are provisional (Power et al., 2011).

Schizophrenia and bipolar disorder are among the most devastating psychiatric illnesses, and have at least somewhat distinct clinical courses and outcomes. However, they also have substantial overlap in phenomenology (Keshavan et al., 2011), cognition (Glahn et al., 2010; Glahn et al., 2006; Schretlen et al., 2007), brain structure (Arnone et al., 2009; Ellison-Wright and Bullmore, 2010), brain function (Sui et al., 2011) and disease risk genes (Lichtenstein et al., 2009; Berrettini, 2000; Badner and Gershon, 2002). Similarities appear to be higher between schizophrenia and the bipolar patients who have a history of psychosis (Potash et al., 2001; Strasser et al., 2005; Selva et al., 2007). Psychosis, the hallmark of schizophrenia, also affects 50–70% of bipolar patients (Guze et al., 1975; Coryell et al., 2001; Dunayevich and Keck, 2000). Numerous studies have examined functional brain connectivity in schizophrenia during rest states, although results have been variable. For example, both increased (Whitfield-Gabrieli et al., 2009; Salvador et al., 2010) and decreased (Camchong et al., 2011; Bluhm et al., 2007; Rotarska-Jagiela et al., 2010) connectivity has been found in the DM network, although the majority of studies have found task-related suppression of the this network (Pomarol-Clotet et al., 2008; Pomarol-Clotet et al., 2010; Kim et al., 2009; Hasenkamp et al., 2011; Schneider et al., 2011). SAL network anomalies were also reported by some authors (White et al., 2010) but not found by others (Woodward et al., 2011). In our earlier studies, we found intact connectivity within each of four networks in schizophrenia patients and their unaffected siblings, but found reduced connectivity between CO-FP, the CO-CER, and FP-CER (Repovs et al., 2011; Repovs and Barch, 2012). Additionally, greater connectivity between the FP-CER networks was robustly predictive of better cognitive performance across groups and predictive of fewer disorganization symptoms among patients. Existing rs-fcMRI studies in bipolar disorder show disrupted connections between the prefrontal cortex and limbic related structures, such as the amygdala and temporal lobe (Anand et al., 2009; Chepenik et al., 2010; Dickstein et al., 2010). Using resting-state techniques others have reported that individuals with bipolar disorder show reduced connectivity within the DMN network (Calhoun et al., 2008), the pregenual anterior cingulate, thalamus and amygdala (Anand et al., 2009). Anticevic et al. (2012) found that bipolar patients exhibited increased amygdala-medial prefrontal cortex connectivity, and reduced connectivity between amygdala and dorsolateral prefrontal cortex, both of which were associated with psychosis history.

Few studies have examined functional networks in both bipolar disorder and schizophrenia. Chai et al. (2011) reported a decoupling of DLPFC and MLPC connectivity in both schizoprhenia and bipolar disorder. These authors also found in bipolar disorder, an increased connectivity of MLPFC with both insula and VLPFC, which were not seen schizophrenia patients or controls. Ongür and Lundy (2010) compared the DMN network in schizophrenia and bipolar disorder, and found that both had less DM network connectivity in medial prefrontal cortex. Meda et al. (2012) reported both shared resting-state network connectivity in schizophrenia and psychotic bipolar disorder between fronto/occipital and anterior default mode/PFC regions, as well as unique patterns of connectivity in each disorder.

The goal of the current study was to examine alterations in functional connectivity within and between the DM, FP, CO, CER and SAL networks, and explore similarities across bipolar disorder and schizophrenia, and can provide insight into pathophysiology of psychiatric disorders, which have been increasingly associated with neural network dysfunction (Zorumski and Rubin, 2011). We hypothesized that subjects with bipolar disorder will have a lesser degree of dyconnectivity in regions primarily involved in cognition (i.e. FP, CO and CER networks), while DM and SAL network connectivity would be abnormal primarily in schizophrenia.

2. Materials and methods

2.1. Participants

The participants (Table 1) for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders at Washington University School of Medicine in St. Louis included: (1) individuals with DSM-IV Schizophrenia (SCZ; $N=25$), (2) individuals with DSM-IV Bipolar Disorder (BPD; $N=35$), and (3) healthy controls ($N=33$). The SCZ and control participants were the same participants reported on in our previous paper on resting state connectivity (Repovs et al., 2011). All participants gave written informed consent for participation. The individuals with SCZ and BPD were all outpatients, and clinically stable for at least two weeks. Controls were required to have no lifetime history of Axis I psychotic or mood disorders and no first-degree relatives with a psychotic disorder.

All subjects were diagnosed on the basis of a consensus between a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2001). Participants were excluded if they: (a) met DSM-IV criteria for substance dependence or severe/moderate abuse during the prior 6 months; (b) had a clinically unstable or severe general medical