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# PATTERNS IN DEFAULT-MODE NETWORK CONNECTIVITY FOR DETERMINING OUTCOMES IN COGNITIVE FUNCTION IN ACUTE STROKE PATIENTS

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**Abstract—*Object:* To investigate whether resting-state functional connectivity (FC) differed in the default mode network (DMN) in stroke patients with and without post-stroke cognitive impairment (PSCI *vs.* Non-PSCI) and to explore the relationship between DMN connectivity and the cognitive performance in stroke patients.**

***Methods:* We totally enrolled twenty healthy controls and 18 stroke patients. The stroke patients were divided into two subgroups on the basis of the cognitive assays. Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores were recorded 10 days and 3 months after the stroke. Independent component analysis was used to isolate the DMN. One-way analysis of variance was performed to detect different FC among groups. Pearson correlation analyses were conducted to determine the relationships between FC strength and the MoCA and MMSE scores.**

***Results:* Compared to healthy controls, both Non-PSCI patients and PSCI patients showed significantly decreased FC in the posterior cingulate cortex/precuneus (PCC/PCu), as well as increased FC in the medial prefrontal cortex (MPFC) and left hippocampus. However, Non-PSCI patients showed more significantly increased FC in the MPFC and hippocampus than PSCI patients did. The FC in the PCC/PCu was related to the MoCA score measured at a 10-day follow-up, and the FC in the left hippocampus predicted the MoCA score measured at 3 months follow-up.**

***Conclusions:* Our findings may be helpful for facilitating further understanding of the potential mechanism underlying PSCI, and suggests that resting-state DMN connectivity could serve as neuroimaging biomarkers for future interventional studies.** 

**Key words: resting-state, functional MRI, post-stroke cognitive impairment, default mode network, functional connectivity.**

## INTRODUCTION

Post-stroke cognitive impairment (PSCI) is a common and difficult clinical problem encountered in stroke patients, which adversely affects stroke outcome (O'Brien et al., 2003). Previous studies have shown that more than 64% of patients after stroke exhibit various degrees of cognitive impairment (Jin et al., 2006); about 25% of patients will develop dementia within one year after stroke (Barba et al., 2000). The current trend is toward an expected increase in these proportions because of the aging population and the subsequent rise in the patients' mean age at the onset of their first-ever stoke (Bejot and Giroud, 2009). Despite its high morbidity, to date, the underlying pathophysiology of PSCI remains poorly understood.

In recent years, resting-state functional magnetic resonance imaging (fMRI) has emerged as an effective, noninvasive imaging technique that is used to investigate the intrinsic functional architecture of the human brain. Low-frequency fluctuations (typically < 0.1 Hz) of the blood oxygenation level-dependent (BOLD) signal in resting-state fMRI are thought to be physiologically meaningful and reflect spontaneous neural activity (Shmuel and Leopold, 2008). Meanwhile, there is increasing evidence that resting-state functional connectivity (FC) is correlated with human cognitive function, such as learning (Lewis et al., 2009), memory (Hampson et al., 2006; Tambini et al., 2010), and intellectual performance (van den Heuvel et al., 2009). Moreover, numerous functional studies have shown that a focal stroke lesion may affect not only the lesion site but also the entire brain networks (Carter et al., 2012; Dacosta-Aguayo et al., 2014). Thus the FC-based analytical approach seems to be more appropriate for clarifying the mechanism of cognitive recovery after stroke. In recent years, structural and FC changes after stroke have been reported by several fMRI studies, and these changes may be related to clinical

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*Abbreviations:* ADL, Activities of Daily Living Scale; ALFF, amplitude of low-frequency fluctuations; CDR, clinical dementia rating; DMN, default mode network; EDI, echo-planar-imaging; EPI, executive dysfunction index; FC, functional connectivity; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FOV, field of view; HIS, Hachinski Ischemic Score; ICA, independent component analysis; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; MoCA, Montreal Cognitive Assessment; MPFC, medial prefrontal cortex; NIHSS, National Institutes of Health Stroke Severity; NPI, neuropsychiatric inventory; PCC, posterior cingulate cortex; PCu, precuneus; PSCI, post-stroke cognitive impairment; SPM8, Statistical Parametric Mapping.

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deficits and functional recovery (van Meer et al., 2012; Yin et al., 2013a; Zhang et al., 2014). However, existing studies have mainly focused on the motor recovery in stroke patients, few studies have been conducted to explore the brain functional changes after stroke in relation to cognitive recovery.

The default-mode network (DMN) is the most important sub-network in the resting-state networks characterized by a deactivation during goal-directed cognitive performance and increased activity in self-referential processing (Raichle and Snyder, 2007, Buckner et al., 2008; Biswal et al., 2010). The DMN consists of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), precuneus (PCu), inferior parietal lobules, hippocampus, inferior temporal cortex, and some other brain regions (Andrews-Hanna et al., 2010). In humans, the function of the DMN has been implicated in attending to external and internal stimuli, as well as self-referential and reflective activity that specifically includes episodic memory retrieval, mental imagery, inner speech, and planning of future events (Gusnard et al., 2001; Fransson, 2005; Buckner and Carroll, 2007). Previous functional neuroimaging studies consistently found that dysfunction of DMN has been implicated in the pathophysiology of Alzheimer's disease and mild cognitive impairment (Greicius et al., 2004; Rombouts et al., 2005; Bai et al., 2009; Hedden et al., 2009). These findings may indicate that this network plays an important role in the pathogenesis of cognitive impairment. However, to date, few studies have examined its utility in predicting cognitive function of stroke patients.

In the current study, we used resting-state fMRI and independent component analysis (ICA) analytical approach to investigate brain DMN functional changes soon after stroke. Meanwhile, we further explore the predictive accuracy of the resting-state FC strength in specific areas on the severity of cognitive impairment after stroke. Based on previous functional studies, we hypothesized that cognitive impairment would be related to resting-state DMN dysfunction in stroke patients.

## EXPERIMENTAL PROCEDURES

### Participants

The medical ethics committee of the Chengdu Military General Hospital (Chengdu, China) approved the current study, and all participants gave written informed consent for their participation according to the Declaration of Helsinki. Twenty stroke inpatients were recruited from the Department of Neurology of the Chinese PLA Chengdu Military General Hospital between January 2013 and December 2013. Patients were admitted to the hospital within 6–72 h after the onset of symptoms. Patients were aged 40–75 years and experiencing their first-ever ischemic stroke, involving the carotid artery system or vertebrobasilar artery system, which met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease. Standard clinical CT or MRI scanning during hospitalization was performed to confirm the diagnosis. Exclusion criteria were as follows: dementia or significant cognitive impairment before stroke; hemorrhagic stroke; consciousness disorders; severe aphasia or dysarthria; history of psychiatric or neurologic disorder; history of lesions affecting one structure of the DMN. Twenty healthy controls were recruited among hospital staff and by advertisements on the Internet. The controls were free of neurological or psychiatric diseases, and Mini-Mental State Examination (MMSE) score $\geqslant$ 27, Montreal Cognitive Assessment (MoCA) score $\geqslant$ 26. All the participants were carefully screened for contraindications prior to MRI scanning, and none of them had contraindications to MRI.

### Neurological assessment and diagnosis of PSCI

On admission, detailed medical history and neurological examination results were recorded. Patients underwent neuropsychological examinations both within 10 days after the stroke and after 3 months. Stroke severity was based on National Institutes of Health Stroke Severity (NIHSS) score (Kasner et al., 1999). Cognitive function was assessed using the following tests: MMSE, MoCA, Hachinski Ischemic Score (HIS), clinical dementia rating (CDR), executive dysfunction index (EDI), neuropsychiatric inventory (NPI), Activities of Daily Living Scale (ADL).

Stroke patients were split into two groups on the basis of the cognitive assays (PSCI group and Non-PSCI group). The PSCI group was diagnosed according to the following criteria (Moorhouse and Rockwood, 2008; Qian et al., 2012; Park et al., 2013): (1) mild cognitive impairment: MMSE = 25 or 26, MoCA = 19–25, CDR = 0.5, and HIS > 4, in order to exclude pure Alzheimer's disease; and EDI > 0.2, which indicate that these subjects had executive dysfunction; subjective cognitive complaints reported by the participant or his/her caregiver; (2) abrupt or insidious onset of cognitive impairment after stroke, followed by a fluctuating, stepwise deteriorative, or gradually progressive course. The Non-PSCI group (no cognitive deficit) had an MMSE score $\geqslant$ 27, a MoCA score $\geqslant$ 26, and an EDI $\leqslant$ 0.2, which indicate that these subjects had no executive dysfunction.

### MRI data acquisition

Images were obtained 5–10 days after stroke using a 3.0-T Philips MR scanner (Philips Medical Systems, Best, The Netherlands) with an eight-channel phased array head coil. After conventional localizer scan and T2 anatomic scan, resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence: 35 axial slices with a slice thickness of 3 mm and no slice gap; repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°; field of view (FOV), $192 \times 192$ mm$^2$; matrix, $64 \times 64$; and isotropic voxel, $3 \times 3 \times 3$ mm$^3$. For each participant, the fMRI scanning lasted for 460 s and 230 volumes were obtained. In addition, a high-resolution structural T1-weighted anatomic sequence was acquired in a sagittal orientation using a 3-dimensional fast-field echo sequence (*3DFFE*): repetition time, 2500 ms; echo time, 2.0 ms; flip angle,