EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, pp. 1–8, 2014 doi:10.1111/ejn.12640

Significance of longitudinal changes in the default-mode network for cognitive recovery after stroke

Ji-Young Park,[1] Yun-Hee Kim,[1,2] Won Hyuk Chang,[2] Chang-hyun Park,[2] Yong-Il Shin,[3] Sung Tae Kim[4] and Alvaro Pascual-Leone[5]

[1]Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University, Seoul, Korea
[2]Department of Physical and Rehabilitation Medicine, Center for Prevention and Rehabilitation, Heart Vascular and Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Rehabilitation Medicine, Pusan National University School of Medicine, Busan, Korea
[4]Department of Diagnostic Radiology and Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[5]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA

Keywords: cognitive function, default-mode network, human, resting-state functional magnetic resonance imaging, stroke

Abstract

Although a considerable number of patients suffer from cognitive impairments after stroke, the neural mechanism of cognitive recovery has not yet been clarified. Repeated resting-state functional magnetic resonance imaging (fMRI) was used in this study to examine longitudinal changes in the default-mode network (DMN) during the 6 months after stroke, and to investigate the relationship between DMN changes and cognitive recovery. Out of 24 initially recruited right-hemispheric stroke patients, 11 (eight males, mean age 55.7 years) successfully completed the repeated fMRI protocol. Patients underwent three fMRI sessions at 1, 3 and 6 months after stroke. Their DMNs were analysed and compared with those of 11 age-matched healthy subjects (nine males, mean age 56.2 years). Correlations between DMN connectivity and improvement of the cognitive performance scores were also assessed. The stroke patients were found to demonstrate markedly decreased DMN connectivity of the posterior cingulate cortex, precuneus, medial frontal gyrus and inferior parietal lobes at 1 month after stroke. At 3 months after stroke, the DMN connectivity of these brain areas was almost restored, suggesting that the period is critical for neural reorganization. The DMN connectivity of the dorsolateral prefrontal cortex in the contralesional hemisphere showed a significant correlation with cognitive function recovery in stroke patients, and should be considered a compensatory process for overcoming cognitive impairment due to brain lesion. This is the first longitudinal study to demonstrate the changes in DMN during recovery after stroke and the key regions influencing cognitive recovery.

Introduction

Brain plasticity has been defined as the brain's ability to acquire new skills and processes, and adapt to a new environment (Pascual-Leone *et al.*, 2005; Nudo, 2006). In addition to its important role in maturation, brain plasticity is a fundamental mechanism for a patient's functional recovery from stroke, as it underlies the capability of the brain to restore itself or compensate for damage caused by lesions (Nudo, 2006; Cramer *et al.*, 2011).

Following a stroke, patients often suffer from cognitive impairments such as attention deficit (Coslett *et al.*, 1993; Barrett *et al.*, 1998), working memory problems (Jo *et al.*, 2009), executive dysfunction (Vataja *et al.*, 2005) and aphasia (van Oers *et al.*, 2010). Functional magnetic resonance imaging (fMRI) with cognitive tasks has played an important role in defining the neural substrates and system-level mechanisms underlying the recovery of such cognitive deficits after stroke. Task-related increases of brain activation in functional networks have been the main focus of fMRI research related to the cognitive deficits resulting from brain disease and the effects of rehabilitation and treatment (Coslett *et al.*, 1993; Kim *et al.*, 2009). However, the interpretation of task-based fMRI can be limited by various confounding factors. For example, patients are often unable to perform tasks due to being unable to fully understand complex instructions or suffering an impaired motor function of the hand for any overt task, especially during the acute stage.

Functional magnetic resonance imaging can be used to capture temporally coherent but not necessarily task-driven activities (Calhoun *et al.*, 2008). The low-frequency fluctuations observed in fMRI signals during the brain's resting state are thought to

Correspondence: Yun-Hee Kim, [2]Department of Physical and Rehabilitation Medicine, as above.
E-mails: yunkim@skku.edu, yun1225.kim@samsung.com

Received 24 November 2013, accepted 24 April 2014

reflect its neural baseline activity, a finding consistent across patients (Veer *et al.*, 2010). Moreover, due to the constraints of the neural network structure, a remarkable overlap has been observed in task-induced activity patterns (Fox *et al.*, 2006; Smith *et al.*, 2009; Veer *et al.*, 2010). The methodological advantage of such a 'resting-state fMRI' evaluation is that it can be performed without an external input or task demand, minimizing the possible confounding factors and making it particularly appealing for longitudinal studies of certain patient populations such as stroke patients, unconscious patients and infants (Fransson *et al.*, 2011).

Several temporally coherent networks have been identified using resting-state fMRI. Among the discovered networks, the default-mode network (DMN) has been the most widely studied (Raichle *et al.*, 2001). The DMN is a network of brain regions that are particularly active when subjects are not focused on the outside world (Greicius *et al.*, 2003). In healthy subjects, the DMN has revealed remarkable structural consistency (Greicius *et al.*, 2003, 2009), with nodes including the medial frontal gyrus (MedFG), posterior cingulate cortex (PCC), precuneus and lateral parietal cortex. The strength of functional connectivity across the DMN decreases markedly with age (Damoiseaux *et al.*, 2008). Unique changes have also been observed in patients with a variety of neuropsychiatric disorders (Greicius *et al.*, 2004). Compared with region-of-interest (ROI)-based correlation analysis (Fox *et al.*, 2006), which is likely to exhibit a user-introduced bias (Qi *et al.*, 2010), a model-free approach involving independent component analysis (ICA) has the benefit of delineating resting-state networks in a data-driven manner, without *a-priori* definitions of the seed regions.

The purpose of the current study was to investigate the longitudinal changes in DMN connectivity using ICA of resting-state fMRI in patients demonstrating cognitive dysfunction after stroke. We observed (i) the disrupted functional connectivity of the DMN in stroke patients and the differences in network connectivity compared with age-matched healthy subjects to examine how the network is restored after stroke and (ii) the contribution of restored DMN connectivity to cognitive recovery after stroke. To the best of the authors' knowledge, this is the first study to investigate longitudinal DMN changes in stroke patients and to explore the relationship between the DMN and cognitive function recovery.

Materials and methods

Subjects

This study was designed as a longitudinal observational study involving repeated fMRI experiments. Patients were recruited using the following inclusion and exclusion criteria. The patients had to (i) have experienced their first-ever stroke, (ii) have suffered a right-hemispheric lesion and (iii) be younger than 70 years old. Patients were excluded if they had (i) any clinically significant or unstable medical disorder, (ii) any neuropsychiatric comorbidity other than stroke and (iii) any contraindication to magnetic resonance imaging participation. Of the 24 stroke patients initially enrolled, 11 (eight males, 55.73 $\pm$ 8.69 years of age) completed three fMRI sessions, and seven of these patients completely finished the comprehensive neuropsychological test battery over a 6-month period (Table 1). Eleven age- and sex-matched healthy subjects (nine males, 56.23 $\pm$ 2.89 years of age) were recruited. Patients were excluded from the control group if they had a lifetime diagnosis of neuropsychiatric disease or a history of head injury. There was no significant age difference between the patients and healthy control group members ($r = 0.089$). Experiments were conducted with the understanding and written consent of each patient, and were therefore performed in accordance with the ethical standards presented in the 1964 Declaration of Helsinki and its later amendments. Ethics approval was provided by the Institutional Review Board at Samsung Medical Center in Seoul, Korea.

Data acquisition

Cognitive assessment

The Mini-Mental State Examination was performed three times for each patient over a period of 6 months (at months 1, 3 and 6 after stroke). In addition, seven patients completed three cognitive assessment repetitions using Seoul-computerized neuropsychological tests (SCNTs; Kim *et al.*, 2001). The SCNTs included attention, verbal memory, nonverbal memory and visuo-motor coordination tests.

Functional magnetic resonance imaging data acquisition

Resting-state fMRI data were acquired three times over a 6-month period from all of the patients and once from the control group

TABLE 1. Demographic characteristics of the participating stroke patients

Patients	Gender	Age (years)	Stroke type	Side	Brain lesion	Risk factor
1	F	64	ICH	Right	Thalamus	HTN
2	M	70	ICH	Right	Pons	cig
3	M	40	ICH	Right	Basal ganglia	HTN, cig, NIDDM
4	M	58	Infarction	Right	MCA territory	cig, NIDDM
5	M	63	Infarction	Right	MCA territory	HTN
6	M	53	Infarction	Right	MCA territory	cig, NIDDM
7	M	59	ICH	Right	Putamen	HTN
8	F	46	Infarction	Right	MCA territory	cig
9	M	58	Infarction	Right	MCA territory	HTN
10	F	54	Infarction	Right	SC	HTN
11	M	67	Infarction	Right	ICA territory	
	F = 3	57.5 ($\pm$8.9)				
	M = 8					

M, male; F, female; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; ICA, internal carotid artery; SC, striatocapsular; HTN, hypertension; cig, cigarette smoking; NIDDM, noninsulin-dependent diabetes mellitus.

members. Each participant's head was positioned within the scanner head coil, with foam padding provided for comfort and to minimize head movement. Functional magnetic resonance images were acquired while the patients were at rest, and the patients were instructed to keep their eyes closed and refrain from initiating goal-directed, attention-demanding activity during the scanning session.

The fMRI data were acquired using an ACHIEVA MR scanner (Philips Medical Systems, Best, The Netherlands) operating at 3 Tesla. During each session, 100 whole-brain images were collected using a T2*-weighted gradient echo planar imaging sequence (repetition time, 3000 ms; echo time, 35 ms; number of slices, 35; slice thickness, 4 mm; reconstruction matrix size, 128 × 128; field of view, 220 × 220 mm). A high-resolution anatomical image was also acquired (repetition time, 3500 ms; echo time, 15 ms; slice thickness, 4 mm; matrix size, 304 × 240; field of view, 220 × 220 mm).

Data analysis

Behavioural data analysis

Friedman tests and repeated-measures ANOVA were used to examine any changes in the Mini-Mental State Examination scores and cognitive function during the first 6 months after stoke. *Post-hoc* analysis and a Bonferroni correction were also performed for the behavioural data analysis.

Functional magnetic resonance imaging data analysis

Data pre-processing and independent component analysis. The fMRI data were pre-processed using Statistical Parametric Mapping 8 software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/), which included motion correction, spatial normalization and smoothing procedures. The first five time points from each functional image were discarded to equilibrate the magnetic field. For each subject, the functional images were realigned using least-squares minimization and normalized to the Montreal Neurological Institute template. The images were resampled to 3 × 3 × 3 mm^3 and smoothed with an 8-mm full-width at half maximum. The data for all of the patients were pre-processed using group ICA from the fMRI toolbox (GIFT, http://icatb.sourceforge.net/; Calhoun *et al.*, 2001), which included two principal component analysis reductions, ICA application and back-reconstruction for each patient. In the first step, the patient data were narrowed down using principal component analysis according to the selected number of components. In the second step, ICA was conducted to separate the data using an extended infomax algorithm. Finally, the independent components and time courses for each patient were back-reconstructed, following which the mean spatial maps for each group were transformed into *z*-scores for display.

A template-matching procedure was used to select the DMN from each individual's independent component, as it reportedly had the advantage of decreasing time and human error (Franco *et al.*, 2009) compared with the visual inspection procedure. For the template-matching procedure, a template of the DMN was developed based on the peak regions reported previously (Greicius *et al.*, 2004). Because varying sphere size has no effect on component identification (Wu *et al.*, 2011; You *et al.*, 2013), each region in the template was made into a sphere with a radius of 5 mm. The differences in average *z*-values of the voxels inside and outside the template were calculated for each component. The ROIs of the template involved the PCC, prefrontal cortex and inferior parietal lobule (IPL), which were assumed to be the core areas associated with the DMN (Buckner *et al.*, 2008). Finally, the component with the greatest difference was determined as the best-fit component (Greicius *et al.*, 2004) and was selected as the DMN for each group.

Group comparisons

One-sample *t*-tests were calculated on the best-matched DMN independent component of each month for 11 stroke patients and 11 healthy volunteers. A height threshold of $P < 0.05$ corrected for multiple comparisons across the whole brain was applied, with $k > 10$ voxels. ANOVA was conducted to compare the differences between the stroke patients and healthy volunteers for each respective month using the $P < 0.05$ threshold corrected for multiple comparisons across the whole brain.

Relationship between functional connectivity and cognitive test scores

Changes in DMN connectivity were observed over 6 months in seven stroke patients who completed three rounds of SCNT, and an ROI approach was taken when investigating the relationship between the alterations of connectivity and cognitive improvement.

TABLE 2. Patients' performance changes in neuropsychological tests after stroke

	1 month		3 months		6 months		
Tests	Mean	(SD)	Mean	(SD)	Mean	(SD)	*P* value
Global cognitive function ($N = 11$)							
MMSE	26.3	(3.1)	28.8	(1.89)	28.9	(1.38)	0.002**
Verbal memory test ($N = 7$)							
Digit span forward	5.56	(0.76)	6.30	(1.39)	5.90	(0.89)	0.072
Digit span backward	3.27	(0.37)	3.74	(0.73)	4.18	(0.95)	0.070
Verbal learning test	5.57	(1.39)	10.00	(3.36)	10.14	(3.44)	0.003**
Non-verbal memory test ($N = 7$)							
Visual span forward	4.53	(1.18)	5.87	(0.94)	5.58	(0.48)	0.023*
Visual span backward	3.67	(1.51)	4.40	(0.93)	4.30	(1.06)	0.246
Visual learning test	7.57	(1.99)	10.71	(3.04)	10.86	(2.67)	0.050†
ROCF delayed recall	6.50	(4.89)	18.25	(9.39)	17.92	(11.90)	0.016*
Visuo-motor coordination ($N = 7$)							
Trail-making A (sec)	89.28	(45.75)	37.86	(8.01)	40.71	(11.68)	0.043*
Trail-making B (sec)	138.40	(50.72)	95.80	(32.77)	80.80	(23.30)	0.108

MMSE, Mini-Mental State Examination; ROCF, Rey–Osterrieth complex figure test. *$P < 0.05$, **$P < 0.01$, †$P = 0.05$ by repeated measure ANOVA.

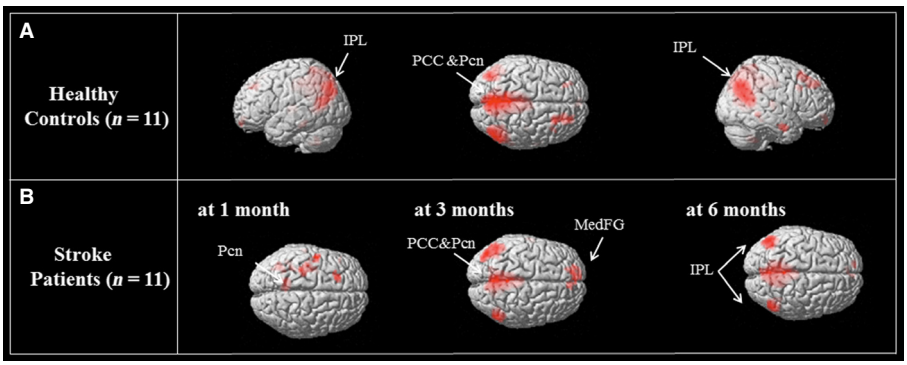

FIG. 1. Default-mode network in healthy control and stroke patients. One-sample *t*-tests were calculated according to the best-matched DMN component of the healthy aging group ($N = 11$) (A) and stroke patients ($N = 11$) at 1, 3 and 6 months post-stroke (B). A height threshold of $P < 0.05$ uncorrected for multiple comparisons was used, with $k > 10$ voxels. Pcn, precuneus.

Repeated-measures ANOVA was performed to determine the ROIs, which showed linearly increased and decreased connectivity over time (Table 3). The average *z*-scores of the defined ROIs (Fig. 3A, Table 3) were extracted using the MarsBaR® toolbox (http://marsbar.sourceforge.net/) in the normalized images. Correlation analysis was performed between the *z*-score difference of each ROI (*z*-score at 3 months − *z*-score at 1 month; *z*-score at 6 months − *z*-score at 3 months) and the delta score of the cognitive function tests (score at 3 months − score at 1 month; score at 6 months − score at 3 months), respectively, to determine the relationship between the changes in cognitive function and changes in connectivity.

Results

Cognitive function changes

The Friedman test indicated that the patients' Mini-Mental State Examination scores changed significantly during the first 6 months after stroke [$\chi^2(2) = 12.867$, $P = 0.002$]. *Post-hoc* Wilcoxon signed-rank tests were conducted using a Bonferroni correction with the significance level set at $P < 0.017$ (0.05/3). There were statistically significant improvements in cognitive function at the third ($Z = -2.536$, $P = 0.011$) and sixth ($Z = -2.533$, $P = 0.011$) month after stroke compared with the first month after stroke. However, there were no significant differences between the third and sixth months after stroke ($Z = -4.414$, $P = 0.679$). Repeated-measures ANOVA indicated significantly improved performance in terms of the verbal learning tests, visual span forward, visual learning tests, Rey–Osterrieth complex figure delayed recall tests and trail-making A among the seven patients who completed the SCNTs. *Post-hoc* analysis revealed that the patients' performance on the verbal learning, visual learning and Rey–Osterrieth complex figure delayed recall tests improved at the third and sixth months compared with the first month after stroke (Table 2).

Default-mode networks of healthy control and stroke patients

The DMNs of the healthy control group included the bilateral precuneus and PCC, IPL, dorsolateral prefrontal cortex (DLPFC) at the middle frontal gyrus (MFG), and MedFG (Fig. 1A). Figure 1B illustrates the DMNs of the patients at 1 month after stroke, featuring distributed sets of brain areas located mainly in the contralesional (left) hemisphere, including the precuneus, precentral and superior frontal gyrus. At 3 and 6 months after stroke onset, the DMN seemed to be gradually recovered especially at the posterior part of the brain.

TABLE 3. DMN areas increased or decreased activation during 6 months post-stroke ($N = 7$)

			Cluster Talairach coordinate Uncorrected						
Lobe	R/L	Regions	BA	Size	x	y	z	T	*P*
Increased activation									
Frontal	R	OF	BA11	46	3	54	−12	10.94	0.0000
	R	MedFG	BA10	17	0	61	20	7.53	0.0000
	R	MFG	BA9	11	21	33	46	7.82	0.0000
	R	MFG	BA9	10	45	21	41	6.27	0.0000
Parietal	R	MFG	BA46	137	48	29	24	6.5	0.0000
	R	IPL	BA40	217	53	−55	31	13.85	0.0000
	L	IPL	BA40	17	−42	−51	50	4.54	0.0000
	R	Precuneus	BA31	31	3	−49	37	16.44	0.0000
	L	Precuneus	BA	149	−33	−75	38	6.17	0.0000
Limbic	R	Cingulate gyrus	BA31		6	−22	41	14.85	0.0000
	L	Cingulate gyrus	BA31		−6	−37	36	14.41	0.0000
Decreased activation									
Frontal	L	MedFG	BA6		−9	2	56	5.6	0.0000
	L	Precentral gyrus	BA6	10	−42	−2	42	6.72	0.0000
	L	SFG	BA6	17	−12	13	50	7.08	0.0000
Insular	L	Insular Cortex	BA13	16	−39	−3	20	7.2	0.0000

A height threshold of $P < 0.0001$ uncorrected for multiple comparisons, $k > 10$ voxels.
OF, orbitofrontal; R, right; L, left.

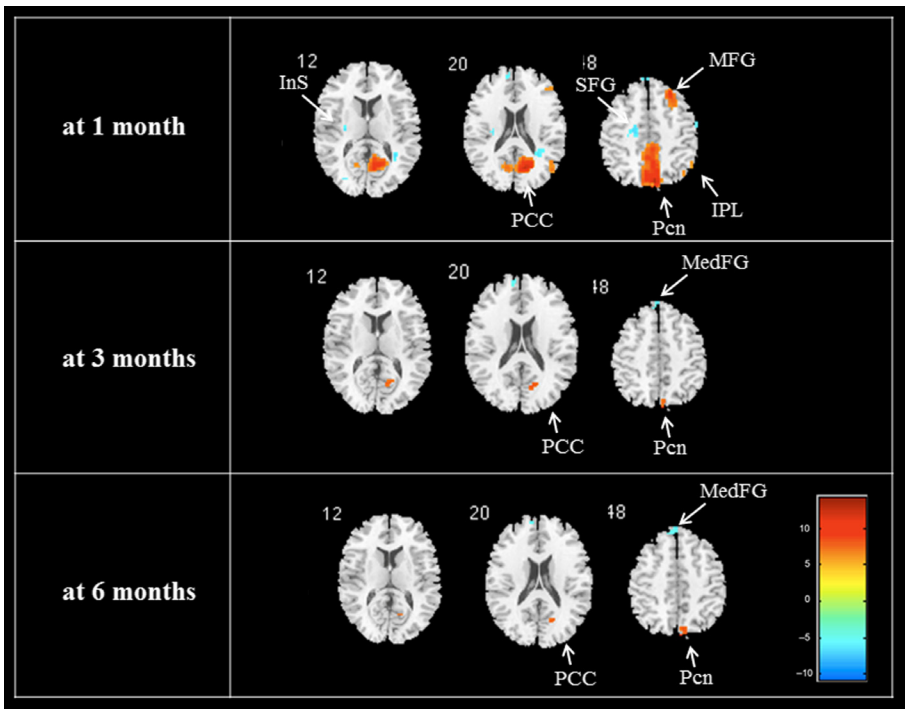

FIG. 2. The DMN differences in patients at 1, 3 and 6 months post-stroke and healthy control patients (N = 11). ANOVA was used to compare the differences between stroke patients and healthy control patients. The red blob indicates the brain areas showing higher correlation in the control group compared with the stroke group and the blue blob indicates the areas showing higher correlation in the stroke group. A height threshold of $P < 0.05$ uncorrected for multiple comparisons was used, with $k > 10$ voxels. PCn, precuneus; SFG, superior frontal gyrus; InS, insular.

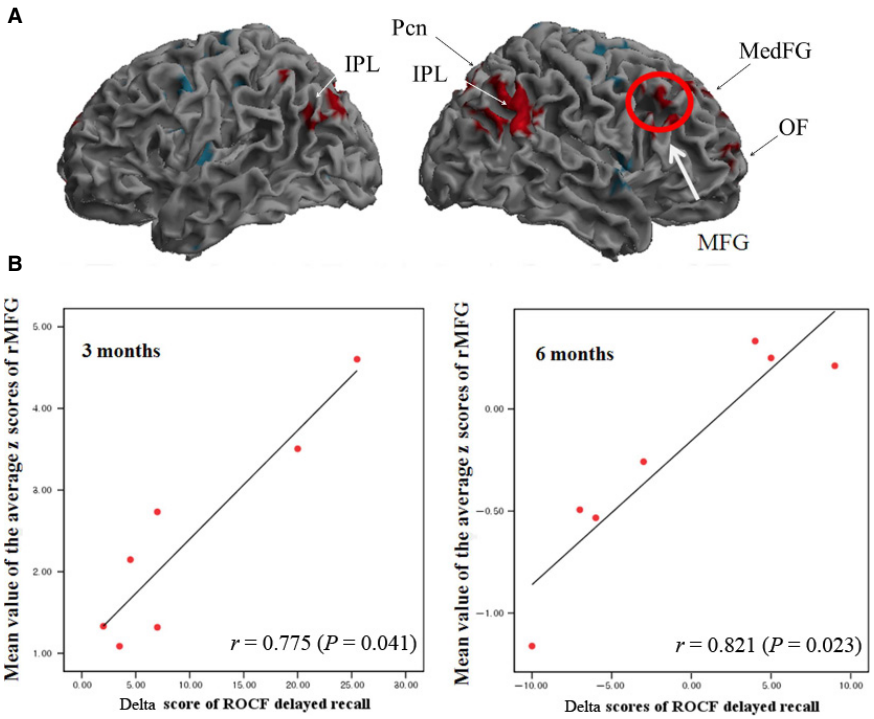

FIG. 3. Neural correlates of cognitive improvement. (A) DMN regions showing increased (red blob) activations during 6 months post-stroke. (B) z-score changes in the rMFG showing significant correlations with the delta score of the Rey–Osterrieth complex figure delayed recall test score during the third month (r = 0.775, $P < 0.041$; left) and sixth month (r = 0.821, $P < 0.023$; right) after stroke (N = 7). Pcn, precuneus; OF, orbitofrontal gyrus; ROCF, Rey–Osterrieth complex figure test; rMFG, right MFG.

The statistical maps resulting from comparing the DMNs between the healthy control group and stroke patients at each time point after stroke are illustrated in Fig. 2. In the first month after stroke, the stroke patients showed decreased DMN connectivity compared with that of the control group. Decreased connectivity was observed in the bilateral PCC and precuneus, right MFG and IPL. In contrast,

the DMNs of the stroke patients at 1 month after stroke demonstrated increased connectivity in the contralesional hemispheric areas, including the left superior frontal lobes and insular cortex. At 3 and 6 months after stroke, the DMNs of the stroke patients showed almost the same connectivity as those of the control group, although decreased connectivity was observed in the PCC and precuneus.

Correlation between default-mode network changes and cognitive recovery

Seven of the 11 stroke patients completed follow-up neuropsychological tests three times. Using repeated-measures ANOVA, brain areas that demonstrated linearly increased or decreased connectivity over 6 months after stroke were defined (Fig. 3A, red blobs). An ROI approach was taken to investigate the relationship between the DMN connectivity alterations over 6 months and cognitive improvement. The ROIs, such as the precuneus, MFG, IPL, MedFG, and orbitofrontal gyrus, were defined as shown in Fig. 3A and Table 3. The relationship between the z-score changes of each ROI and the changes in SCNT scores was tested. As a result, the alteration of right MFG connectivity (Fig. 3A, red circle) was found to be significantly correlated with the improvement of the Rey–Osterrieth complex figure delayed recall score at 3 months ($r = 0.775$, $P < 0.041$) and 6 months ($r = 0.821$, $P < 0.023$) after stroke (Fig. 3B).

Discussion

In this longitudinal fMRI study, DMN connectivity changes were examined over time in patients experiencing cognitive dysfunction after stroke. The major findings were as follows: (i) the stroke patients restored most of their DMN connectivity until 3 months after stroke, suggesting that this is the critical period for neural reorganization; and (ii) the increased connectivity shown during recovery indicated a correlation with cognitive improvement, suggesting that reorganization plays an important role in cognitive recovery.

The stroke patients demonstrated markedly decreased DMN connectivity in the PCC, precuneus and MFG at 1 month after stroke. At 3 months after stroke, the connectivity was gradually restored in the PCC, precuneus, MedFG and bilateral IPLs. DMN connectivity with the DLPFC (especially the MFG) of the right hemisphere was found to be correlated with cognitive function recovery in the stroke patients. However, at 6 months after stroke, the patients still exhibited decreased DMN connectivity in the PCC and precuneus areas compared with the healthy control group members, indicating persistent post-stroke cognitive sequelae. To the authors' knowledge, this is the first study to investigate significant longitudinal changes in the DMNs of stroke patients and their relationship with cognitive function recovery.

The interpretation of task-based fMRI results cannot rule out the possible confounding effect of differences in task performance or cognitive strategies for stroke patients. Resting-state fMRI has the advantage of being able to investigate the mechanisms underlying cognitive recovery and brain reorganization and minimizes their confounding effects (Rocca *et al.*, 2010). Recent studies examining functional connectivity in the resting state reported that the regions involved in focused attention are 'connected' based on their common temporal activity patterns during rest (Fox *et al.*, 2005). Functional connectivity analysis revealed a cortical network consisting of two anticorrelated brain areas. The task-negative areas included the precuneus/PCC, MedFG, IPL and inferior temporal gyrus, whose activity was negatively correlated with cognitive tasks and positively correlated with the control conditions. The DMN is a task-negative network that is active during rest and relatively suppressed during active tasks (Raichle *et al.*, 2001). It is thought to be engaged in task-independent thought, internal and external monitoring (Gusnard *et al.*, 2001) and mind wandering (Mason *et al.*, 2007), and its activity decreases when cognitive demand is increased (Esposito *et al.*, 2009). Studies using resting-state fMRI have demonstrated differences in the DMNs of patients suffering from Alzheimer's disease (Sorg *et al.*, 2007) and attention deficit hyperactivity disorder (Zang *et al.*, 2007), implying a relationship with the pathophysiology of the disease.

Abnormal functional connectivity of default-mode network after stroke

According to the results of this study, at 1 month after stroke, the DMNs of the stroke patients comprised a distributed set of brain areas mainly in the contralesional hemisphere and showed decreased connectivity akin to that of traumatic brain injury patients (Johnson *et al.*, 2012). The stroke patients demonstrated clear cognitive deficits at 1 month after stroke compared with 3 or 6 months after stroke. The abnormal DMN connectivity suggests that goal-oriented behaviour may be affected and elicit a less accurate performance (Weissman *et al.*, 2006).

Although the spatial maps of the stroke patients' DMNs looked similar to those of the healthy control group members at 6 months after stroke, there were two differences in the spatial patterns. First, the stroke patients showed decreased PCC connectivity, suggesting greater variability in their spatial maps. It has been suggested that the PCC notices internal and external changes (Pearson *et al.*, 2011) and plays a chief regulatory role in focusing internal and external attention (Leech & Sharp, 2014). In addition, patients suffering from conditions such as traumatic brain injury (Nakashima *et al.*, 2007), early Alzheimer's disease (Minoshima *et al.*, 1997) and schizophrenia (Haznedar *et al.*, 2004) have shown abnormal levels of metabolism along with cognitive impairments.

Second, increased functional connectivity was found in the stroke patients' medial frontal regions at 6 months after stroke compared with the control group. Increased activity has been observed in the frontal area of healthy elderly people compared with young individuals experiencing a loss of cognitive function (Cabeza *et al.*, 2002), which may reflect compensatory recruitment. These findings are in agreement with an earlier study that demonstrated a correlation between intrinsic DMN activities and cognitive performance in healthy participants (Weissman *et al.*, 2006). Drastic changes were observed in the stroke patients' DMN maps between 1 and 3 months after stroke, suggesting that the restoration of neural network connectivity was most prominent during this period. Therefore, it may be interpreted that this period is important for therapeutic or rehabilitative intervention to enhance the recovery of network functions.

Neural correlates of cognitive improvement

Most of the stroke patients' DMN connectivity was restored during recovery. Thus, how DMN connectivity changes in stroke patients over time and how the alteration influences cognitive outcomes must be investigated. This study examined the relationship between brain regions demonstrating increased or decreased connectivity during the 6-month period after stroke and cognitive test scores. The results showed a significant correlation between increased right DLPFC connectivity (especially the MFG) and improvement in nonverbal memory, as demonstrated by the delayed recall of the visual learn-

ing test during the 6-month period after stroke. The greater the connectivity observed between the DLPFC and DMN, the more the patients improved in their cognitive tests.

The DLPFC is a key region involved in human memory processing. Although it has been argued that left-hemispheric and right-hemispheric strokes generate different types of memory impairment, the left hemisphere reportedly specializes in verbal processing and the right hemisphere specializes in nonverbal processing (Mori *et al.*, 1986; Gillespie *et al.*, 2006; Sepulcre *et al.*, 2009). Fronto-parietal activity reportedly plays a central role in fMRI and positron emission tomography studies of attention (Corbetta & Shulman, 1998), working memory (Pessoa & Ungerleider, 2004; Klingberg, 2006) and episodic memory retrieval (Cabeza *et al.*, 2003). Research has demonstrated that compensatory activation in the frontal (Cabeza *et al.*, 2003) and parietal (Anderson *et al.*, 2000) lobes increases in healthy elderly patients such that high-performing healthy elders recruit bilateral PFC regions and exhibit decreased hemispheric asymmetry. Furthermore, patients suffering mild cognitive impairment have exhibited increased activity in the left prefrontal cortex and IPL (Qi *et al.*, 2010), and Alzheimer's disease patients have demonstrated increased recruitment in the prefrontal (Gould *et al.*, 2006) and frontal–parietal lobes. In this context, increased connectivity of the right DLPFC with the DMNs in stroke patients can be considered a compensatory process for overcoming cognitive deficits due to right-hemispheric lesions, and may be proposed as a marker of the post-stroke recovery of cognitive functions.

This study had some limitations. First, the sample size was relatively small. Although 24 patients were initially recruited, many failed to complete the three required fMRI scans and the full battery of cognitive tests. Second, all of the patients exhibited heterogeneous lesions. Nevertheless, this was the first longitudinal study to demonstrate the neural network changes during cognitive recovery after stroke, and to define the key regions influencing cognitive recovery. Its results may offer clues for further research that involves a larger number of patients.

Conclusions

Longitudinal DMN studies investigate changes in neural response patterns over time, and may provide insight into the mechanisms underlying cognitive recovery after stroke. The findings of this study collectively suggest that impaired DMN connectivity recovers over time and that increased connectivity of the ipsilesional DLPFC within the DMN may help to compensate for functional deficits and may be linked to cognitive function recovery. Furthermore, decreased DMN activity even at 6 months after stroke may reflect lasting cognitive sequelae.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This study was supported by a KOSEF grant (MOST) (no. M10644000022-06N4400-02210) and a National Research Foundation (NRF) grant (no. 20110016960), both funded by the Korean government. A.P.-L. was supported in part by Harvard Catalyst, the Harvard Clinical and Translational Science Center (the National Center for Research Resources, the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic health care centres).

Abbreviations

DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; IPL, inferior parietal lobule; MedFG, medial frontal gyrus; MFG, middle frontal gyrus; PCC, posterior cingulate cortex; ROI, region of interest; SCNT, Seoul-computerized neuropsychological tests.

References

Anderson, N.D., Iidaka, T., Cabeza, R., Kapur, S., McIntosh, A.R. & Craik, F.I. (2000) The effects of divided attention on encoding- and retrieval-related brain activity: a PET study of younger and older adults. *J. Cognitive Neurosci.*, **12**, 775–792.

Barrett, A.M., Beversdorf, D.Q., Crucian, G.P. & Heilman, K.M. (1998) Neglect after right hemisphere stroke: a smaller floodlight for distributed attention. *Neurology*, **51**, 972–978.

Buckner, R.L., Andrews-Hanna, J.R. & Schacter, D.L. (2008) The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, **1124**, 1–38.

Cabeza, R., Anderson, N.D., Locantore, J.K. & McIntosh, A.R. (2002) Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage*, **17**, 1394–1402.

Cabeza, R., Dolcos, F., Prince, S.E., Rice, H.J., Weissman, D.H. & Nyberg, L. (2003) Attention-related activity during episodic memory retrieval: a cross-function fMRI study. *Neuropsychologia*, **41**, 390–399.

Calhoun, V.D., Adali, T., Pearlson, G.D. & Pekar, J.J. (2001) A method for making group inferences from functional MRI data using independent component analysis. *Hum. Brain Mapp.*, **14**, 140–151.

Calhoun, V.D., Kiehl, K.A. & Pearlson, G.D. (2008) Modulation of temporally coherent brain networks estimated using ICA at rest and during cognitive tasks. *Hum. Brain Mapp.*, **29**, 828–838.

Corbetta, M. & Shulman, G.L. (1998) Human cortical mechanisms of visual attention during orienting and search. *Philos. T. Roy. Soc. B.*, **353**, 1353–1362.

Coslett, H.B., Schwartz, M.F., Goldberg, G., Haas, D. & Perkins, J. (1993) Multi-modal hemispatial deficits after left hemisphere stroke. A disorder of attention? *Brain*, **116**, 527–554.

Cramer, S.C., Sur, M., Dobkin, B.H., O'Brien, C., Sanger, T.D., Trojanowski, J.Q., Rumsey, J.M., Hicks, R., Cameron, J., Chen, D., Chen, W.G., Cohen, L.G., deCharms, C., Duffy, C.J., Eden, G.F., Fetz, E.E., Filart, R., Freund, M., Grant, S.J., Haber, S., Kalivas, P.W., Kolb, B., Kramer, A.F., Lynch, M., Mayberg, H.S., McQuillen, P.S., Nitkin, R., Pascual-Leone, A., Reuter-Lorenz, P., Schiff, N., Sharma, A., Shekim, L., Stryker, M., Sullivan, E.V. & Vinogradov, S. (2011) Harnessing neuroplasticity for clinical applications. *Brain*, **134**, 1591–1609.

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M. & Rombouts, S.A. (2008) Reduced resting-state brain activity in the "default network" in normal aging. *Cereb. Cortex*, **18**, 1856–1864.

Esposito, F., Aragri, A., Latorre, V., Popolizio, T., Scarabino, T., Cirillo, S., Marciano, E., Tedeschi, G. & Di Salle, F. (2009) Does the default-mode functional connectivity of the brain correlate with working-memory performances? *Arch. Ital. Biol.*, **147**, 11–20.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C. & Raichle, M.E. (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. USA*, **102**, 9673–9678.

Fox, M.D., Snyder, A.Z., Zacks, J.M. & Raichle, M.E. (2006) Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat. Neurosci.*, **9**, 23–25.

Franco, A.R., Pritchard, A., Calhoun, V.D. & Mayer, A.R. (2009) Interrater and intermethod reliability of default mode network selection. *Hum. Brain Mapp.*, **30**, 2293–2303.

Fransson, P., Aden, U., Blennow, M. & Lagercrantz, H. (2011) The functional architecture of the infant brain as revealed by resting-state fMRI. *Cereb. Cortex*, **21**, 145–154.

Gillespie, D.C., Bowen, A. & Foster, J.K. (2006) Memory impairment following right hemisphere stroke: a comparative meta-analytic and narrative review. *Clin. Neuropsychol.*, **20**, 59–75.

Gould, R.L., Arroyo, B., Brown, R.G., Owen, A.M., Bullmore, E.T. & Howard, R.J. (2006) Brain mechanisms of successful compensation during learning in Alzheimer disease. *Neurology*, **67**, 1011–1017.

Greicius, M.D., Krasnow, B., Reiss, A.L. & Menon, V. (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl. Acad. Sci. USA*, **100**, 253–258.

Greicius, M.D., Srivastava, G., Reiss, A.L. & Menon, V. (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl. Acad. Sci. USA*, **101**, 4637–4642.

Greicius, M.D., Supekar, K., Menon, V. & Dougherty, R.F. (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb. Cortex*, **19**, 72–78.

Gusnard, D.A., Raichle, M.E. & Raichle, M.E. (2001) Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.*, **2**, 685–694.

Haznedar, M.M., Buchsbaum, M.S., Hazlett, E.A., Shihabuddin, L., New, A. & Siever, L.J. (2004) Cingulate gyrus volume and metabolism in the schizophrenia spectrum. *Schizophr. Res.*, **71**, 249–262.

Jo, J.M., Kim, Y.H., Ko, M.H., Ohn, S.H., Joen, B. & Lee, K.H. (2009) Enhancing the working memory of stroke patients using tDCS. *Am. J. Phys. Med. Rehab.*, **88**, 404–409.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W. & Slobounov, S. (2012) Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. *NeuroImage*, **59**, 511–518.

Kim, Y.H., Shin, S.H., Park, S.H. & Ko, M.H. (2001) Cognitive assessment for patient with brain injury by computerized neuropsychological test. *J. Korean Acad. Rehabil. Med.*, **25**, 209–216.

Kim, Y.H., Yoo, W.K., Ko, M.H., Park, C.H., Kim, S.T. & Na, D.L. (2009) Plasticity of the attentional network after brain injury and cognitive rehabilitation. *Neurorehab. Neural Re.*, **23**, 468–477.

Klingberg, T. (2006) Development of a superior frontal–intraparietal network for visuo-spatial working memory. *Neuropsychologia*, **44**, 2171–2177.

Leech, R. & Sharp, D.J. (2014) The role of the posterior cingulate cortex in cognition and disease. *Brain*, **137**, 12–32.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T. & Macrae, C.N. (2007) Wandering minds: the default network and stimulus-independent thought. *Science*, **315**, 393–395.

Minoshima, S., Giordani, B., Berent, S., Frey, K.A., Foster, N.L. & Kuhl, D.E. (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann. Neurol.*, **42**, 85–94.

Mori, E., Yamadori, A. & Mitani, Y. (1986) Left thalamic infarction and disturbance of verbal memory: a clinicoanatomical study with a new method of computed tomographic stereotaxic lesion localization. *Ann. Neurol.*, **20**, 671–676.

Nakashima, T., Nakayama, N., Miwa, K., Okumura, A., Soeda, A. & Iwama, T. (2007) Focal brain glucose hypometabolism in patients with neuropsychologic deficits after diffuse axonal injury. *Am. J. Neuroradiol.*, **28**, 236–242.

Nudo, R.J. (2006) Plasticity. *NeuroRx*, **3**, 420–427.

van Oers, C.A., Vink, M., van Zandvoort, M.J., van der Worp, H.B., de Haan, E.H., Kappelle, L.J., Ramsey, N.F. & Dijkhuizen, R.M. (2010) Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. *NeuroImage*, **49**, 885–893.

Pascual-Leone, A., Amedi, A., Fregni, F. & Merabet, L.B. (2005) The plastic human brain cortex. *Annu. Rev. Neurosci.*, **28**, 377–401.

Pearson, J.M., Heilbronner, S.R., Barack, D.L., Hayden, B.Y. & Platt, M.L. (2011) Posterior cingulate cortex: adapting behavior to a changing world. *Trends Cogn. Sci.*, **15**, 143–151.

Pessoa, L. & Ungerleider, L.G. (2004) Neural correlates of change detection and change blindness in a working memory task. *Cereb. Cortex*, **14**, 511–520.

Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L. & Li, K. (2010) Impairment and compensation coexist in amnestic MCI default mode network. *NeuroImage*, **50**, 48–55.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. & Shulman, G.L. (2001) A default mode of brain function. *Proc. Natl. Acad. Sci. USA*, **98**, 676–682.

Rocca, M.A., Valsasina, P., Absinta, M., Riccitelli, G., Rodegher, M.E., Misci, P., Rossi, P., Falini, A., Comi, G. & Filippi, M. (2010) Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology*, **74**, 1252–1259.

Sepulcre, J., Masdeu, J.C., Pastor, M.A., Goni, J., Barbosa, C., Bejarano, B. & Villoslada, P. (2009) Brain pathways of verbal working memory: a lesion-function correlation study. *NeuroImage*, **47**, 773–778.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R. & Beckmann, C.F. (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc. Natl. Acad. Sci. USA*, **106**, 13040–13045.

Sorg, C., Riedl, V., Muhlau, M., Calhoun, V.D., Eichele, T., Laer, L., Drzezga, A., Forstl, H., Kurz, A., Zimmer, C. & Wohlschlager, A.M. (2007) Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*, **104**, 18760–18765.

Vataja, R., Pohjasvaara, T., Mantyla, R., Ylikoski, R., Leskela, M., Kalska, H., Hietanen, M., Juhani Aronen, H., Salonen, O., Kaste, M., Leppavuori, A. & Erkinjuntti, T. (2005) Depression-executive dysfunction syndrome in stroke patients. *Am. J. Geriat. Psychiat.*, **13**, 99–107.

Veer, I.M., Beckmann, C.F., van Tol, M.J., Ferrarini, L., Milles, J., Veltman, D.J., Aleman, A., van Buchem, M.A., van der Wee, N.J. & Rombouts, S.A. (2010) Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Front. Syst. Neurosci.*, **4**, 41.

Weissman, D.H., Roberts, K.C., Visscher, K.M. & Woldorff, M.G. (2006) The neural bases of momentary lapses in attention. *Nat. Neurosci.*, **9**, 971–978.

Wu, X., Li, R., Fleisher, A.S., Reiman, E.M., Guan, X., Zhang, Y., Chen, K. & Yao, L. (2011) Altered default mode network connectivity in Alzheimer's disease—a resting functional MRI and Bayesian network study. *Hum. Brain Mapp.*, **32**, 1868–1881.

You, Y., Bai, L., Dai, R., Cheng, H., Liu, Z., Wei, W. & Tian, J. (2013) Altered hub configurations within default mode network following acupuncture at ST36: a multimodal investigation combining fMRI and MEG. *PLoS One*, **8**, e64509.

Zang, Y.F., He, Y., Zhu, C.Z., Cao, Q.J., Sui, M.Q., Liang, M., Tian, L.X., Jiang, T.Z. & Wang, Y.F. (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.*, **29**, 83–91.