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Research paper

Dynamic functional–structural coupling within acute functional state change phases: Evidence from a depression recognition study

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ABSTRACT

Background: Dynamic functional–structural connectivity (FC–SC) coupling might reflect the flexibility by which SC relates to functional connectivity (FC). However, during the dynamic acute state change phases of FC, the relationship between FC and SC may be distinctive and embody the abnormality inherent in depression. This study investigated the depression-related inter-network FC–SC coupling within particular dynamic acute state change phases of FC.
Methods: Magnetoencephalography (MEG) and diffusion tensor imaging (DTI) data were collected from 26 depressive patients (13 women) and 26 age-matched controls (13 women). We constructed functional brain networks based on MEG data and structural networks from DTI data. The dynamic connectivity regression algorithm was used to identify the state change points of a time series of inter-network FC. The time period of FC that contained change points were partitioned into types of dynamic phases (acute rising phase, acute falling phase,acute rising and falling phase and abrupt FC variation phase) to explore the inter-network FC–SC coupling. The selected FC–SC couplings were then fed into the support vector machine (SVM) for depression recognition.
Results: The best discrimination accuracy was 82.7% ($P=0.0069$) with FC–SC couplings, particularly in the acute rising phase of FC. Within the FC phases of interest, the significant discriminative network pair was related to the salience network *vs* ventral attention network (SN–VAN) ($P=0.0126$) during the early rising phase (70-170ms).
Limitations: This study suffers from a small sample size, and the individual acute length of the state change phases was not considered.
Conclusions: The increased values of significant discriminative vectors of FC–SC coupling in depression suggested that the capacity to process negative emotion might be more directly related to the SC abnormally and be indicative of more stringent and less dynamic brain function in SN–VAN, especially in the acute rising phase of FC. We demonstrated that depressive brain dysfunctions could be better characterized by reduced FC–SC coupling flexibility in this particular phase.

1. Introduction

The human brain is a complex network of structurally and functionally interconnected regions. The previous studies suggested that depressive brain dysfunction might result from abnormal functional networks (Wei et al., 2013; Kaiser et al., 2015; Mulders et al., 2015; Nugent et al., 2015). Several studies suggested that brain function emerges from interaction patterns across the entire network (van den Heuvel et al., 2009; Allen et al., 2011). Major depressive disorder is characterized by deficits in emotional processing and executive functions and associated with the deregulation of brain networks. In addition, depressive symptoms might be associated with brain functional networks (Drevets et al., 2008; Buckner 2010; Price and Drevets, 2010; Hamilton et al., 2015). The functional impairment and deregulation of functional networks, such as default mode network (DMN), salience network (SN), affective network and executive control network, were identified in depressed patients (Davey et al., 2012; Wei et al.,

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2013). The DMN was hypothesized to regulate emotion (Raichle et al., 2001). Key regions of the DMN seemed to be crucial for several emotion regulation strategies (Milad et al., 2007; Delgado et al., 2008). Several lines of evidence suggested that the DMN (Raichle et al., 2001) exhibited unique dynamic interactions with other networks to regulate emotion, such as fronto-parietal network (FPN) (Milad et al., 2007; Delgado et al., 2008). The FPN was considered a task-positive network associated with the emotional process of depression (Vincent et al., 2008; Koenigs and Grafman 2009). The reduction of functional connectivity (FC) between the subgenual cingulate and ventromedial frontal cortex might influence executive attentional processes in depressed patients (Davey et al., 2012). The ventral attentional network (VAN) interrupted and reset attention to behaviorally salient stimuli and was modulated by exposure to emotional stimuli, whereas the task of the dorsal attentional network (DAN) was to maintain the locus of attention in the face of distraction, select stimuli according to prior information or goals, and coordinate responses (Corbetta et al., 2008). Regions in the cingulo-opercular network (CON) had also been implicated in the processing of negative affect (Shackman et al., 2011). The CON provided stable 'set-maintenance' over entire task epochs (Dosenbach et al., 2007). Furthermore, a wealth of evidence indicated a disruption during the processing of emotional stimuli in dACC, one of the main regions in the CON (Amir et al., 2005; McClure et al., 2007; Simmons et al., 2008; Hayes et al., 2009; Shin and Liberzon, 2010; Etkin et al., 2014). The abnormal connectivity of visual network (VIS) might implicate impaired emotional visual information processing in major depressive disorder (MDD) (Zeng et al., 2012; Ma et al., 2013). The visual processing dysfunction in the pathophysiology of MDD supported that neural response in visual areas to emotional stimuli might be a useful biomarker for identifying patients (Furey et al., 2013). Moreover, structural studies elucidated trait factors underlying brain changes in major depressive disorder (Du et al., 2012). The cortical volume of the caudal anterior cingulate cortex and white matter integrity of the corpus callosum were reported to be reduced in depressed patients, suggesting fundamental structural alteration of brain gray and white matter (Han et al., 2014). Regions constituting the DMN were among the most structurally connected (Hagmann et al., 2010). Depressed patients showed the lowered structural connectivity between the nodes of the DMN and the frontal-thalamo-caudate regions (Korgaonkar et al., 2014). The SN had been suggested to be involved in emotion perception (Levens and Phelps, 2010) as an integrative hub of bridging communication between emotion perception and the executive control network (Craig, 2009; Kurth et al., 2010). Both structural connectivity (SC) and FC had been demonstrated between the insula and the anterior cingulate cortex (Taylor et al., 2009), with likely extension into the inferior frontal region (Seeley et al., 2007). Taken together, the functional and structural imaging data had enabled the mapping of high-resolution functional and structural networks, which were called the functional and structural 'human connectome' (Hagmann et al., 2008). The combination of FC and SC should provide more advantages in depression study (Sui et al., 2014).

Along with advances in neuroimaging techniques and multimodal imaging analyses, researchers had explored the combination of FC and SC (Stephan et al., 2001; Zhang et al., 2011; Cabral et al., 2012; van den Heuvel et al., 2013; Dyrba et al., 2015). The large-scale functional and structural properties were disrupted in most neurological and psychiatric diseases (Menon, 2011), including depression (Bassett et al., 2011). Moreover, emerging studies supported that the quantification of the disrupted dynamics might elucidate the cause of disorder and allow for more targeted drug treatment and diagnostic or prognostic indicators (Cribben et al., 2013; Hutchison et al., 2013), especially when exploring the dynamic organizational (conditional) changes of FC (Bassett et al., 2011). Furthermore, strong evidence also supported a relationship between the dynamic functional networks and their corresponding structural architecture (Cabral et al., 2012). However, the dynamic functional-structural connectivity (FC–SC) relationship in depression remains to be explored.

In this study, we investigated the anatomical structure of brain networks and the corresponding functional aspects of spatiotemporal brain dynamics in depression. Particularly, we were interested in the FC–SC couplings when the dynamic FC encounters acute state changes and their effect on depression discrimination. The static SC provided the base of emergent spatiotemporal brain functional dynamics, and the dynamic FC–SC coupling might reflect the flexibility with which SC constrains FC. During the acute state change phases of FC, SC may somewhat restrict FC. Thus, the differences in FC–SC coupling related to depression would appear in the acute state change phases of FC and reflect the dysfunctions in depressed patients.

Based on the above considerations, we constructed functional brain networks based on magnetoencephalography (MEG) data and structural networks from diffusion tensor imaging (DTI) data. A simplified dynamic connectivity regression (DCR) algorithm was used to find the change points of intra-network FC in response to emotional stimuli. DCR is a data-driven method for detecting change points of a time series when the number of change points and their location are not known in advance (Cribben et al., 2012). The time periods of FC were then partitioned into blocks, and the interval FC–SC coupling was detected. The FC–SC relationship characterized the depression-related brain dysfunctions well within a certain dynamic state change phase of FC. The whole analysis protocol is illustrated in Fig. 1.

2. Materials and methods

2.1. Subjects

Twenty-six depressive patients were recruited from in-patient facilities at the Brain Hospital affiliated with Nanjing Medical University. Eligibility screening procedures included a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), the Brief Psychiatric Rating Scale (BPRS) and the Hamilton Depressive Rating Scale (HDRS). Patients had a minimum score of 22 rated with the 17-item HDRS on the day of scanning. Patients without other psychiatric illnesses and who were not currently taking medications were enrolled. According to the DSM-IV, an expert psychiatrist confirmed the initial diagnoses of depression, which was made by the participants'treating psychiatrists.

Twenty-six healthy control participants matched in gender, age and educational level participated in this study. None of them were suffering from any psychiatric illness or a history of psychiatric illness at the time of the study. The demographic data for all subjects are provided in Table 1. This study was approved by the Medical Ethics Review Committee of the Brain Hospital affiliated with Nanjing Medical University, and written informed consents were obtained from all subjects.

2.2. Sad facial affect recognition task

The faces task of the MEG was programmed for all subjects. A pseudo-randomized series of faces with sad and neutral emotional expressions were presented using the Chinese facial expression video system, which has previously been successfully employed to detect depressive dysfunction (Lu et al., 2014). The separated clips were displayed, including 40 sad facial images, 40 neutral facial