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Common and distinct dysfunctional patterns contribute to triple network model in schizophrenia and depression: A preliminary study

Yuchao Jiang[a,1], Mingjun Duan[a,b,1], Xi Chen[a], Xin Chang[a], Hui He[a], YingJia Li[a], Cheng Luo[a,*], Dezhong Yao[a,*]

[a] Key Laboratory for NeuroInformation of Ministry of Education, Center for Information in Medicine, High-Field Magnetic Resonance Brain Imaging Key Laboratory of Sichuan Province, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China
[b] Department of psychiatry, Chengdu Mental Health Center, Institute of Chengdu Brain Science, Chengdu, China

ABSTRACT

Background: Schizophrenia (SCH) and depression (DEP) are prevalent psychiatric disorders and share common and distinguished elements in their pathophysiology. A triple network model composed of the default mode network (DMN), salience network (SN) and central executive network (CEN) may represent a major abnormality across several psychiatric disorders including SCH and DEP. However, common and distinct dysfunctional patterns between SCH and DEP across three core networks remain unclear.

Method: Resting-state functional magnetic resonance imaging (fMRI) was obtained in 20 patients with SCH, 20 patients with DEP and 20 healthy controls (HC). Both functional connectivity (FC) and Granger causal connectivity across DMN, SN and CEN were evaluated to uncover common and distinct dysfunctional patterns between SCH and DEP.

Results: Two patient groups showed identical abnormal causal connectivity between key nodes of DMN and SN, as well as opposing aberrant FC of DMN-CEN and SN-CEN. Compared with HC, the FC between CEN and DMN was increased in SCH while decreased in DEP. Conversely, DEP showed enhanced FC between CEN and SN, whereas SCH showed decreased FC.

Limitations: The sample size was relatively small, and all participants were taking medication.

Conclusions: Our results identified common patterns including dysconnectivity between DMN and SN, which may contribute to shared cognitive and affective impairment in DEP and SCH. Moreover, opposing dysconnectivity patterns of DMN-CEN may be associated with different self-referential processing abnormalities. These opposing dysconnectivity patterns may indicate an unbalanced recruitment between SN and CEN. Therefore, this study provides dysconnectivity patterns to advance the understanding of the triple network model with regard to psychiatric disorders.

1. Introduction

Schizophrenia (SCH) and depression (DEP) are two serious psychiatric disorders that have both common and distinct clinical features. For example, both diseases share many common characteristic symptoms and signs such as cognitive and affective impairment. Moreover, self-referential processes are altered in patients with SCH (van der Meer et al. 2010) and those with DEP (Sheline et al. 2009) but have distinct manifestations. SCH is characterized by a typically reduced level of self-reference, whereas DEP is characterized by extensive self-attribution.

Resting-state functional magnetic resonance imaging (fMRI) studies have shown that the disruption of the coordinated activity of multiple brain networks is crucial for various pathological psychiatric conditions (Dong et al. 2017; Duan et al. 2015; Menon 2011). Specifically, previous studies have focused on disturbances in three important networks: the central executive network (CEN), the salience network (SN) and the default mode network (DMN) (Whitfield-Gabrieli and Ford 2012). The CEN, a frontoparietal system that includes the dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL) (Seeley et al. 2007), is crucial for manipulating information about the external environment. The DMN, which includes the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), angular gyrus and medial temporal gyrus, plays an important role in monitoring self-referential mental processes (Luo et al. 2011). The SN, which is composed of the

* Corresponding authors at: University of Electronic Science and Technology of China, Second North Jianshe Road, Chengdu 610054, China.
E-mail addresses: chengluo@uestc.edu.cn (C. Luo), dyao@uestc.edu.cn (D. Yao).
[1] These authors contributed equally to this work.

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anterior insula, dorsal anterior cingulate cortex (dACC) and temporoparietal junction (TPJ), is involved in detecting, filtering and integrating relevant salient external stimuli and interoceptive signals (Seeley et al. 2007). As such, a triple network model that synthesizes the extant findings regarding these networks has been proposed to understand pathophysiological dysfunction across several psychiatric disorders (Menon 2011). In this model, dysfunction in one network may affect the other two. In addition, the abnormal integration of information within and across these networks is important in linking the concomitant impaired cognitive features characteristic of psychopathology (Pessoa 2008). An aberrant organization among the three networks might also be associated with abnormal interactions between external stimuli and internal events with regard to self-referential processes (Menon and Uddin 2010). Therefore, additional investigations of the disruptions across core networks are necessary to advance the understanding of the fundamental brain mechanisms that underlie psychopathology.

SCH and DEP have been generally identified in relation to the aberrant functioning and organization of the CEN, SN and DMN (Nekovarova et al. 2014). However, whether common and distinct dysfunctional patterns exist across three networks with regard to SCH and DEP remains unclear. Here, we speculate that identical and opposite aberrant connectivity patterns exist across the three core networks in patients with SCH and those with DEP. Exploring the identical and opposite dysconnectivity patterns could not only help to characterize the dynamic interaction and functional integration of information across the core networks, but also enhance the insights concerning the shared and disparate psychopathologies that underlie the abnormalities in the triple network model with regard to patients with SCH or DEP.

To test our hypothesis, we used the functional connectivity (FC) analysis and Granger causal analysis (GCA) (Hamilton et al. 2011) to investigate the undirected and directed connectivity across the DMN, SN and CEN. In addition, we evaluated whether the altered connectivity in patients is correlated with certain clinical variables.

2. Methods

2.1. Participants

Twenty patients with SCH diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), 20 patients with DSM-IV major depressive disorder, and 20 healthy controls (HC) were recruited from Chengdu Mental Health Centre. Participants with histories of major neurological disorders, brain structural abnormalities or substance-related disorders were excluded. A history of a psychiatric disorder in a first- or second-degree relative was an additional exclusion criterion. None of the patients with SCH had a history of a major depressive episode. Written informed consent was obtained after the study was completely described to each participant. The study was approved by the Ethics Committee of Chengdu Mental Health Centre. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) and the 24-item Hamilton Rating Scale for Depression (HAMD-24) for patients with SCH and those with DEP, respectively. All patients were taking medication (e.g., antidepressants and neuroleptics). Medication use almost perfectly aligned with the patients' diagnostic categories (Supplement 1).

2.2. Image acquisition

A 3-Tesla MRI scanner (GE DISCOVERY MR 750, USA) was used to collect imaging data at the Centre for Information in Medicine of the University of Electronic Science and Technology of China. The gradient-echo echo-planar imaging (EPI) sequence was used to acquire the functional images. The main scan parameters were as follows: TR/TE = 2 s; TE = 30 ms; flip angle = 90°; field of view = 24 cm × 24 cm; matrix size = 64 × 64; slice thickness = 4 mm (no gap), slice = 35. All participants were instructed to relax and close their eyes without falling asleep. Each functional resting-state session lasted 510 s, resulting in 255 volumes. All of these datasets were also included in our previous study (Chen et al. 2017), in which the target was other than the current study.

2.3. Data preprocessing

The data preprocessing steps included (1) removing the first five time points for signal equilibrium and to allow the participants to adapt to the scanning noise; (2) slice timing; (3) realignment; (4) coregistering the individual T1 image to the functional space and segmenting; (5) nuisance signal regression (including Friston 24-parameter motion correction (Satterthwaite et al. 2013), five CompCorr signals (Chai et al. 2012) of white matter and cerebrospinal fluid (CSF), and linear trend); (6) temporal scrubbing using the "bad" time points (frame-wise displacement (FD) (Power et al. 2012) > 0.5) as a regressor; (7) normalizing to MNI space ($3 \times 3 \times 3\ mm^3$) using segment information; (8) band-pass filtering (0.01–0.1 Hz); and (9) smoothing (FWHM = 4 mm). The unsmoothed data was used in the cluster analysis to avoid blurring between insular subregions (Moran et al. 2013). The global mean signal was not regressed out because it may distort between-group comparisons of inter-regional correlation (Saad et al. 2012). In addition, we also compared the differences of various head-motion parameters between groups (Supplement 2).

2.4. Definition of the triple network

The seed-based FC analysis was used to identify the three core networks. The 8-mm spheres of the DLPFC (48,18,17) (Whitfield-Gabrieli et al. 2009) and PCC (−5,−49,40) (Fox et al. 2005) were defined as the seed regions for the CEN and DMN. However, a functional parcellation was used to identify the seed of the SN because the signal of insular subregions might be effected by the CSF and vessel in lateral fissure. In general, the insula can be divided into three subregions: the dorsal anterior insula [dAIns], ventral anterior insula [vAIns] and posterior insula [PIns]. The right dAIns was selected as the seed to define the SN (Touroutoglou et al. 2012). Here, we functionally parcellated the right insula into three regions using an identified method (Supplement 3) same as our previous studies (Cao et al. 2016; Chen et al. 2016), and chose the dAIns as the seed. Then, whole brain voxel-wise Pearson's correlation analyses were used to define the masks of the SN, CEN and DMN separately. In detail, Fisher-Z-transformed correlation coefficients [z(r)] were computed between the average time series of each seed and the whole brain voxels. Finally, one-tailed one sample *t*-tests were performed to determine the significant connectivity with seed (Touroutoglou et al. 2012). Multiple comparisons correction for all FC analyses was performed with an individual p of 0.001 and a minimum cluster size based on Gassian Random Field (GRF) theory, which corresponds to $P_{corrected} = 0.05$. Thus, the voxels positively correlated with the seeds were considered including the three networks.

2.5. Voxel-wise functional connectivity and effective connectivity analyses

For the FC analysis, the Z-transformed coefficient mentioned above was further analyzed in the union mask of CEN, SN and DMN to investigate the undirected FC among the three groups.

For the effective connectivity analysis, the seed-based voxel-wise GCA was performed with regard to the mask of the CEN, SN and DMN with three seeds: dAIns, DLPFC and PCC. First, we used a vector autoregression (i.e., Granger) approach that examined the time lagged effects between two nodes to infer the causal effects between regions (Chen et al. 2011). The signed-path coefficient generated using a time lag order of 1 TR (2 s) was used to estimate the probable excitatory or inhibitory effect of the directed physiological influence (Hamilton et al. 2011; Zang et al. 2012). The bivariate GCA accounted for the