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State-related functional integration and functional segregation brain networks in schizophrenia

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ABSTRACT

Altered topological properties of brain connectivity networks have emerged as important features of schizophrenia. The aim of this study was to investigate how the state-related modulations to graph measures of functional integration and functional segregation brain networks are disrupted in schizophrenia. Firstly, resting state and auditory oddball discrimination (AOD) fMRI data of healthy controls (HCs) and schizophrenia patients (SZs) were decomposed into spatially independent components (ICs) by group independent component analysis (ICA). Then, weighted positive and negative functional integration (inter-component networks) and functional segregation (intra-component networks) brain networks were built in each subject. Subsequently, connectivity strength, clustering coefficient, and global efficiency of all brain networks were statistically compared between groups (HCs and SZs) in each state and between states (rest and AOD) within group. We found that graph measures of negative functional integration brain network and several positive functional segregation brain networks were altered in schizophrenia during AOD task. The metrics of positive functional integration brain network and one positive functional segregation brain network were higher during the resting state than during the AOD task only in HCs. These findings imply that state-related characteristics of both functional integration and functional segregation brain networks are impaired in schizophrenia which provides new insight into the altered brain performance in this brain disorder.

1. Introduction

Schizophrenia appears to be characterized by functional disruptions in cortical connectivity of various types (Friston and Frith, 1995; Pettersson-Yeo et al., 2011). Along with recent papers applying graph theory-based analysis to brain imaging studies in schizophrenia (Bullmore and Sporns, 2009; Bassett and Gazzaniga, 2011), altered topological properties of brain connectivity networks have emerged as important features of this mental illness (Xia and He, 2011; Fornito et al., 2012). However, most of these studies examined the graph metrics of whole brain network (nodes across the whole brain) which characterize functional brain integration (Liu et al., 2008; Lynall et al., 2010; Bassett et al., 2012). Little is known about the topological properties of connectivity within local brain regions that characterize functional brain segregation (specialization).

Functional segregation (the segregated or modular deployment of functional specialization within brain regions) and functional integration (of different brain areas in terms of functional and effective connectivity) are two fundamental, complementary rather than exclusive principles of brain organization (Friston, 2002, 2009; Fox and Friston, 2012). Spatial independent component analysis (ICA) (McKeown and Sejnowski, 1998; McKeown et al., 1998; Calhoun et al., 2001b; Calhoun and Adali, 2012) is a powerful tool to study the segregation and integration of brain function. Each spatial brain component represents a network that includes particular brain regions with specific functions, whereas functional network connectivity (FNC) (Jafri et al., 2008; Calhoun et al., 2009a; Lui et al., 2010; Meda et al., 2012; Yu et al., 2012) examines the integration among components using the temporal correlation of ICA time courses. Recently, graph theory-based analysis of brain connectivity has been widely implemented to reveal the characters of functional segregation and functional integration in human brain (de Pasquale et al., 2013). The clustered connectivity of brain network communities (Salvador et al., 2005; Ferrarini et al., 2009; He et al., 2009; Meunier et al., 2009, 2010; Smith et al., 2009; Shen et al., 2010) represents functional

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segregation and specialization, whereas hubs underpin efficient communication and information integration (Bullmore and Sporns, 2012; Sporns, 2013). Our previous work (Yu et al., 2011a,b, 2013) successfully combined graph theory-based analysis and ICA to characterize the topological properties of integrated whole brain network connectivity in both healthy controls (HCs) and schizophrenia patients (SZs) during the resting state. However, the topological properties of both functional integration and functional segregation brain networks underlying other brain states (such as during performance of a specific task) remain largely unknown.

The study of brain activity and connectivity underlying different states (such as during rest or a task) has recently become a topic of intense focus for the functional Magnetic Resonance Imaging (fMRI) community (Raichle, 2010). Maintaining a mental state and switching between states (cognitive flexibility) are crucial human brain abilities which are vital for both self-regulation and adaptation to varying environments (Leber et al., 2008; Tang et al., 2012). Previous studies have revealed different brain networks involved in different states (Fox et al., 2006; Sridharan et al., 2008), for example the rest-related default mode network (DMN) (Raichle et al., 2001; Greicius et al., 2003; Raichle and Snyder, 2007) and task-related executive-control network (Seeley et al., 2007). Further studies revealed dysconnectivity in brain networks underlying a specific state (e.g. resting state) in SZs (Wolf et al., 2011; Woodward et al., 2011; Karbasforoushan and Woodward, 2012; Yu et al., 2012). However, it is not known if the state-induced modulations of topological measures of brain networks are also disrupted in schizophrenia (Ma et al., 2012).

Considering the unanswered questions above, the aim of this study was to evaluate the graph metrics of both functional integration and functional segregation networks underlying different brain states in schizophrenia. Since both resting state and auditory oddball (AOD) tasks are popular approaches to study schizophrenia using fMRI (Calhoun et al., 2006a, 2009a; Greicius, 2008; Pearlson and Calhoun, 2009; Rosazza and Minati, 2011; Ethridge et al., 2012), topological measures of functional integration (here are weakly coupled inter-component networks) and functional segregation (here are tightly coupled intra-component networks) brain networks underlying these two states were evaluated by ICA and graph theory-based analysis in both HCs and SZs (see Materials and methods section). We predicted that the state-related difference of graph measures of functional segregation and functional integration brain networks would be altered in SZs which might underline the deficits in cognitive functions in this brain disease (Zemlan et al., 1984; Flaum and Schultz, 1996; van Os et al., 2010; Marin, 2012). We also wished to provide a new framework in which to investigate brain dysconnectivity at multiple levels, in order to demonstrate more comprehensively how brain networks are impacted by schizophrenia.

2. Materials and methods

2.1. Participants

Participants consisted of 23 (seven females) HCs (age: 32 ± 9, range 23–50) and 23 (four females) SZs (age: 36 ± 12, range 21–52). Subject ages showed no significant group difference (two-sample t-test, $P = 0.16$). All participants provided written, informed, IRB-approved consent from Hartford Hospital and Yale University and were compensated for their participation. Schizophrenia was diagnosed according to DSM-IV-TR criteria on the basis of a structured clinical interview (First et al., 1995) administered by a research nurse and by review of the medical records. All patients had chronic schizophrenia [Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987), positive score: 16 ± 6, range 7–28; negative score: 15 ± 5, range 7–27] and all were taking stable medication doses (including the atypical antipsychotic medications aripiprazole, clozapine, risperidone, quetiapine and olanzapine, first-generation antipsychotics including fluphenazine, and miscellaneous mood-stabilizing, hypnotic and anti-cholinergic medications including zolpidem, zaleplon, lorazepam, benztropine, divalproex, trazodone, clonazepam). All participants except 1 HC and 2 SZs were right-handed. Healthy participants were free of any DSM-IV-TR Axis I disorder or psychotropic medication and had no family history of Axis I disorders.

2.2. Experimental design

All participants were scanned during both an AOD task and while at rest. The two scans were randomly ordered. The AOD consists of detecting an infrequent sound within a series of regular and different sounds. The stimulus paradigm, data acquisition techniques, and previously found stimulus-related activation are described fully elsewhere (Kiehl et al., 2005). When performing resting state scan, participants were instructed to rest quietly without falling asleep with their eyes open without fixation.

2.3. Image acquisition

FMRI data were acquired on a Siemens Allegra 3 T dedicated head scanner. Resting state and AOD functional scans were acquired using gradient-echo echo-planar-imaging with the following parameters: repeat time (TR) 1.5 s, echo time (TE) 27 ms, field of view 24 cm, acquisition matrix 64 × 64, flip angle 70°, voxel size 3.75 × 3.75 × 4 mm^3, gap 1 mm, 29 slices, and ascending acquisition. Six "dummy" scans were acquired at the beginning to allow for longitudinal equilibrium. The AOD consisted of two 8-min runs (249 × 2 volumes) and the resting state scan consisted of one 5-min run (204 volumes).

2.4. Preprocessing

FMRI data were preprocessed using the SPM software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Data were motion corrected and then spatially normalized into the standard Montreal Neurological Institute (MNI) space (voxel size: 3 × 3 × 3 mm^3, resulting in 53 × 63 × 46 voxels). To reduce spurious correlations between voxels (van den Heuvel et al., 2008; Zalesky et al., 2012) in functional segregation networks in this study, the normalized data were spatially smoothed with a small (5 × 5 × 5 mm^3) full width at half maximum Gaussian kernel.

2.5. Group ICA

Group spatial ICA (Calhoun et al., 2001a, 2009b; Calhoun and Adali, 2012) was performed once on the fMRI data (three sessions, one session for resting state data, two sessions for AOD data) using the GIFT software (http://mialab.mrn.org/software/gift). Subject-specific data reduction by principle component analysis (PCA) retained 100 principal components (PCs) using a standard economy-size decomposition. Reduced data for all 46 participants were then decomposed into 75 aggregate components (Kiviniemi et al., 2009; Smith et al., 2009; Abou-Elseoud et al., 2010; Allen et al., 2011). Single subject time courses and spatial maps were back-reconstructed (Calhoun et al., 2001a; Erhardt et al., 2011). The Infomax ICA algorithm (Bell and Sejnowski, 1995) was repeated 10 times in ICASSO (http://research.ics.aalto.fi/ica/icasso) and resulting components were clustered to estimate the reliability of the decomposition. 42 independent components (ICs) which did not contain large edge effects or ventricles and located on the cerebral cortex by visual inspection were selected to do further analysis.

2.6. Functional integration and functional segregation brain networks

Weighted brain networks were built in this study. For functional integration brain network, 42 × 42 weighted positive (W^+) and negative (W^-) connection networks were built based on the correlations (r_{ij}) (see Eqs. (1), (2)) among ICA time courses of the 42 ICs in each subject underlying both states (rest and AOD).

$$W_{ij}^{+} = \begin{cases} r_{ij} & \text{if } r_{ij} > 0 \\ 0 & \text{if } r_{ij} \le 0 \end{cases} \quad (1)$$