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Research paper

Functional connectivity between salience, default mode and frontoparietal networks in post-stroke depression

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ABSTRACT

Background: Previous studies have demonstrated altered resting state functional connectivity (rsFC) in patients with post-stroke depression (PSD). It remains unclear whether rsFC is changed at the network level as was shown for major depressive disorder (MDD). To address this question, we investigated rsFC of resting sate networks (RSNs) in PSD.

Methods: Eleven subjects with PSD underwent fMRI scanning at rest before and after treatment. The severity of depression was assessed using the aphasic depression rating scale (ADRS). We performed functional network connectivity (FNC) analysis for RSNs, region of interest – FC analysis (ROI-FC) and calculation of brain matter volumes in ROIs overlapping with RSNs and in other brain regions associated with mood maintenance.

Results: We found positive correlation of FNC between anterior default mode network (aDMN) and salience network (SAL) with depression severity before treatment, the latter accompanied by the increase of white matter in the middle frontal and left angular gyri. FNC of aDMN and left frontoparietal network (LFP) decreased after treatment. ROI-FC and the brain matter volumes of several regions of DMN, LFP and SAL also showed a correlation with ADRS or significant change after treatment.

Limitations: Limitations include small sample size and methodological issues concerning altered hemodynamics in stroke. However, we took complex preprocessing steps to overcome these issues.

Conclusion: Present results of altered rsFC in PSD are consistent with previous findings in MDD. The convergence of results obtained in PSD and MDD supports the validity of rsFC approach for investigation of brain network dysfunctions underling these psychiatric symptoms.

1. Introduction

According to meta-analysis studies, post-stroke depression (PSD) symptoms occur in 33% of stroke survivors, ranging from 19% to 44% (Hackett and Anderson, 2005) and are associated with to poor physical and social outcomes and slow rehabilitation (Astrom, 1996; Chemerinski and Robinson, 2000; Chemerinski et al., 2001; Narushima and Robinson, 2002; Pan et al., 2008; Robinson, 2003; Shimoda and Robinson, 1998). Studies of PSD origin focused either on lesion characteristics, including location, size, volume, or on psychosocial factors, such as personality, disability, and social support (Bhogal et al., 2004; Davidson et al., 2002; Nys et al., 2006). Some studies examined the relationship between the severity of PSD and brain lesions or other correlative factors (Carson et al., 2000; Santos et al., 2009; Singh et al., 1998). Due to different definitions of depression, duration of disease, measurement issues, and small patient samples, the pathogenesis of PSD is controversial (Bhogal et al., 2004; Santos et al., 2009; Singh et al., 1998).

In the present study, we focused at evaluation of resting state functional network connectivity (rsFNC) changes at the large-scale network level in ischemic stroke patients with PSD. Functional connectivity (FC) analysis was widely applied to study disintegration of

Abbreviations: ACC, anterior cingulate cortex; ADRS, Aphasic Depression Rating Scale; CC, correlation coefficient; DARTEL, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra; DMN, default mode network; EPI, echo-planar imaging; FC, functional connectivity; fMRI, functional MRI; FPN, frontoparietal network; FWHM, full width at half maximum; HRF, hemodynamic response function; LFP, left frontoparietal network; MDD, major depressive disorder; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; NIHSS, The National Institutes of Health Stroke Scale; PCC, posterior cingulate cortex; PSD, post-stroke depression; RFP, right frontoparietal network; ROI, region of interest; rsFNC, resting state functional network connectivity; RSN, resting state networks; SAL, salience network; SCG, subcallosal gyrus; SMG, supramarginal gyrus; SPM, statistical parametric mapping

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brain networks in stroke patients and mechanism of neural plasticity during recovery (Warren et al., 2009; Brownsett et al., 2014; van Hees et al., 2014; Zhu et al., 2014). While standard task-related functional magnetic resonance imaging (fMRI) is limited in stoke survivors, application of resting-state fMRI is more feasible since it requires neither patient's ability to communicate nor sophisticated experimental design. Mulders et al. (2015) have reviewed recent results of resting state fMRI studies in major depressive disorder (MDD) in the context of the connections within and between RSNs and highlighted four repeated findings: increased connectivity within the anterior part of the default mode networks (aDMN); increased connectivity between aDMN and salience network (SAL); decreased connectivity between DMN and frontoparietal networks (FPN, also referred as control FPN or central executive network) and altered connectivity between aDMN and posterior part of the DMN (pDMN). The default mode network (DMN) was originally found in the PET study of Raichle et al. (2001). The main feature of this network is in the presence of its activity at rest and its deactivation during the cognitive task performance. The default mode network includes precuneus, posterior cingulate gyrus, inferior parietal lobule, frontal pole. The impairment of the connectivity within the DMN is associated with mental disorders (Broyd et al., 2009), Alzheimer disease (Wang et al., 2007) schizophrenia (Bluhm et al., 2007) and particularly in major depressive disorder (Greicius et al., 2007). Vincent et al. (2008) also revealed the fronto-parietal network (FPN) interposed between the attention network and DMN in the inferior parietal lobule and prefrontal cortex and assumed that its role lies in the information integration and transfer from one network to another. The SAL consists of the anterior part of the cingulate gyrus and orbitofrontal insular cortex (Seeley et al., 2007). This network is associated with cognitive functions including filtration of the input information, the error and inconsistencies processing (Miller and Cohen, 2001; Seeley et al., 2007). The above-mentioned networks are believed to execute cognitive functions. This assumption is supported by the studies, reporting about a strong association between the functional impairment of these networks and mental pathology (Greicius, 2008; Menon, 2011; Mulders et al., 2015). Importantly, that functional hubs of these three networks are also parts or have connections with limbic system, so this is not surprising that altered FC within and between areas of these networks has been repeatedly shown in studies of depression disorders (Dutta et al., 2014; Mulders et al., 2015; Palmer et al., 2015). To the present day, a few studies explored changes in functional connectivity in PSD (Lassalle-Lagadec et al., 2012; Liu et al., 2014; Vicentini et al., 2016; Zhang et al., 2014), three of them reporting only DMN impairment in PSD. Moreover, so far no neuroimaging studies reported the effect of medication and other stroke rehabilitation procedures on the intrinsic brain (FC) in PSD. Even in case of patients without stroke, the majority of studies of MDD examined the antidepressant effects on the local regional brain activity, while an effect of antidepressants at a large-scale brain network level was rarely explored.

In this article, we investigated rsFNC of three networks (DMN, SAL, and FPN) to check whether their functional relationship may depend on depression severity or alter due to depression and/or antidepressant treatment in patients with PSD. Since our previous study (Balaev et al., 2016) showed that the change of rsFNC might depend on local FC changes and/or the alteration of matter volume even in intact regions in stroke patients, we also tested FC and gray and white matter volumes of the brain regions overlapped with DMN, SAL and FPN, and other brain regions associated with the mood maintenance (Dutta et al., 2014).

2. Materials and methods

2.1. Participants

Eleven patients after single episode of ischemic stroke at sub-acute (i.e. > 1 month after accident) and chronic stages (i.e. > 6 month after accident) of post-stroke rehabilitation (45–78 years old, mean age 63.9 ± 8.4, 9 females; Table 1) were recruited through the Center for Speech Pathology and Neurorehabilitation. Patients with clinical or radiological evidence of previous cerebrovascular accident and MRI contraindications were excluded from the study. Intensive head movements during fMRI scanning were also the cause of exclusion from the further analysis. All selected patients had their first mild to moderate ischemic stroke (NIHSS score ranging from 3 to 10 at the acute stage of stroke, the values were taken from the previous clinical records of stroke patients). Clinical evaluation of PSD patients was performed by two psychiatrists (with 5 years minimum experience) of the Center for Speech Pathology and Neurorehabilitation. All patients had mild severity of post-stroke depression (mean scores 12 ± 2 before treatment and 4 ± 1 after treatment, Table 1) according to Aphasic Depression Rating Scale (ADRS). Each subject was scanned twice – in a short time after the PSD diagnosis and after treatment with selective serotonin reuptake inhibitors (between session interval: 25 ± 4 days)

Table 1
Demographic and clinical characteristics of stroke patients.

Number of patients	11
Age (years)	64 ± 9
Sex (female)	9
Time after stroke, months	7 ± 4
Stroke localization	Bilateral: 2 Right hemisphere: 3 Left hemisphere: 3 Pons: 3
Time between sessions (days)	25 ± 5
Depression score	12 ± 2 before the treatment 4 ± 1 after the treatment

2.2. Ethics statement

This study was approved by the Ethics Committee of Institute of Higher Nervous System and Neurophysiology of Russian Academy of Science and the Center for Speech Pathology and Neurorehabilitation (Moscow, Russia). All subjects provided their written informed consent after receiving a complete description of this study.

2.3. Data acquisition

Magnetic resonance imaging (MRI) was performed in a 1.5 T MAGNETOM AVANTO MRI Scanner (Siemens, Germany). Participants were instructed to remain calm, with their eyes closed, not falling asleep and not thinking about anything. To minimize head movement, foam pads were used to fix the head during MRI acquisition. Protocol included acquisition of high-resolution T1-weighted anatomic rapid gradient-echo image (T1 MPRAGE sequence): (TR 1900 ms, TE 3.4 ms, FA 15°, 176 slices with slice thickness 1 mm and slice gap of 0.5 mm; field of view 256 mm with matrix size 256 × 256). Then each participant underwent T2*-weighted echo planar imaging (EPI) session containing 180 volumes (9 min). Parameters of the EPI sequence were the same for both sessions: TR 3 s, TE 50 ms, FA 90°, 35 slices with slice thickness of 3 mm and slice gap of 0.8 mm, the field of view was 252 mm and matrix size 64 × 64.

2.4. Patient lesion mapping

Stroke lesion volume was calculated manually by drawing an outline of the lesion on the T1-weighted image of each patient with BrainVoyager QX 2.6 (Brain Innovation, Maastricht, The Netherlands) (Goebel et al., 2006). A lesion overlap image is presented on Fig. 1 (constructed for all 11 patients on the template image by means of MRIcron software (Rorden et al., 2007)). Regions overlapping with lesions for each subject are listed in Table S2.