Dysfunction of anterior insula in the non-affected hemisphere in patients with post-stroke depression: A resting-state fMRI study

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Abstract.
BACKGROUND: Post-stroke depression (PSD) is a consequential neuropsychiatric sequela that occurs after stroke. However, the pathophysiology of PSD are not well understood yet.
OBJECTIVE: To explore alterations in functional connectivity (FC) between anterior insula and fronto-cortical and other subcortical regions in the non-affected hemisphere in patients with PSD compared to without PSD and healthy control.
METHODS: Resting-state FC was estimated between the anterior insula and cortical and subcortical brain regions in the non-affected hemisphere in 13 patients with PSD, 12 patients without PSD, and 13 healthy controls. The severity of depressive mood was measured by the Beck Depression Inventory (BDI)-II.
RESULTS: Patients with PSD showed significant differences in FC scores between the anterior insula and the superior frontal, middle frontal, and orbitofrontal gyrus in the non-affected hemisphere than healthy control or patients without PSD ($P < 0.05$). In post-hoc, patients with PSD showed higher FC scores between the anterior insula and the superior frontal region than patients without PSD ($P < 0.05$). Furthermore, alterations in FC of the superior frontal, middle frontal, and orbitofrontal gyrus were positively correlated with depression severity, as measured with the BDI-II ($P < 0.001$).

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CONCLUSIONS: This dysfunctional connection between anterior insular and fronto-limbic connections in the non-affected hemisphere might be associated with suggestive mechanism of PSD and could be used as an imaging biomarker in PSD.

1. Introduction

Post-stroke depression (PSD) is a common and serious neuropsychiatric sequela after stroke and may interfere with both functional recovery and long-term outcomes [1]. PSD, which affects nearly 30% to 50% of patients within the first year after stroke, is linked to severe disability, slow motor recovery, and negative response to rehabilitation, and therefore it is a significant burden for patients [1]. PSD is known as a multifactorial process involving neurobiological and sociobehavioral factors; however, the neurophysiologic mechanisms are not well understood [2].

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has been introduced as a powerful tool for investigating neural mechanisms underlying cognitive and neuropsychiatric disorders [3,4]. Rs-fMRI measured spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal at rest and functional connectivity (FC) was considered to be the reason for this spontaneous brain activity in distributed networks [5]. A small but growing body of evidence has begun to emerge using rs-fMRI to examine FC in patients with PSD [6–8]. In these rs-fMRI studies of PSD, dysfunction of the default mode network and the affective network showed an association with the severity of depression [6–8].

Insular cortex is a crucial role in processing various functions such as cognitive, social, memory, and emotional system [9]. The anterior insula has been shown to be involved in the salience network as well in the affected networks when emotional stimuli are presented to participants in fMRI studies with tasks [9,10]. Anterior insula, with its extensive connections to fronto-limbic areas, has become a region of interest in major depressive mood (MDD) over the last decade [10–15]. Previous studies have reported structural and functional abnormalities of insular cortex and its related to fronto-limbic regions in patients with MDD. Reduction in gray matter density of fronto-limbic cortices [15] and volume of insular cortex [12] were reported and disruption of functional connectivity between anterior insula and fronto-limbic regions were revealed [10,11,13,14]. However, to date there has been no investigation regarding FC between anterior insula and fronto-limbic connections in the non-affected hemisphere in PSD.

The objective of the current study was to demonstrate patterns in resting-state FC in the whole brain and anterior insula at one month after stroke and to identify possible alterations in FC scores between the anterior insula and fronto-limbic and subcortical brain regions. To explore possible alterations in FC in patients with PSD, we compared FC scores between the insula and the multiple brain regions indicated across the three groups, such as patients with PSD, patients without PSD, and healthy controls.

2. Methods

2.1. Participants

In this cross-sectional study, twenty-five patients with stroke (16 females, 9 males) with unilateral left or right middle cerebral artery (MCA) infarction and 13 age-matched healthy control subjects (8 females, 5 males) were recruited. All participants were right-handed. None of the subjects had severe visual or

perceptual impairments, or a previous history of affective disorders. All patients underwent rs-fMRI within one month (25.6 ± 5.75 days) from the onset of stroke, and all had severe hemiplegia with no hand or finger motion at that time. The risk factors for stroke were assessed in all patients. The risk factors included diabetes, hypertension, smoking, alcohol, and dyslipidemia. Other factors possibly associated with PSD were assessed using the National Institutes of Health Stroke Scale (NIHSS), Modified Barthel Index (MBI), and modified Rankin Scale (mRS). We used the Beck Depression Inventory (BDI)-II to evaluate the severity of depression immediately before rs-fMRI scanning. All participants had an interview by a psychiatrist and then were diagnosed as PSD according to DSM-V criteria. Five or more of the following symptoms present during the same 2-week period; depressed most of the day, subjective hopeless or observative tearful nearly every day, markedly diminished interest/pleasure in all, significant weight changes, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or inappropriate guilt, diminished ability to concentrate, and recurrent thoughts of death, suicidal ideation, or a suicidal attempt. There were at least one of the symptoms is either depressed mood or loss of interest/pleasure in PSD. One group (patients without PSD group: $n = 12$, 8 female patients, 4 male patients, 63.08 ± 15.18 years) was composed of patients with no depression after stroke, while the other group (patients with PSD group: $n = 13$, 8 female patients, 5 male patients, 68.92 ± 9.81 years) was composed of individuals with diagnosed as PSD. All subjects provided written informed consent and agreed to participate in the rs-fMRI study. The study protocol was approved by the local Institutional Review Board (IRB no. 2012-05-023).

2.2. Rs-fMRI data acquisition

A 3.0T GE Signa Exite (Milwaukee, WI, USA) scanner was used to obtain the rs-fMRI images and T1-weighted images. The rs-fMRI images were acquired for BOLD signals using the following parameters: echo planar imaging (EPI) sequence, echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, flip angle (FA) = 90°, field of view (FOV) = 22 cm, acquisition matrix = 64 × 64 and 4 mm thickness with no gap (voxel size = 3.43 × 3.43 × 4 mm, resolution = 0.29 pixel/mm). The total scan volumes were 240 volumes without dummy scans (six volumes), and the total scan time was 8 min 12 s, including dummy scans. During scanning participants were required to keep their eyes closed, to stay awake, and to avoid thinking. An anatomical T1-weighted image was acquired using the following parameters: 3D fast spoiled gradient echo sequence, TE = 3 ms, TR = 7.8 ms, FA = 20°, FOV = 21 cm, acquisition matrix = 256 × 256, 1.3 mm thickness with no gap (voxel size = 0.82 × 0.82 × 1.3 mm, resolution = 1.21 pixel/mm), and scan time was 2 min 36 s.

2.3. Rs-fMRI data analysis

The statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/) program on MATLAB (MathWorks, Inc., Natick, MA, USA) was used for pre-processing and statistical analysis of rs-fMRI images and T1-weighted images. The rs-fMRI images and T1-weighted images from patients with a left lesion were flipped to change it from a left lesion to a right lesion because the whole brain analysis was performed on contralesional and ipsilesional hemispheres. All rs-fMRI data, including flipped data, were preprocessed using a slice timing correction, spatial realignment, normalization, and smoothing. Rs-MRI data were obtained by an interleaved method, and slice timing was performed to correct the time between slices. Then, corrected rs-MRI data were realigned to the first image to correct the head movement between scans, and the translation parameters for the x (left/right), y (anterior/posterior),

and z (superior/ inferior) directions were obtained for each brain volume compared to the first volume. The realigned rs-fMRI data were used for outlier detection using the Artifact Detection Tool (ART). The realigned rs-fMRI data were mean adjusted by proportional scaling and spatially normalized in a Montreal Neurological Institute (MNI) template (voxel size = $2 \times 2 \times 2$ mm, resolution = 0.5 pixel/mm). Finally, the full-width at half maximum (FWHM) of the Gaussian kernel in 8 mm was used to smooth the normalized rs-fMRI data. The mean displacement (displacement = square root $[x^2 + y^2 + z^2]$) was calculated to estimate the head motion. No experiment had a mean displacement over 2 mm. There was no mean displacement difference ($P = 0.985$) between the groups without PSD (mean displacement, 0.43 $\pm$ 0.06 mm), with PSD (mean displacement, 0.46 $\pm$ 0.07 mm) or healthy controls (mean displacement, 0.51 $\pm$ 0.12 mm).

Pre-processed data were entered the CONN tool (http://web.mit.edu/swg/software.htm, version 15.b) to determine FC using a seed-based method. The coordinates of the anterior insula in the non-affected hemisphere [9,16] was identified using MarsBaR software (http://marsbar.sourceforge.net/) and the meta data of the Neurosynth site (http://www.neurosynth.org). Noise due to cerebrospinal fluids, white matters, or head motions, and sources of artifacts in time series data from the ART were corrected for as nuisance covariates. Individual FC maps from the anterior insula in the non-affected hemisphere were made for the seed-to-voxel connectivity maps in the first-level analysis. Then, the results of the first-level analysis were used for within-group, analysis of variance (ANOVA), post-hoc, and multiple regression analyses for the seed-to-voxel connectivity maps in the second-level analysis.

Lesion boundaries were determined using T1-weighted images from each patient with the aid of MRIcron software (http://people.cas.sc.edu/rorden/mricron/index.html). To mask the regions of damage, normalized T1-weighted images were used as a reference, and masking areas were manually drawn by a rehabilitation doctor who was blinded to the study. Masked images were combined using the SPM12 program and displayed using MRIcroGL software (http://www.cabiatl.com/mricrogl/). In addition, the lesion volume was calculated to compare the total lesion size between patients without PSD group and with PSD group, and the comparison was tested using the non-parametric Mann-Whitney test.

2.4. Thresholding criteria & statistical analysis

To compensate for multiple comparisons across the brain, spatial extent thresholds were calculated using AlphaSim with Monte Carlo simulations from the SPM REST toolbox (http://restfmri.net/). Input parameters for minimum cluster size were determined by performing a 5000 Monte Carlo simulation with a cluster connection radius of 5 mm and a FWHM of 8 mm to satisfy the Family Wise Error (FWE) rate correction of $P_{FWE} < 0.001$ for the T-contrast.

All statistical analyses on clinical data were performed using SPSS software (SPSS Inc., Chicago, IL, USA, version 18), and differences with a $P < 0.05$ were defined as statistically significant. Where data were on the ratio scale, age and FC score, normal distribution was assessed using the Shapiro-Wilk normality test on the groups. Then, where the data were normal, a one-way ANOVA and two sample t-test were performed to determine differences between the groups. The Kruskal-Wallis test was performed where data were not normally distributed. Where data were on the nominal scale, i.e., sex, the chi-square test was used to identify differences between the groups.

3. Results

3.1. General characteristics

The mean age of the 25 patients with stroke was 66.12 $\pm$ 12.75 years (range, 32–85 years) and that

Table 1
Demographics and clinical data in patients without PSD and with PSD

Clinical values	Without PSD	With PSD	P-value
Demographic data			
Sex (Male: Female)	4:8	5:8	1.000
Age[a]	63.08 ± 15.18	68.92 ± 9.81	0.253
Risk factors of stroke			
DM[b]	4/12	6/13	0.688
HTN[b]	9/12	8/13	0.673
Dyslipidemia[b]	4/12	5/13	1.000
Smoking[b]	5/12	4/13	0.688
Alcohol[b]	7/12	4/13	0.238
Type of stroke			
Cortical: Subcortical	5:7	8:5	0.320
Right: Left lesion	7:5	10:3	0.319
Severity of impairment after stroke			
BDI[a]	8.33 ± 3.98	23.23 ± 9.65	0.000^*
NIHSS[a]	8.73 ± 4.54	10.33 ± 3.05	0.578
MBI[a]	49.18 ± 12.09	41.83 ± 17.09	0.178
mRS[a]	2.64 ± 1.43	3.33 ± 0.77	0.218
MMSE-K[a]	25.18 ± 4.35	23.00 ± 6.10	0.252

[a]Data are mean $\pm$ standard deviation. [b]Data are selected patients/total patients. $^*P <$ 0.05 indicated. BDI: Beck Depression Inventory; DM: Diabetes Mellitus; HTN: Hypertension; NIHSS: National Institutes of Health Stroke Scale; MBI: Modified Barthel Index; mRS: modified Rankin Scale; MMSE-K: Mini-Mental State Examination-Korean version.

for 13 healthy control subjects was 64.61 ± 6.13 years (range, 55–72 years). No differences in age were observed between patients without PSD, patients with PSD, or healthy controls ($P = 0.385$). The BDI-II scores of patients without PSD, patients with PSD, and healthy controls were 8.33 ± 3.95, 23.23 ± 9.65, and 5.38 ± 3.04, respectively. There was no statistical difference in BDI-II scores between the patients without PSD group and the healthy control group ($P = 0.483$). The PSD group had significantly different BDI-II scores when compared to other two groups ($P < 0.001$). The group differences in demographics, risk factors of stroke, type of stroke, and severity of impairment after stroke are summarized in Table 1. The comparison of lesion volume showed no statistical difference between the without PSD group and with PSD group ($P = 0.06$).

3.2. FC maps

A one sample within-group analysis showed the FC map between the anterior insula and the other brain areas in the non-affected hemisphere for the three groups (Fig. 1). The detailed brain areas showing FC with the anterior insula in the non-affected hemisphere are summarized in the Supplement (Tables S1–S3). While a one sample within-group analysis also showed FC between the anterior insula in the non-affected hemisphere and brain areas in the affected hemisphere, the brain areas in the affected hemisphere were not included in Supplementary Tables S1–S3. The main reason for excluding brain areas in the affected hemisphere was that the affected hemisphere is the damaged side of the brain, and thus only brain areas in the intact hemisphere were considered for analysis since damage-related physiological factors, such as a microbleeding, can be possible confounders for analysis.

The ANOVA of the FC maps revealed that the superior frontal, middle frontal, and orbitofrontal regions of the non-affected hemisphere were significantly different between the three groups (Fig. 2A and Supplementary Table S4). A post-hoc two-sample t-test was then performed for further comparison
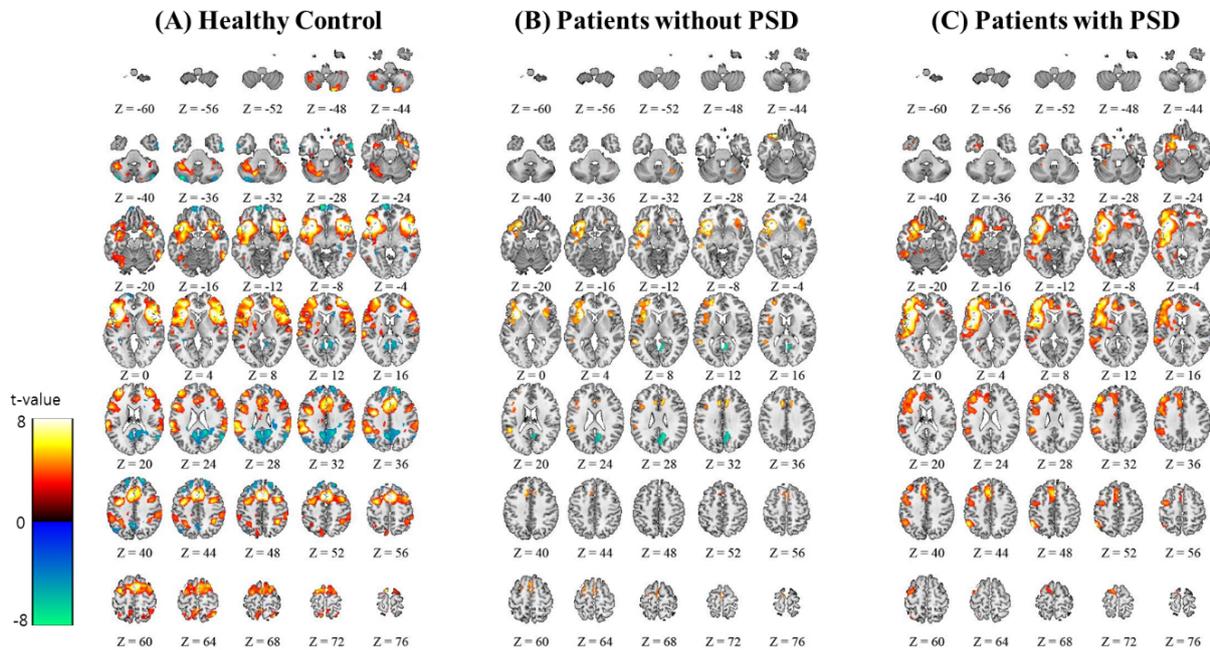
Fig. 1. The functional connection with the anterior insula from the within subject analysis with a Family Wise Error (FWE)-corrected threshold of $P < 0.001$ for multiple comparisons. In the maps, left part corresponds to the non-affected hemisphere and right part corresponds to the affected hemisphere.

between groups. First, comparison of patients with PSD and healthy control groups showed FC differences in the superior frontal, middle frontal, and orbitofrontal regions (Fig. 2B and Supplementary Table S5). There was no difference in FC between patients with PSD group and healthy control groups. Second, the comparison of patients with PSD group and without PSD group showed a difference in FC in the superior frontal region (Fig. 2B and Supplementary Table S5). Third, the comparison between patient without PSD group and healthy control groups showed no statistical difference in FC. All post-hoc analyses were performed at a FWE rate correction of $P_{FWE} < 0.001$ performed using the Monte Carlo simulation in the REST Tool box.

3.3. FC score

FC scores in the superior frontal, middle frontal, and orbitofrontal areas of the non-affected hemisphere are represented in Fig. 3. The FC scores in the superior frontal area were as follows: -0.17 ± 0.13 (healthy group), -0.03 ± 0.12 (patients without PSD group), and 0.12 ± 0.10 (patients with PSD group). In the middle frontal area, the FC scores were as follows: -0.15 ± 0.08 (healthy group), -0.03 ± 0.18 (patients without PSD group), and 0.17 ± 0.20 (patients with PSD group). The FC scores in the orbitofrontal area were as follows: -0.16 ± 0.13 (healthy group), -0.02 ± 0.12 (patients without PSD group), and 0.12 ± 0.11 (patients with PSD group). In these three brain areas, the FC scores were significantly different among three groups.

3.4. Correlation between FC and BDI-II scores

The FC scores in the superior frontal ($r = 0.585$, $P < 0.001$), middle frontal ($r = 0.545$, $P < 0.001$), and orbitofrontal ($r = 0.597$, $P < 0.001$) areas of the non-affected hemisphere showed positive

(A) ANOVA

(B) Post hoc two sample

With PSD > Healthy Control

With PSD > Without PSD
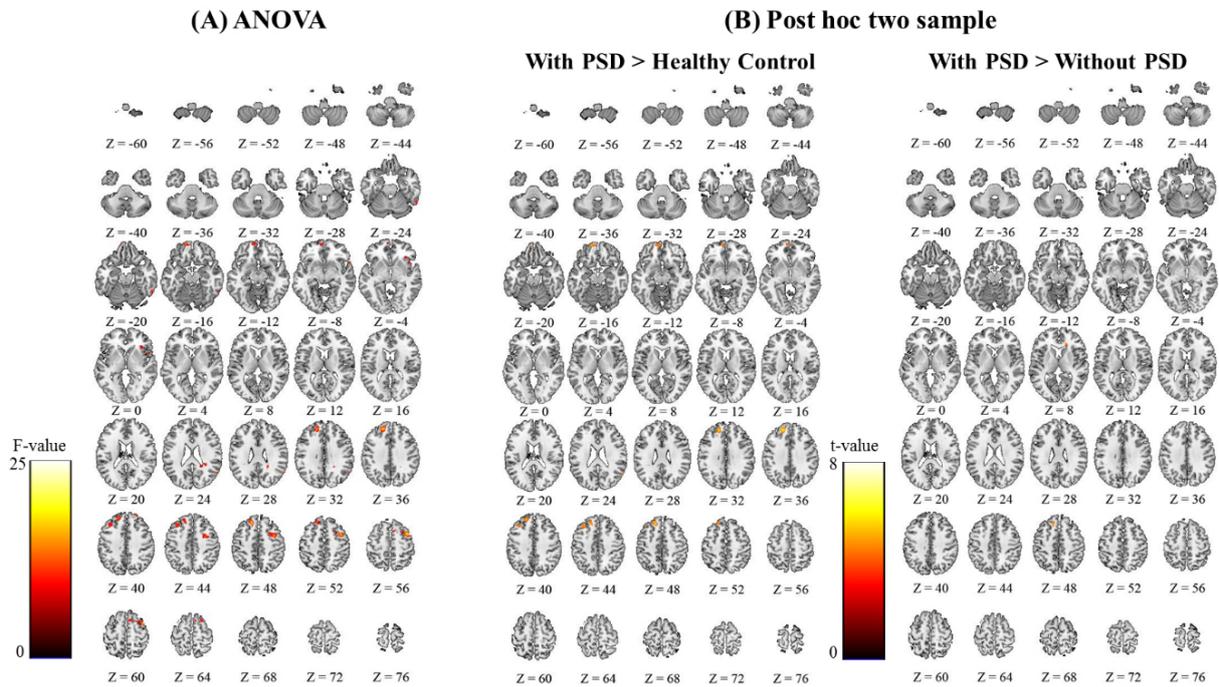
Fig. 2. Significant functional connectivity differences at the whole brain level were revealed by ANOVA and post-hoc two sample test. The SPM{F}s and SPM{t}s with a Family Wise Error (FWE)-corrected threshold of $P < 0.001$ for multiple comparisons.
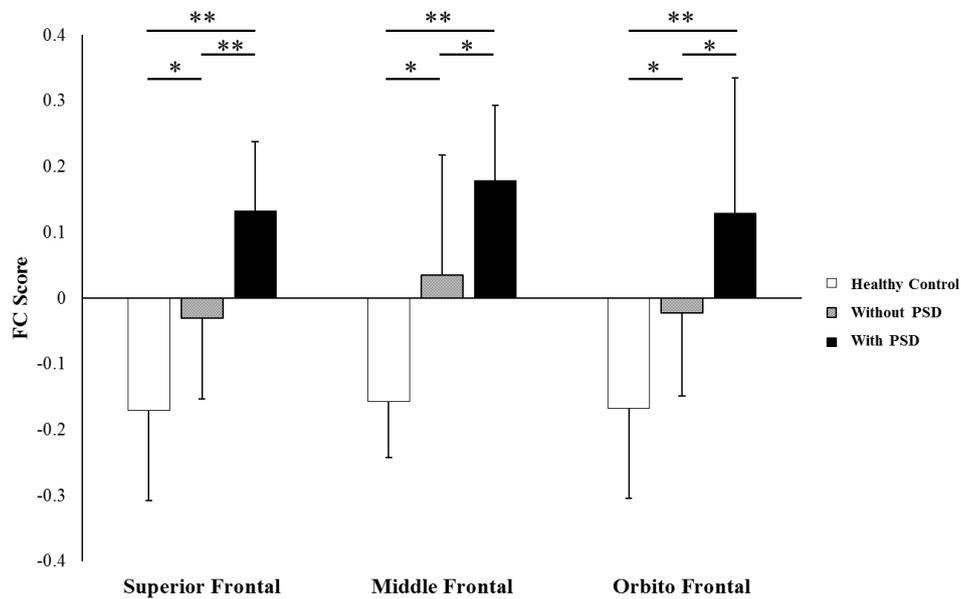
Fig. 3. The functional score between the non-affected hemispheric anterior insula and the superior frontal, middle frontal, and orbitofrontal gyrus regions showed significantly statistical differences between patients with PSD group and each of the other groups (patients without PSD group and healthy control group). $^{*}P < 0.05$, $^{**}P < 0.01$ indicated.
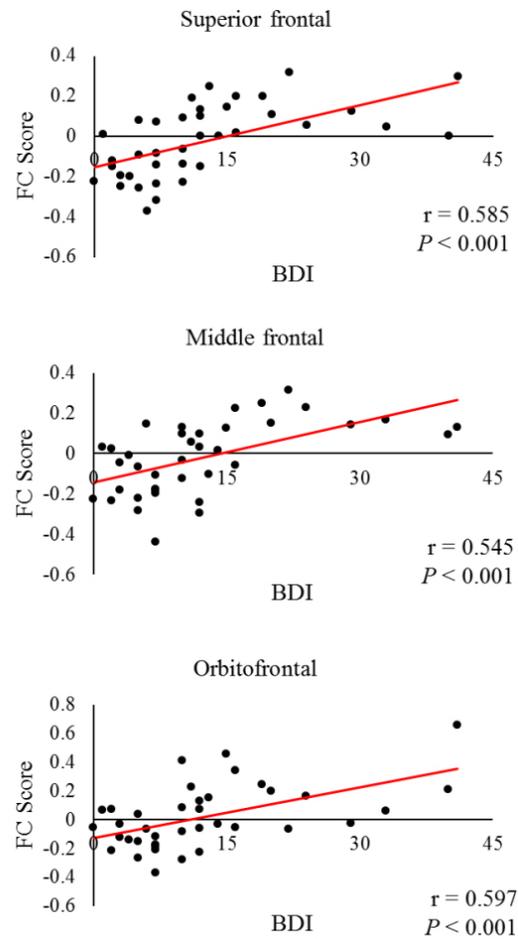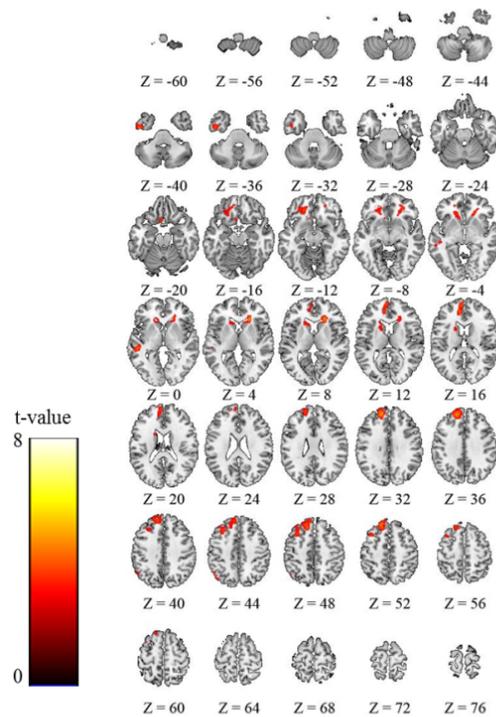
Fig. 4. Correlation map showed that FC scores in the superior frontal, middle frontal, and orbitofrontal regions in the non-affected hemisphere strongly correlates with BDI-II scores.

correlations with BDI-II scores (Fig. 4). These positive correlations thresholded to a family-wise error (FWE) rate correction of $P_{FWE} < 0.001$.

4. Discussion

The main finding of the current study was that the mean FC scores between the anterior insula and fronto-limbic areas in the non-affected hemisphere showed much higher positive scores in patients with PSD than the mean FC scores in patients without PSD and healthy controls. Furthermore, in these fronto-limbic areas, the FC scores showed positive correlations with depression severity. These findings therefore suggest that FC alterations between the non-affected anterior insula and fronto-limbic region are strongly associated with PSD

In this study, we have focused on alteration of FC in the non-affected hemisphere in patients with PSD compared to without PSD and healthy control. Previous imaging studies on PSD have focused on the specific lesion location and laterality in the affected hemisphere [17,19–22]. However, location

and laterality of stroke lesion related to occurring PSD have not yet been determined. Increased risk factor of PSD was related to location of stroke lesion such as the frontal lobe, basal ganglia, and limbic system [17]. However, systemic review offered no support for the hypothesis that the risk of PSD was affected by the lesion location [18]. Also, laterality was one of the first characteristics of stroke lesions. Stroke patients with right hemispheric lesions represented more frequently depressive mood than those with left hemispheric lesions in 6 months after stroke onset [19,20]. There were, however, other studies with contradictory finding that the higher prevalence in left hemispheric lesions were associated with the severer of PSD [21,22]. There are not clear pattern of the relationship between laterality of the affected hemisphere and PSD [23]. Therefore, this current study has been interesting in suggesting mechanism of PSD in not the affected hemisphere but the non-affected hemisphere at 1 month after stroke.

In this study, the anterior insula showed a negative correlation (i.e., anticorrelation) with posterior cingulate cortex (PCC), precuneus, and angular gyrus in the control group but not in the PSD group. More specifically, patients without PSD group showed a negative correlation between the anterior insula and PCC only, though no correlation was observed in the group with PSD. Using rs-fMRI, it has been demonstrated that some brain networks are organized into anticorrelated networks [24,25]. That is a set of brain regions has been found to be anticorrelated with regions of the task-positive network. It consists of brain regions that are commonly activated in tasks which demand attentional control. Therefore, our results showed that the negative correlation pattern observed in some brain networks is also altered in patients with PSD. One the other hand, a previous rs-fMRI study of PSD has focused on dysfunction of the default mode network (DMN). Lassalle-Lagadec et al. [6] showed that FC alterations in the DMN after stroke were correlated with the severity of depression and that FC alterations in the DMN were associated with anxiety severity suggesting a strong association between early FC alterations in the DMN and the risk of PSD.

In relation to MDD, the anterior insula and fronto-cortical areas have gained increasing attention as key brain regions in the pathophysiology of depression [26]. The anterior insula has wide and extensive connections to cortical and limbic regions. It plays a consequent role as a coordination between cognitive control networks and DMN [9,10]. The rich connection between the anterior insula and frontal areas suggests a unique role for the anterior insula in functions related to both emotional processing and self-information processing [27,28]. Also, reduction in gray matter density of fronto-limbic cortices [15] and volume of insular cortex [12] were reported and disruption of functional connectivity between anterior insula and fronto-limbic regions were revealed [10,11,13,14]. Therefore, we chose the anterior insula as a key node in this study and evaluated FC between the insula and all brain regions. One sample FC maps, which were obtained using the anterior insula in the non-affected hemisphere as a seed location, revealed the FC between the anterior insula and cortical and sub-cortical brain areas in all three groups.

Studies using rs-fMRI have demonstrated an important role for cortical-subcortical interactions in MDD. Some studies using rs-fMRI have found decreased FC between ventral striatum (VS) and the ventromedial prefrontal cortex in adult patients with depression compared to healthy controls [29,30]. Another study found that the FC between the VS and prefrontal cortex is associated with depression severity [31]. However, in the current study, the between group analysis did not show FC alterations in patients with PSD.

Among the fronto-cortical brain areas, the superior frontal, middle frontal, and orbitofrontal cortex in the non-affected hemisphere showed high FC scores with the anterior insula in patients with PSD. Furthermore, the degree of connectivity in these brain regions correlated with the severity of depression, suggesting that the more severe the depression, the stronger the coherence in these systems. Functional imaging studies indicated that these frontal areas are closely associated with impairments in blocking

out negative, repetitive thoughts in individuals with depression [30–32]. Therefore, it is tempting to propose that the strong links, i.e., the high positive FC between the insula and these fronto-limbic areas, contribute to difficulties in disengaging from negative stimuli in patients with PSD, as a result lengthening the duration of exposure to depressive items. Based on the strong resting BOLD measures, which were weak or inconsistent in healthy controls, patients with PSD appear to experience difficulties in attentional disengagement from negative stimuli and keep their attentional focus on negative stimuli. Previously, it was demonstrated that patients with depression inclined attention for negative stimuli but declined attention for positive stimuli compared with healthy controls [33]. Therefore, taken together, the strong positive connectivity between the anterior insula and frontal brain areas might be related to self-centered ruminations in patients with PSD.

This study has several limitations. First, we did not examine other emotional or psychological measures, such as anxiety levels in patients with PSD. In general, patients with depression often have a high level of anxiety. Therefore, we cannot exclude the possibility that the observed findings resulted from other emotional or psychological syndromes. Second, The lesion volumes between the without PSD and the with PSD group was not significantly different, but the P-values were 0.06 that are considered to be marginal. Third, due to the inherent disease nature of stroke, neurovascular coupling is expected to be different between patients with stroke and healthy controls, and thus the BOLD effect itself might be different in patients with stroke compared to healthy controls.

5. Conclusion

In conclusion, when compared to patients without PSD and healthy controls, patients with PSD show much higher positive FC scores between the anterior insula and fronto-limbic areas. Furthermore, FC alterations in fronto-limbic regions were strongly correlated with depression severity as measured with the BDI-II. While the current study was limited in its ability to study the concrete relationship between depression and the alteration in FC owing to its sample size, we speculate that the positive FC in patients with PSD might be used as a potential imaging biomarker for PSD.

Conflict of interest

None to report.

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Supplementary material

Table S1
The coordinates of functional connection with the non-affected hemispheric anterior insula (left side in figures) from the within subject analysis on the healthy control group was thresholded at a family-wise error (FWE) rate correction $P_{FWE} < 0.001$, and the minimum cluster size was extended to 148 voxels

Brain region	Side	Cluster size	MNI-coordinates			Peak T
			x	y	z	
Dorsolateral Prefrontal	L	1952	−12	20	46	9.45
	R	2128	32	54	12	8.85
Ventrolateral Prefrontal	L	1649	−38	22	−2	26.84
	R	1166	50	14	0	15.06
Orbito Frontal	L	691	−34	24	−6	35.51
	R	728	46	24	−10	11.60
Postcentral Gyrus	L	667	−36	−4	40	10.28
Supplementary Motor Area	L	903	−8	10	54	14.45
	R	947	8	10	58	11.35
	R	156	36	−46	46	7.24
Supra Marginal	L	661	−66	−28	24	8.30
	R	537	58	−38	26	7.10
Superior Temporal	L	943	−58	10	−2	16.40
	R	372	56	12	−2	9.06
Inferior Temporal	L	317	60	−54	−22	9.07
Anterior Cingulate	L	643	−4	16	38	8.62
	R	700	6	28	36	9.14
Insula	L	1169	−32	22	−4	55.30
	R	1003	34	28	−2	15.16
Striatum	L	270	−28	12	−6	9.79
	R	195	32	14	−2	7.38
Cerebellum	L	405	−42	−50	−38	6.29
Superior Frontal	L	451	−16	70	−2	−6.62
	R	541	16	56	36	−8.56
Medial Orbitofrontal	L	391	−10	62	−6	−9.32
Post Cingulate	L	164	−8	−54	32	−6.69
	R	162	14	−48	26	−6.39
Precuneus	L	697	−8	−54	34	−6.82
	R	579	16	−50	24	−6.67
Angular	L	187	−52	−66	40	−4.83
	R	291	60	−60	24	−8.60
Inferior Temporal	R	230	58	0	−32	−9.47
Middle Temporal	R	205	60	2	−32	−9.47
Cerebellum	R	220	−36	−76	−36	−8.62

Table S2
The coordinates of functional connection with the non-affected hemispheric anterior insula (left side in figures) from the within subject analysis on patients with PSD group was thresholded to satisfy a family-wise error (FWE) rate correction $P_{FWE} < 0.001$, and the minimum cluster size was extended to 86 voxels

Brain regions	Side	Cluster size	MNI-coordinates			Peak T
			x	y	z	
Dorsolateral Prefrontal	L	1751	−42	48	2	9.58
Ventrolateral Prefrontal	L	1956	−36	24	−2	18.66
Orbito Frontal	L	1355	−36	22	−6	34.15
Precentral Gyrus	L	533	−50	2	16	5.79
Supplementary Motor Area	L	242	−4	22	44	6.87
Inferior Parietal	L	284	−54	−52	52	8.29
Supra Marginal	L	154	−52	−42	28	5.64
Superior Temporal	L	979	−46	12	−12	11.01
Middle Temporal	L	202	−48	−18	−8	7.00
Anterior Cingulate	L	420	−12	40	14	5.96
Hippocampus	L	249	−32	−10	−14	6.49
Insula	L	1462	−34	22	−4	72.25
Striatum	L	500	−32	−14	−6	9.36
Amygdala	L	138	−30	−4	−14	7.35

Table S3
In the within subject analysis, the coordinates of functional connection with the non-affected hemispheric anterior insula (left side in figures) on patients without PSD group was thresholded to satisfy a family-wise error (FWE) rate correction $P_{FWE} < 0.001$, and the minimum cluster size was extended to 75 voxels

Brain regions	Side	Cluster size	MNI-coordinates			Peak T
			x	y	z	
Dorsolateral Prefrontal	L	436	−26	46	10	8.75
Ventrolateral Prefrontal	L	622	−36	24	−2	14.70
Orbitofrontal	L	703	−34	24	−6	19.90
Supplementary Motor Area	L	282	−2	18	62	5.63
Superior Temporal	L	731	−40	20	−16	8.22
Middle Temporal	L	222	−54	−46	10	10.67
Anterior Cingulate	L	115	−8	20	32	7.41
Insula	L	1010	−34	22	−4	26.73
Precuneus	L	308	−2	−56	10	−9.71
Occipital	L	142	−2	−58	8	−9.62
Cerebellum	L	99	0	−52	6	−9.29

Table S4
The coordinates of functional connection with the non-affected hemispheric anterior insula (left side in figures) from the ANOVA analysis on the three groups was thresholded to satisfy a family-wise error (FWE) rate correction $P_{FWE} < 0.001$, and the minimum cluster size was extended to 29 voxels

Brain regions	Side	Cluster size	MNI-coordinates			Peak F
			x	y	z	
Superior frontal	L	281	−16	44	34	18.30
Middle frontal	L	92	−32	28	44	11.88
Orbitofrontal	L	95	−16	58	−18	15.37

Table S5

The coordinates of functional connection differences in the post-hoc two sample t-test were thresholded to a family-wise error (FWE) rate correction $P_{FWE} < 0.001$ performed by using Monte Carlo simulation in the REST Tool box. The minimum cluster size in patients with PSD > healthy control, patients with PSD > patients without PSD was 28 voxels and 12 voxels, respectively. There was no significant difference in the opposite case and between patients without PSD and healthy control

Brain regions	Side	Cluster size	MNI-coordinates			Peak T
			x	y	z	
Patients with PSD > healthy control						
Superior frontal (BA9)	L	258	−16	44	34	6.05
Middle frontal (BA8)	L	87	−32	28	44	4.86
Orbitofrontal (BA11)	L	126	−16	58	−18	5.54
Patients with PSD > patients without PSD						
Superior frontal (BA8)	L	37	−14	30	48	5.07