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Association of resting-state functional connectivity with cognitive reappraisal, positive symptom, and general functioning in first-episode psychosis

초발 정신증에서의 휴지기 뇌연결성과 인지적 재해석, 양성증상 및 전반적 기능과의 관계

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노 경 진

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Association of resting-state functional connectivity with cognitive reappraisal, positive symptom, and general functioning in first-episode psychosis

by

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A Thesis Submitted to the Department of Clinical Medical Sciences, Graduate School Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Clinical Medical Sciences at Seoul National University College of Medicine

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Abstract

Association of resting-state functional connectivity with cognitive reappraisal, positive symptom, and general functioning in first-episode psychosis

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Background and Aim: Although impaired cognitive reappraisal is apparent in the early stages of psychosis, limited studies have been conducted revealing the neurobiological basis. We aimed at investigating the neurobiological basis of impaired cognitive reappraisal in early psychosis using resting-state functional connectivity of brain regions related to cognitive reappraisal.

Methods: Resting-state functional magnetic imaging was obtained from 36 first-

episode psychosis (FEP) patients, 32 clinical high risk (CHR) individuals, and 48 healthy controls (HCs). Whole-brain functional connectivity maps were generated with regions known to be related to cognitive reappraisal as seed regions and compared FEP, CHR and HC groups. We examined whether resting-state functional connectivity was correlated with reappraisal success ratio, positive symptom severity and social functioning using correlation analysis controlling for covariates.

Results: FEP patients showed increased functional connectivity between left superior parietal lobe and left inferior frontal gyrus compared to HC. Also, greater functional connectivity between left superior parietal lobe and left inferior frontal gyrus exhibited lesser reappraisal success ratio after controlling for covariates in FEP group. In addition, decreased functional connectivity was related to lesser positive symptom severity and better global functioning in FEP group.

Conclusions: There is alteration of fronto-parietal intrinsic network reflecting emotion dysregulation in the early phase of psychosis. Impaired emotion regulation is related to increased positive symptom and decreased global functioning. This study may provide a potential target for ameliorating newly formed psychotic symptoms especially in early stages of psychosis.

Keyword: Resting-state functional connectivity, Cognitive reappraisal, First-episode psychosis, Clinical high risk, Schizophrenia

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List of Abbreviations

ANCOVA: analysis of covariance

ANOVA: analysis of variance

CHR: clinic-high risk

dlPFC: dorsolateral prefrontal cortex

FC: functional connectivity

FDR: false discovery rate

FEP: first-episode psychosis

fMRI: functional magnetic resonance imaging

GAF: global assessment of functioning

GFS:S: Global Functioning Scale: Social

GFS:R: Global Functioning Scale: Role

HC: healthy control

IAPS: International Affective Picture System

IFG: inferior frontal gyrus

IQ: intelligence quotient

mPFC: medial prefrontal cortex

OZP: olanzapine

PANSS: the Positive and Negative Syndrome Scale

ROI: region of interest

SIPS: the Structured Interview for Prodromal Symptoms

SOPS: the Scale of Prodromal Symptoms

SPL: superior parietal lobe

vmPFC: ventromedial prefrontal cortex

vlPFC: ventrolateral prefrontal cortex

Introduction

Study background

Limited studies have been conducted on affective disturbance in schizophrenia and prodromal stages of psychosis despite its clinical importance. Considering that a significant proportion of the schizophrenia and clinical high risk (CHR) individuals experience depression and emotional disturbance leading to decreased quality of life (1, 2), it is important to focus on the affective symptoms present in schizophrenia and early psychosis patients.

According to a recent meta-analysis study, schizophrenia patients tend to perceive neutral and positive stimuli negatively although the ability to momentarily feel positive emotion in a specific situation did not decrease (3). The negative emotionality may reflect the emotion regulation deficit in schizophrenia (4, 5). Emotion regulation, which refers to the ability to control the intensity and duration of experiencing positive and negative emotions, can be largely divided into an antecedent-focused strategy and a response-focused strategy (6). Antecedent-focused strategies work by controlling emotions before emotional reactions are expressed. On the other hand, response-focused strategies execute their effects by suppressing emotions after emotional reaction occurs, leading to less effective control of emotion compared to antecedent-focused strategies (6). The self-report studies conducted on impaired emotion regulation in schizophrenia and CHR individuals suggested that patients with schizophrenia spectrum disorder tended to utilize response-focused strategies including suppression rather than cognitive reappraisal which in one of the best-known antecedent-focused strategies (7-9). Particularly, cognitive reappraisal, defined as the attempt to reinterpret an emotion-

eliciting situation in a way that alters its meaning and changes its emotional impact (10) is impaired in schizophrenia (11, 12). Impaired utilization of cognitive reappraisal may lead to negative emotionality contributing to formation and maintenance of positive psychotic symptoms especially in the early phase of psychosis (13, 14). Also, lower use of cognitive reappraisal was related to poor functional outcome (15, 16).

To reveal neurophysiological correlates of impaired cognitive reappraisal in schizophrenia, Strauss et al. utilized even-related potential (ERP) paradigm developed by Foti and Hajcak (17), in which a preceding audio description was provided before the upcoming image to promote cognitive reappraisal (18). In contrast to healthy controls whose late positive potential (LPP) attenuated when given unpleasant images preceded by neutral audio description compared to the ones by negative audio description, there was no difference between the amplitude of LPP for unpleasant images preceded by neutral and that by negative audio description in schizophrenia, suggesting that schizophrenia patients were unable to downregulate negative emotion by cognitive reappraisal (18). Similar findings were reported in early psychosis including first-episode psychosis (FEP) patients and CHR individuals (19). Taken together, disrupted emotion regulation especially impaired cognitive reappraisal in schizophrenia and early psychosis is reflected in neurophysiological correlates. In addition to the ERP studies which allowed us to evaluate the aberrant neural response with high temporal resolution, neuroimaging studies are needed to elucidate the underlying neural substrate of impaired emotion regulation.

Prior study using the Foti and Hajcak cognitive reappraisal paradigm (17) in task fMRI study in healthy subjects showed that increased activation of prefrontal

cortical areas and inactivation of the amygdala in the antecedent neutral description followed by unpleasant images (20). Similar results have been shown when participants were asked to self-generate their own neutralizing explanation seeing unpleasant images (21, 22). The most recent meta-analysis including such 48 task fMRI studies on cognitive reappraisal in healthy individuals showed that prefrontal cortex including medial, dorsolateral, ventrolateral prefrontal cortex (mPFC, dlPFC, vlPFC) and dorsal anterior cingulate cortex were activated while amygdala and insula were inactivated (23). In this comprehensive meta-analysis, Buhle et al. reported the importance of the functional interplay between frontal and limbic regions in the process of adequate regulation of emotion (23). In addition, Pico-Perez et al. revealed that resting-state cortico-amygdala functional connectivity was related to emotion regulation ability in healthy participants through resting-state functional magnetic resonance imaging (fMRI) study (24). However, limited neuroimaging studies have been performed in individuals in schizophrenia and the early phase of the illness (25). There was each one study that investigated the neural correlates through fMRI in chronic schizophrenia and CHR individuals, respectively (24, 25). Fan et al. included 27 patients with chronic schizophrenia and 18 healthy controls who performed the Mayor Salovey Caruso Emotional Intelligence (MSCEIT) managing task to measure emotional intelligence (24). Functional connectivity between ventromedial prefrontal cortex (vmPFC) and dlPFC showed positive correlation with PANSS-positive symptoms (24). Also, vmPFC-right medial temporal lobe/parahippocampal gyrus/amygdala was positively correlated with emotion management (24). In the Velde study in 2015, less activation of the left vlPFC during cognitive reappraisal task in 15 CHR individuals were shown compared to 16 healthy participants (25). However, there was no other functional

imaging research studying on the cognitive reappraisal in individuals at the early phases of psychosis including first episode psychosis (FEP) patients and CHR individuals who experience newly formed psychotic symptoms.

Purpose of study

In this study, we aimed at investigating the neurobiological basis reflecting the impaired cognitive reappraisal in the schizophrenia patients, especially in the early stages of psychosis including FEP patients and CHR individuals using resting-state fMRI. We obtained resting state fMRI considering relatively ease of data collection in individuals who suffer from their symptoms (26, 27). Also, resting state fMRI data allow us to study intrinsic network architecture (28-30), which is considered to contribute to shaping task-based neural activity and its associated behaviors (26, 28, 29, 31). Thus, we compared the resting-state FC of the cognitive reappraisal related brain regions including bilateral amygdala, right middle frontal gyrus, right inferior frontal gyrus, right medial frontal gyrus, left middle frontal gyrus, bilateral superior parietal lobule, and left middle temporal gyrus (23). In the study, we hypothesized early psychosis individuals (FEP patient and CHR individuals) would show different resting-state functional connectivity associated with emotion regulation compared to healthy control. Also, we hypothesized that there would be significant correlation of functional connectivity with cognitive reappraisal ability. In addition, we expect the presence of significant association between the functional connectivity and psychotic symptom severity and/or global functioning.

Methods

Participants

Thirty-six FEP patients, 32 CHR individuals, and 48 healthy controls (HC) were included in this study. We recruited FEP patients and CHR individuals between October 2017 and December 2020 via the inpatient and outpatient clinics in the Department of Seoul National University Hospital (SNUH) and the Seoul Youth Clinic (www.youthclinic.org) (32). A patient with FEP was defined as an individual who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria of schizophrenia, schizoaffective disorder, or schizophreniform disorder for less than two years. CHR was diagnosed using the Korean version of the Structured Interview for Prodromal Symptoms (SIPS) (33). All CHR individuals were assessed according to the Structured Interview for Prodromal Syndromes (33). The CHR individuals met at least one of the prodromal states of psychosis criteria: attenuated positive syndrome (APS), brief intermittent psychotic syndrome (BIPS), and/or genetic risk with deterioration (GRD). APS is characterized as experiencing attenuated form of psychotic symptoms during previous 12 months. BIPS is defined by the presence of positive symptoms that started during the past 3 months and the symptoms last several minutes a day at least once per month. GRD group includes individuals with schizotypal personality disorder or who have a family history of psychosis within a first-degree relative and 30% decrease in the Global Assessment of Functioning (GAF) over the past year (33). HCs were recruited via the Internet advertisement. They were excluded if they had a past or current DSM-IV Axis I psychiatric history or family history of schizophrenia within third-degree relatives.

Among all participants, it was confirmed that no participant had neurological disease or significant head trauma, evidence of severe medical illness, sensory impairments, history of substance abuse or dependence (except nicotine) or intellectual disability (intelligent quotient [IQ] < 70) for 3 groups.

All study participants understood the study procedures and provided written informed consent according to the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of SNUH (IRB number: 2111-195-1280).

Demographic factors and clinical characteristics

The demographic factors included age, sex, and years of education. IQ was measured by the Korean Weschler Adult Intelligence Scale (34), and handedness using the Annett Handedness Inventory (35). The severity of psychotic symptoms of FEP patients was measured using the Positive and Negative Syndrome Scale (PANSS) (36). The severity of prodromal symptoms in CHR individuals was assessed using the Scale of Prodromal Symptoms (SOPS) (37). The functional status of all the participants in the study was examined using global functioning scale: social and role (GFS:S and R) (38, 39). Medication usage of antipsychotics was documented and converted into a daily olanzapine equivalent dose (40).

Emotion regulation measurement

Trial sequence, stimuli, and audio descriptions were identical to that of Kim et al (19), which adopted the emotional regulation task paradigm of Foti and Hajcak (17). Each trial was composed of a sequence of fixation on a gray cross on a black background (1000ms), an audio description of the upcoming picture (3~6000ms),

fixation (1000ms), passive viewing of a picture stimulus (3000ms) from the International Affective Picture System (IAPS), and the participants' rating for negative feelings from 1 (Not at all) to 4 (Extremely unpleasant) (time unlimited). (Figure 1). The next trial sequence began after participants' rating was made. The task consisted of 6 practice trials (2 negative condition and 4 neutral condition trials) and 2 blocks of 75 experimental trials (25 trials for each condition in an experimental block). Among total of 75 trials per block, 25 were neutral images and 50 were unpleasant images selected from the International Affective Picture System (IAPS) (17, 41). Neutral and unpleasant images were significantly differed on IAPS normative valence (mean ± standard deviation; 5.05 ± 1.21 for neutral images and 2.82 ± 1.64 for unpleasant images) and arousal ratings (2.91 ± 1.93 for neutral images and 5.71 ± 2.16 for unpleasant images) (17). The 25 neutral images were preceded by neutral audio description in the neutral condition. For example, the audio description of neutral image depicting men playing chess together (IAPS #2580) was "These men play chess three times a week". Of the 50 unpleasant images, 25 were preceded by an audio description that can neutralize the upcoming unpleasant stimulus to promote the use of cognitive reappraisal strategy for emotion regulation, which were cognitive reappraisal conditions. The other 25 were preceded by a negative audio description that explained negative aspects to make the participants attend to negative feelings, which were negative conditions. Each unpleasant image had 2 possible corresponding descriptions for cognitive reappraisal condition and negative condition. If a negative description was given in the first block, then a neutralizing description was provided with the same unpleasant image in the second block. For example, the audio description of unpleasant image showing a diver being attacked by shark (IAPS #1930) would be "This is a shark that attacked and killed a

diver" in negative condition and "This is the mechanical shark from the movie "Jaws"" in cognitive reappraisal condition. As opposed to usual emotion regulation studies in which participants had to self-generate their own reappraisal (42-44), a prior explanation was provided to minimize the inter- and intra-individual variability of the content of cognitive reappraisal which participants adopt as other emotion regulation studies (17, 18, 20). To measure the cognitive reappraisal ability, reappraisal success ratio was calculated. The reappraisal success ratio was calculated by subtracting the negative emotion rating score of negative condition from that of cognitive reappraisal condition, and then dividing it by negative emotion rating score of negative condition.

Image acquisition and data preprocessing

Functional MRI data were obtained on a 3T Trio MR scanner (Siemens Magnetom Trio, Erlangen, Germany) using a 12-channel head coil. The T1-weighted anatomical images were acquired using magnetization-prepared rapid gradient echo (echo time [TE]/repetition time [TR] = 1.89/1670 ms, field of view [FOV] = 250 mm, flip angle = 9°, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm3, 208 sagittal slices). We collected functional images using a gradient echoplanar imaging (EPI) pulse sequence (TE/TR = 30/3500 ms, FOV = 240 mm, flip angle = 90°, matrix = 128 × 128, voxel size = 1.9 × 1.9 × 3.5 mm3, 35 axial slices, 116 volumes). During resting-state image acquisition, participants were instructed to relax with eyes closed but to not fall asleep. To ensure that they had not fallen asleep, a questionnaire was completed after the scan. To reduce possible motion artifacts, head cushions were used, and the subjects were asked to move as little as possible during the acquisition.

Resting-state fMRI images were acquired for 6 minutes and 58 seconds. After image acquisition, all acquired images were visually inspected and confirmed by independent radiologists for any problems that could have occurred during image acquisition.

CONN toolbox v17f (www.nitrc.org/projects/conn), implemented in the Statistical Parametric Mapping software package, version 12 (SPM12; www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, UK) was utilized for preprocessing the images. For gradient field stabilization, the first four echo-planar image (EPI)s were removed. The remaining 112 contiguous EPI functional images were first processed by slice-timing correction and subsequently realigned to correct for head motions. Two subjects from the FEP group, three subjects from the CHR group, and two subject from the HC group were excluded for exceeding the head motion criteria, i.e., translation >2.0 mm and rotation >2.0°, in any direction. The images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) partitions and were spatially normalized to the Montreal Neurological Institute (MNI) standardized space. The functional images were resampled to a $2 \times 2 \times 2$ mm^3 voxel dimension and spatially smoothed using an 8-mm full-width half-maximum (FWHM) isotropic Gaussian kernel. We removed confounding variables including six head motion parameters (with their first-order derivatives) and nuisance signals from the white matter and cerebrospinal fluid. In addition, we conducted linear detrending and temporal bandpass filtering ($0.008 < f < 0.09$ Hz).

Functional connectivity analysis

We measured the functional connectivity patterns of the regional mean time series in the resting-state fMRI data using nine different seed regions-of-interest (ROI) related to cognitive reappraisal (23). The nine spherical ROIs reported in Buhle et al. were defined as the following: Two 5-mm radius spheres for right amygdala (30, -3, -15) and left amygdala (-18, -3, -15). Seven 8-mm radius sphere for right middle frontal gyrus (60, 24, 3), right inferior frontal gyrus (51, 15, 48), right medial frontal gyrus (9, 30, 39), left middle frontal gyrus (-33, 3, 54), right superior parietal lobule (63, -51, 39), left superior parietal lobule (-42, -66, 42), and left middle temporal gyrus (-51, -39, 3) (23).

For each participant, seed-based FC analysis was performed using Pearson's bivariate correlation between the time series of each ROI pair and those of the remaining entire brain voxels. We transformed the correlation coefficients to a normal distribution by Fisher's z transformation. Using a generalized linear model, one-way analysis of covariance (ANCOVA) with the baseline age and sex as a covariate was performed to reveal the group effect in regions related to cognitive reappraisal. Clusters with significant group differences were defined by a cluster-extent threshold of the corrected false discovery rate (FDR) of $p < 0.05$, in addition to an uncorrected voxel-level threshold of $p < 0.001$. The minimum cluster size to define the clusters at the corrected threshold was 40 voxels. Then, we applied the Bonferroni-corrected value of $p<0.005$ to address multiple comparison issues of the 9 seed regions.

Statistical analyses

The demographic and clinical characteristics of participants of 3 groups were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-square test or Fisher's exact test for categorical variables. Negative emotion rating scores was compared by using repeated measures ANCOVA with condition (negative, cognitive reappraisal, and neutral) as the within-subject factor and group (FEP, CHR, and HC) as the between-subject factor adjusting for age and sex as covariates. Reappraisal success ratio was compared among the groups using ANOVA. Post hoc Fisher's least significant difference analysis was performed to find specific negative emotion rating score across the groups and conditions. When a significant group-by-condition interaction was found, a paired samples *t*-test was used to reveal the specific negative emotion rating score across the conditions within each group. For the post-hoc tests and correlation analyses of functional connectivity among three groups, the Region of Interest Extraction Tool in the CONN toolbox was used to extract Fisher's Z transformed signal intensity values of the selected clusters. The post-hoc tests were performed using the Bonferroni correction. For the group in which the post-hoc analysis results showed significant group difference, Pearson's correlation analysis and partial correlation analyses were performed to measure the correlation between an individuals' connectivity intensities and clinical characteristics including reappraisal success ratio, negative emotion rating score on neutral stimulus, PANSS positive symptom, and global functioning scale: social and role (GFS: S and R) without and with adjusting for covariates. Covariates included age, sex, IQ, education and OZP equivalent dose. SPSS software version 23.0 (IBM Corp.) was used for the statistical analyses. Significant levels were set at $p < 0.05$.

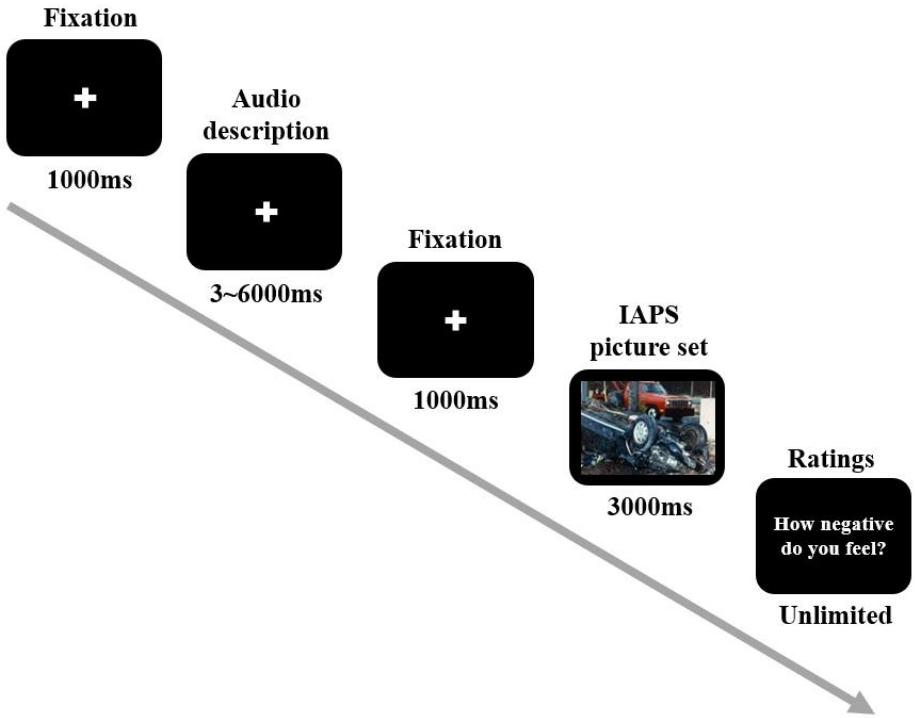


Figure 1. Sequence within a trial of the emotion regulation task. Each trial was composed of sequence of fixation with a cross on a black background (1000ms), an audio description of the upcoming picture (3~6000ms), fixation (1000ms), passive viewing of a picture stimulus (3000ms) from the International Affective Picture System (IAPS), and a participant rating of one's negative feeling scale from 1 to 4 (time unlimited).

Results

Characteristics of the participants (Table 1)

Demographic and clinical characteristics of the participants are summarized in Table 1. The mean age of FEP group (24.4 ± 4.57 years) was significantly higher than that of HC (22.0 ± 3.00 years), and the mean age of HC was higher than that of CHR group (19.8 ± 3.30 years). The percentage of women in FEP was significantly higher than that of CHR individuals and HC participants (p = 0.008). HC group showed higher IQ (111.9 ± 11.9) than other two groups (99.8 ± 13.6 for FEP, 100.3 ± 13.3 for CHR, F = 12.0, p < 0.001). CHR individuals had lesser years of education (12.5 ± 1.85) compared to FEP (14.1 ± 2.15) and HC groups (13.9 ± 1.60) (F = 6.83, p = 0.002). HC participants showed significantly higher GFS: S and R (8.77 ± 0.72 and 8.54 ± 0.74) than CHR (5.28 ± 1.22 and 5.58 ± 1.26) and FEP groups (5.31 ± 1.31 and 5.63 ± 1.26) (F = 147.2, p < 0.001 and F = 108.8, p < 0.001). The olanzapine equivalent dose of antipsychotics in FEP group was 16.0 ± 11.9 and that of CHR was 0.78 ± 2.2.

Negative emotion rating scores and reappraisal success ratio (Table 2, Figure 2)

The results of the negative emotion ratings scores and reappraisal success ratio are summarized in Table 2. Repeated measures ANCOVA with condition as the within-subject factor, group as the between-subjects factors, and age and sex as a covariate showed that there was a significant effect of group (F = 4.91, p=0.009) and condition

(F = 435.0, p < 0.001). A significant group-by-condition interaction was found (F = 3.64, p = 0.014). A post hoc Fisher's least significant difference analysis showed that the FEP patients and CHR individuals reported more negative feelings in the cognitive reappraisal (p = 0.003 and p = 0.019) and neutral conditions (p = 0.009 and p < 0.001) than the HC participants did. Reappraisal success ratio was significantly smaller in FEP patients (0.24 ± 0.15, p=0.048) and CHR individuals (0.20 ± 0.15, p=0.003) compared to HC group (0.30 ± 0.13) (Figure 2).

Table 1. Demographic and Clinical Characteristics of Patients with First-Episode Psychosis (FEP), individuals at Clinical High Risk (CHR) for Psychosis, and Healthy Controls (HC)

	FEP	CHR	HC	Statistical Analysis[a]		
	(N=36)	(N=32)	(N=48)	F or T of $\chi 2$	*P*	Post hoc Analysis
Age	24.4 ± 4.57	19.8 ± 3.30	22.0 ± 3.00	13.7	<0.001	FEP>HC>CHR
Sex (male/female)	14/24	25/7	31/17	15.2	<0.001	
Handedness (right/left)	35/1	31/1	41/7	5.01	0.070	
IQ	99.8 ± 13.6	100.3 ± 13.3	111.9 ± 11.9	12.0	<0.001	HC>CHR, HC>FEP
Education	14.1 ± 2.15	12.5 ± 1.85	13.9 ±1.60	6.83	0.002	HC>CHR, FEP>CHR
PANSS						
Positive symptoms	12.8 ± 4.58	-	-	-	-	
Negative symptoms	14.7 ± 5.43	-	-	-	-	
General symptoms	28.9 ± 8.07	-	-	-	-	
SOPS						
Positive symptoms	-	10.6 ± 3.07	-	-	-	
Negative symptoms	-	12.7 ± 6.74	-	-	-	
Disorganization	-	4.53 ± 3.24	-	-	-	
General symptoms	-	8.16 ± 4.18	-	-	-	

GFS:S	5.31 ± 1.31	5.28 ± 1.22	8.77 ± 0.72	147.2	<0.001	HC>CHR, HC>FEP
GFS:R	5.63 ± 1.26	5.58 ± 1.20	8.54 ± 0.74	108.8	<0.001	HC>CHR, HC>FEP
Antipsychotic dose[b]	16.0 ± 11.9	0.78 ± 2.2	0	67.5	<0.001	HC<FEP, CHR<FEP

IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale; SOPS, Scale of Prodromal Symptoms; GFS:S, Global Functioning Scale: Social; GFS:R, Global Functioning Scale: Role. Data are given as the mean ± standard deviation.

[a]Analysis of variance, independent t-test, or Welch's t-test if the variances were not equal; $\chi 2$ analysis or Fisher's exact test for categorical data.

[b]Olanzapine equivalent dose of antipsychotics prescribed at the time of magnetic resonance imaging.

Table 2. Negative Emotion Ratings in the 3 Conditions and Reappraisal Success Ratio

	FEP	CHR	HC	Statistical Analysis[a]					
	(N=36)	(N=32)	(N=48)		F	P	Post hoc Analysis[b]		
Negative emotion rating score							FEP vs CHR	FEP vs HC	CHR vs HC
NEG condition	3.08 ± 0.73	2.81 ± 0.58	2.82 ± 0.64	Group	4.91	0.009*	0.089	0.076	0.926
CR condition	2.31 ± 0.62	2.24 ± 0.61	1.94 ± 0.46	Condition	435.0	<0.001**	0.584	0.003**	0.019*
NEU condition	1.42 ± 0.44	1.56 ± 0.55	1.17 ± 0.34	Group x Condition	3.64	0.014	0.199	0.009*	<0.001**
Reappraisal Success Ratio	0.24 ± 0.15	0.20 ± 0.15	0.30 ± 0.13		4.94	0.009*	0.304	0.048*	0.003**

[a]Repeated measures of analysis of covariance with age and sex as covariates

[b]Post hoc Fisher's least significant difference analysis

*The mean difference is significant at the 0.05 level

**The mean difference is significant at the 0.005 level

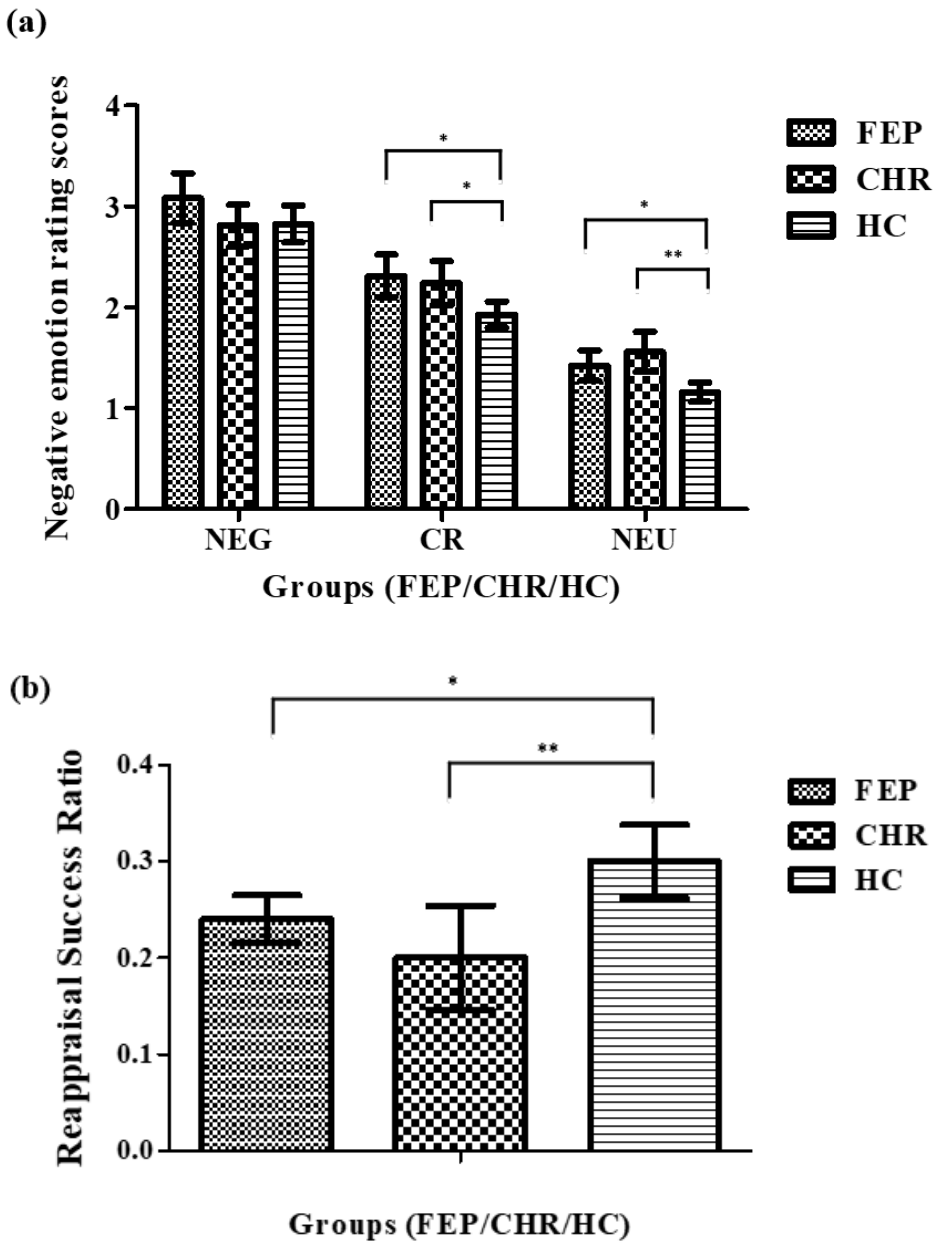


Figure 2. Comparison of negative emotion rating scores and reappraisal success ratio among first-episode psychosis (FEP), clinical high risk (CHR) for psychosis, and healthy control (HC) groups. (a) Comparison of negative emotion rating scores among 3 groups across the negative (NEG), cognitive reappraisal (CR), and neutral (NEU) conditions. (b) Comparison of reappraisal success ratio across 3 groups. Reappraisal success ratio was calculated by subtracting the negative emotion

rating score of negative condition from that of cognitive reappraisal condition, and then dividing it by negative emotion rating score of negative condition. The bars indicate the means for each condition and group, and the vertical lines indicate the standard errors. * indicates that the mean difference is significant at the 0.05 level; ** indicates that the mean difference is significant at the 0.005 level.

Functional connectivity analysis (Table 3, Figure 3)

Information regarding the clusters demonstrating the significant differences and the post-hoc analysis results is summarized in Table 3 and Figure 3. One-way ANCOVA model was used to reveal the significant spatial group differences of the three groups. Significant group differences were observed in the left superior parietal lobe (SPL) seed-to-brain networks. The FEP group exhibited greater FC between the left SPL and left inferior frontal gyrus (IFG) than CHR and HC group. The CHR group demonstrated an intermediate strength between the FEP and HC group in the left SPL functional connectivity although CHR and HC group did not show statistically significant difference. There was a trend level of group effect of left amygdala and right superior parietal lobule functional connectivity among 3 groups.

Table 3. Between Group Differences in Functional Connectivity of left and right superior parietal lobe, and left amygdala.

Seed Region	Brain Region	MNI Coordinate	Size of Clusters	Cluster *p* value	Group	Functional Connectivity		FEP-HC	CHR-HC	FEP-CHR
		(x, y, z)	(# of Voxels)	(FDR corrected)		Mean	SD			
Left SPL	Left inferior frontal gyrus	56 +28 +08	157	0.0022	FEP	0.189	0.16	<0.001	0.745	0.038
					CHR	0.141	0.18			
					HC	0.042	0.17			
Left amygdala	Right precentral gyrus	+30 -24 +62	108	0.0185	FEP	0.063	0.10	0.455	0.004	<0.001
					CHR	-0.067	0.14			
					HC	0.036	0.15			
Right SPL	Right superior frontal gyrus	+22 +06 +46	119	0.0163	FEP	0.087	0.16	0.668	0.015	0.001
					CHR	-0.061	0.15			
					HC	0.044	0.17			

MNI: Montreal Neurological Institute; FDR: false discovery rate; SD: standard deviation; FEP: first-episode psychosis; CHR: clinical high risk for psychosis; HC: healthy control; SPL: superior parietal lobe.

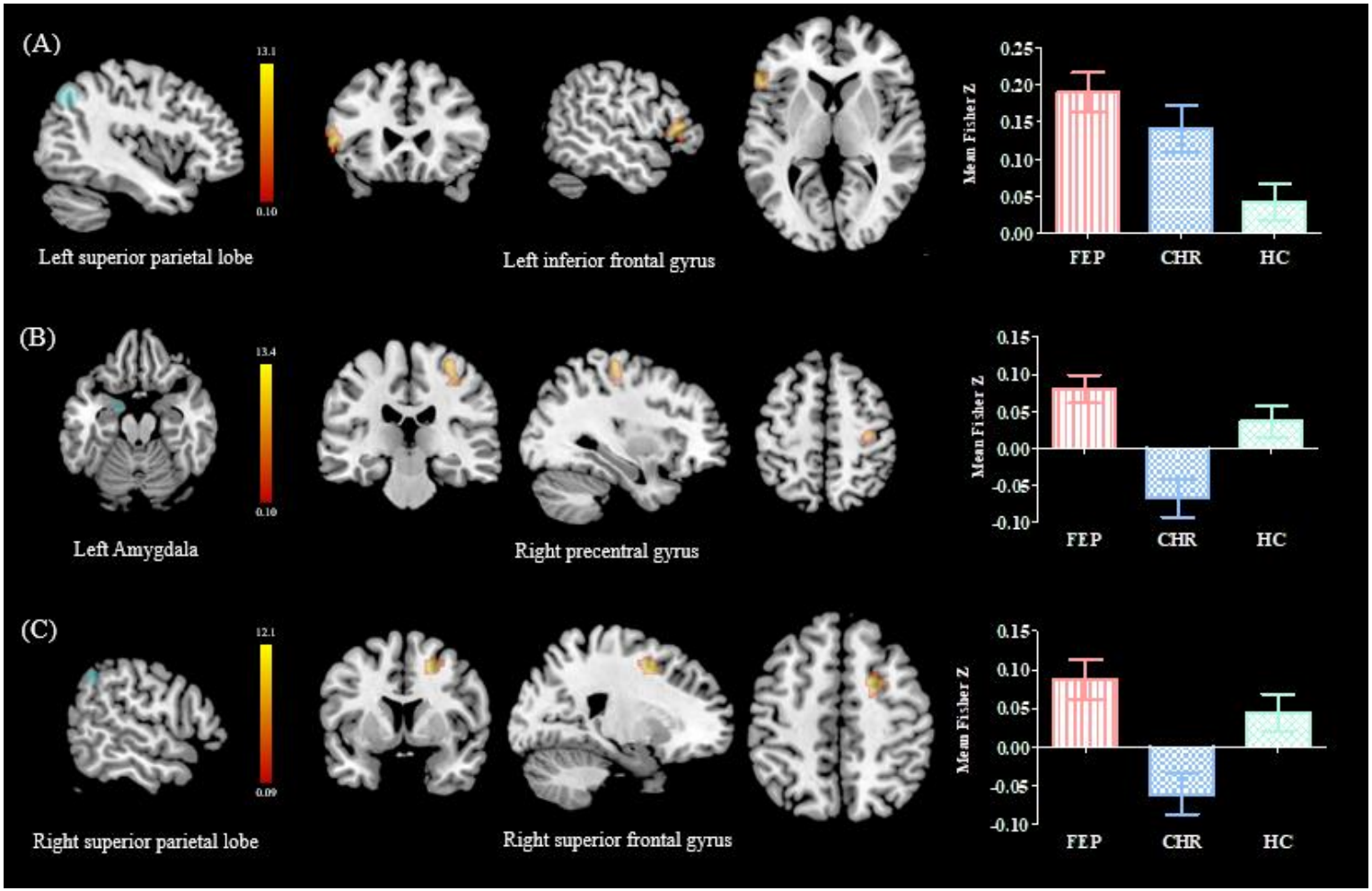

(A)
13.1
0.10
Left superior parietal lobe
Left inferior frontal gyrus
Mean Fisher Z
0.25
0.20
0.15
0.10
0.05
0.00
FEP
CHR
HC
(B)
13.4
0.10
Left Amygdala
Right precentral gyrus
Mean Fisher Z
0.15
0.10
0.05
0.00
-0.05
-0.10
FEP
CHR
HC
(C)
12.1
0.09
Right superior parietal lobe
Right superior frontal gyrus
Mean Fisher Z
0.15
0.10
0.05
0.00
-0.05
-0.10
FEP
CHR
HC

Figure 3. Significant difference in functional connectivity among groups. The differences among first-episode psychosis (FEP) patients, clinical-high risk for psychosis (CHR) individuals, and the healthy controls (HC) were revealed by one-way analysis of covariance (ANCOVA) ($p < 0.05$, false discovery rate corrected). Significant differences were revealed between the (A) left superior parietal lobe (SPL) and left inferior frontal gyrus (IFG). Trend level of group effect was shown between the (B) left amygdala and right precentral gyrus, and (C) right superior parietal lobe and right superior frontal gyrus.

Association of the functional connectivities and reappraisal success ratio/negative emotion rating score (Figure 4, 5)

In FEP patients, the level of increased connection strength between the left SPL seed and left IFG was negatively correlated with reappraisal success ratio with (r = -0.369, p = 0.041) or without (r = -0.362, p = 0.030) adjusting for covariates including age, sex, IQ, education and OZP equivalent dose (Figure 4). The connectivity between left SPL seed and left IFG was positively correlated with negative emotion rating score on neutral stimulus (r = 0.362, p = 0.042) adjusting for covariates (Figure 5). We performed an exploratory correlation analysis in CHR individuals, which showed no significant association between left SPL-left IFG connectivity and reappraisal success ratio with (r = -0.122, p = 0.538) or without (r = -0.260, p = 0.151) adjusting for covariates. Also, in CHR group, there was no association between left SPL-left IFG connectivity and negative emotion rating score on neutral stimulus with (r = -0.013, p = 0.949) or without (r = -0.111, p = 0.544) adjusting for covariates.

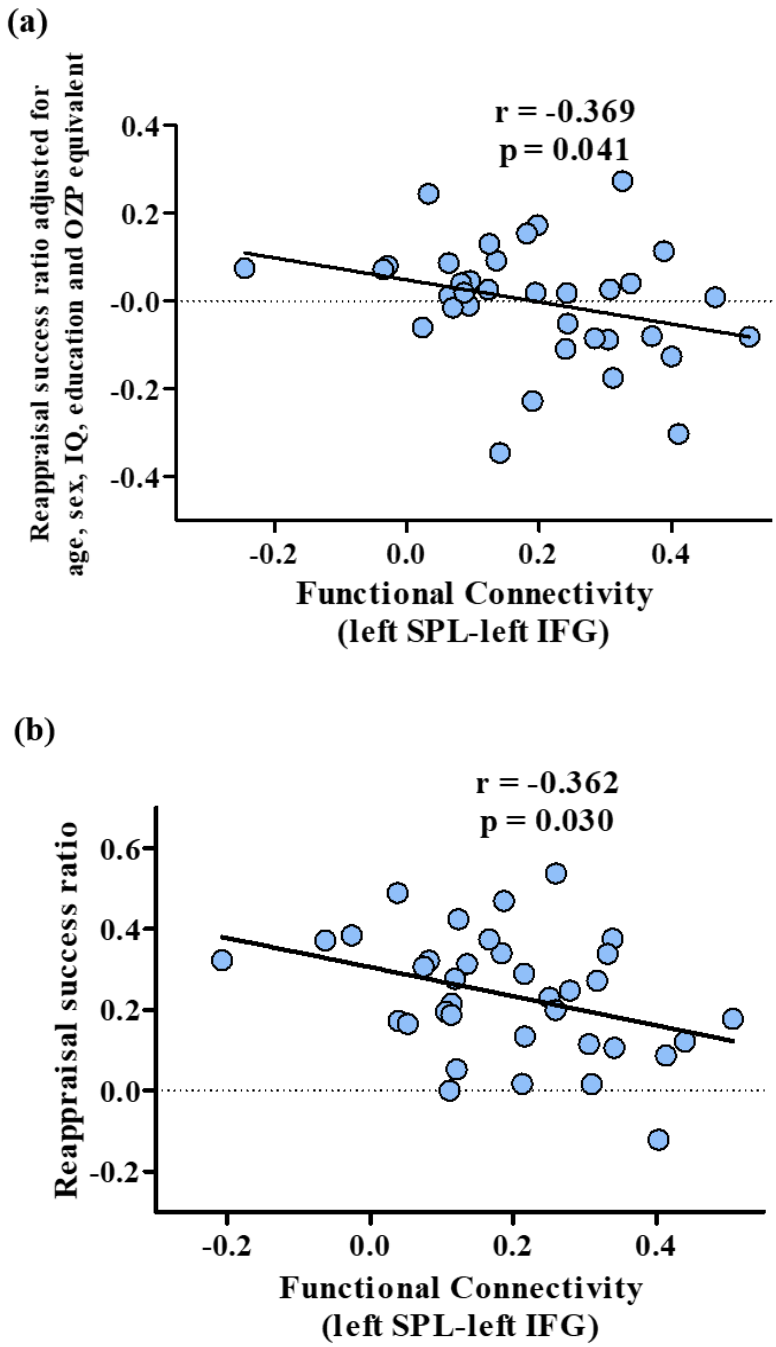


Figure 4. The correlation between left superior parietal lobe-left inferior frontal gyrus functional connectivity and reappraisal success ratio (a) with or (b) without adjusting for covariate including age, sex, intelligence quotient (IQ), education and olanzapine equivalent dose.

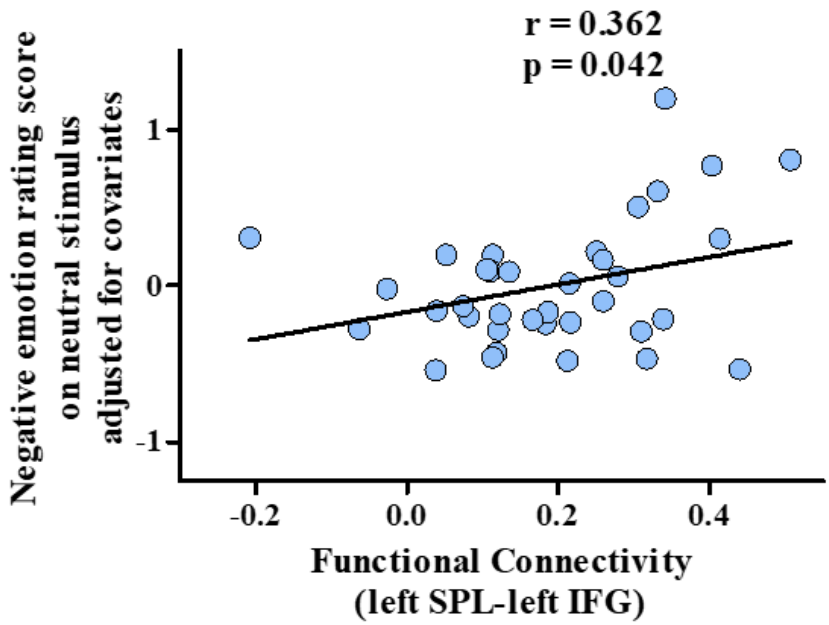


Figure 5. The correlation between left superior parietal lobe-left inferior frontal gyrus functional connectivity and negative emotion rating score on neutral stimulus adjusting for covariates including age, sex, intelligence quotient (IQ), education and olanzapine equivalent dose.

Association of the functional connectivities and psychotic symptom severity/global functioning scale (Figure 6, 7)

In FEP group, the left SPL and left IFG connectivity showed positive correlation with PANSS positive score with (r = 0.370, p = 0.031) or without (r = 0.394, p = 0.017) adjusting for the covariates (Figure 6). Also, left SPL-left IFG connectivity was negatively correlated with GFS: R with (r = -0.431, p = 0.014) or without (r = -0.401, p = 0.015) adjusting for the covariates. Global functioning scale: social showed trend level of association with (r = -0.343, p = 0.059) adjusting for covariates and significant level of association not adjusting for covariates (r = -0.332, p = 0.048) (Figure 7). We additionally performed exploratory analyses in CHR individuals, which showed no association between the fronto-parietal connectivity and SOPS positive (r = -0.141, p = 0.475) after controlling for covariates. In CHR group, GFS: S (r = -0.330, p = 0.066) showed trend level of association with the fronto-parietal connectivity although GFS:R (r = -0.190, p = 0.298) did not.

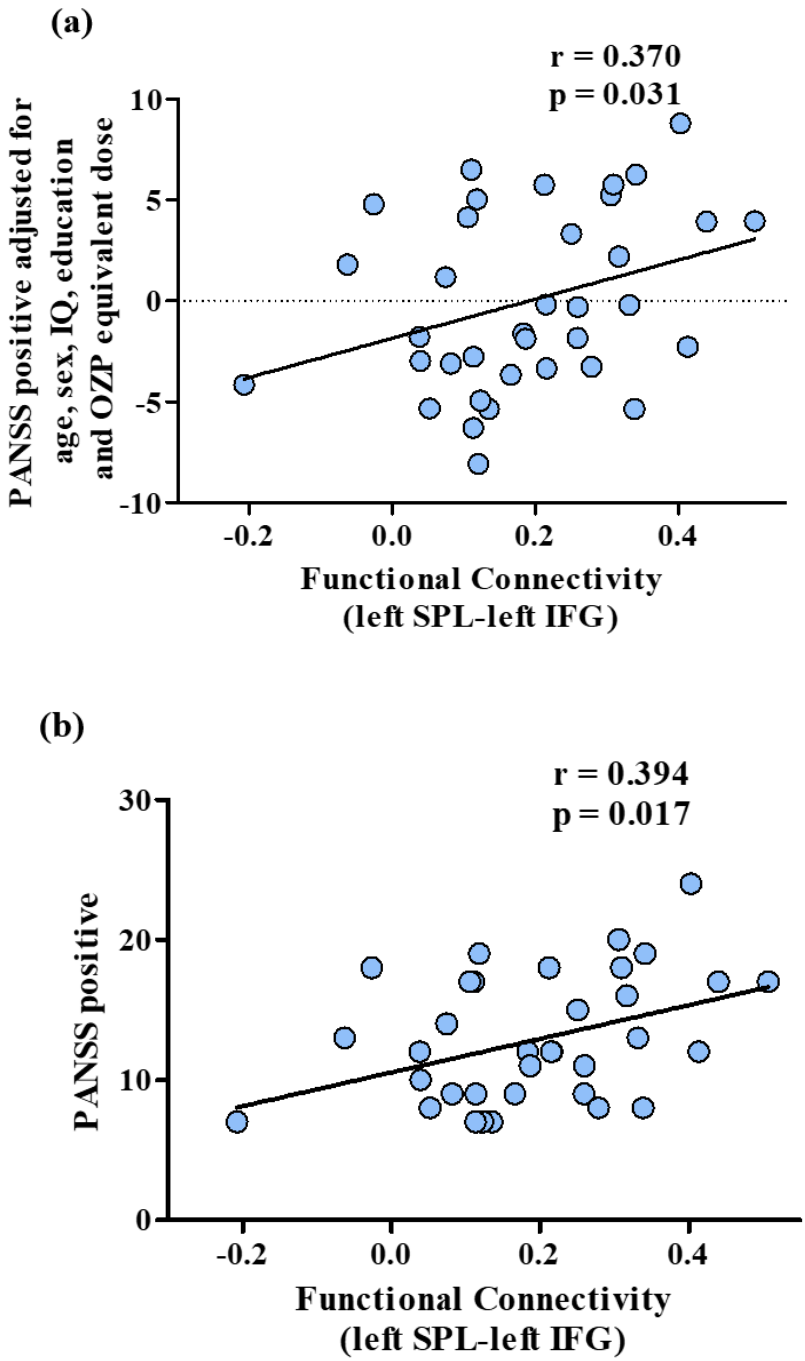
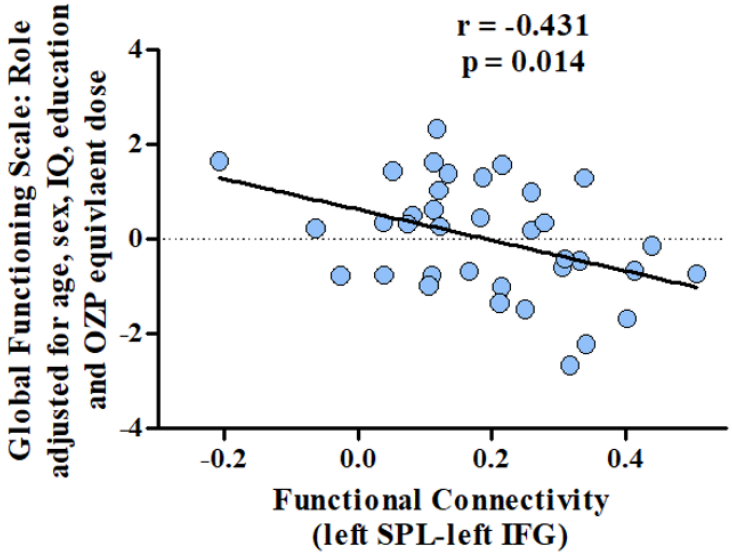
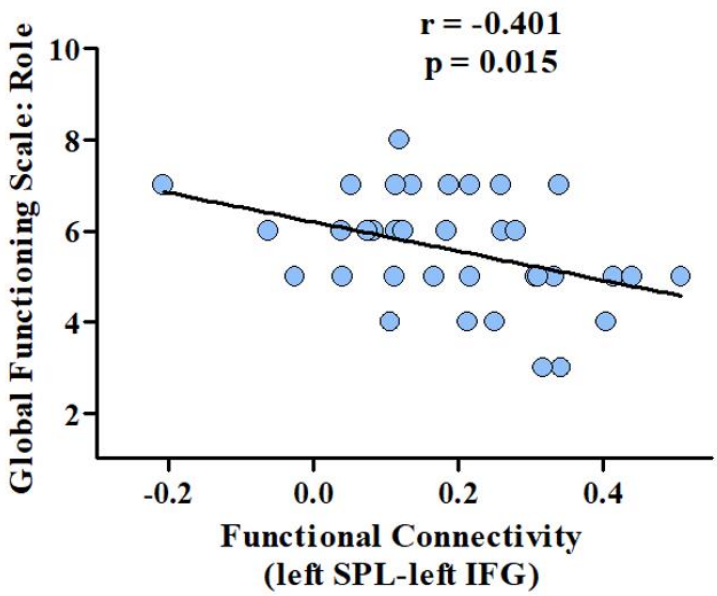


Figure 6. The correlation between left superior parietal lobe-left inferior frontal gyrus functional connectivity and positive and negative syndrome scale (PANSS) positive (a) with or (b) without adjusting for covariate including age, sex, intelligence quotient (IQ), education and olanzapine (OZP) equivalent dose.

(a)


r = -0.431
p = 0.014
Global Functioning Scale: Role adjusted for age, sex, IQ, education and OZP equivlaent dose
4
2
0
-2
-4
-0.2
0.0
0.2
0.4
Functional Connectivity (left SPL-left IFG)

(b)


r = -0.401
p = 0.015
Global Functioning Scale: Role
10
8
6
4
2
-0.2
0.0
0.2
0.4
Functional Connectivity (left SPL-left IFG)

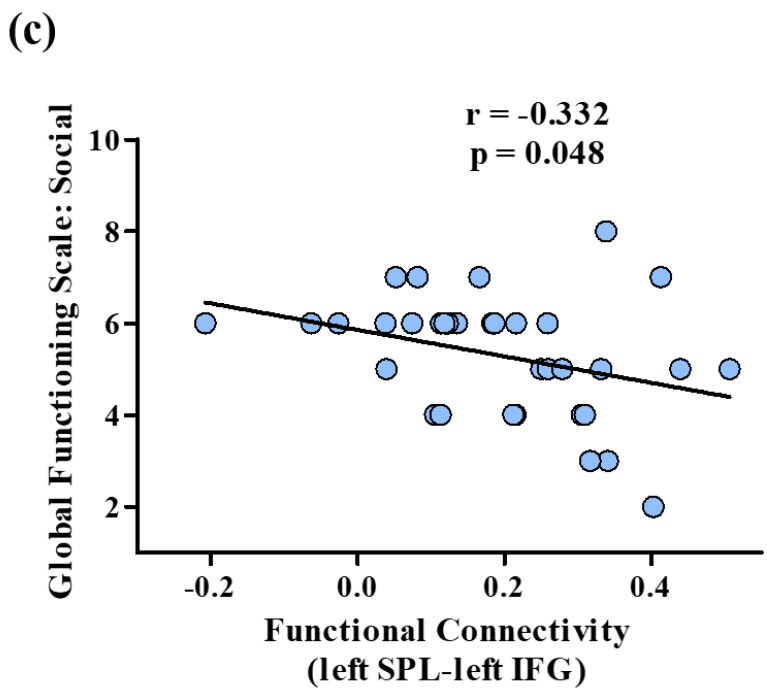


Figure 7. The correlation of left superior parietal lobe-left inferior frontal gyrus functional connectivity (FC) and global functioning scale. The FC correlation with (a) global functioning scale: role with adjusting for covariates including age, sex, intelligence quotient (IQ), education and olanzapine (OZP) equivalent dose, (b) global functioning scale: role without adjusting for covariates, and (c) global functioning scale: social without adjusting for covariates.

Discussion

This study investigated the resting-state FC of the regions related to cognitive reappraisal in FEP patients and CHR individuals. Group effect of resting state FC between left SPL and left IFG was observed in FEP, CHR, and HC group. Especially, FEP patients showed greater FC between left SPL and left IFG compared to CHR and HC. Notably, the strength of altered network between the left SPL and left IFG was negatively correlated with reappraisal success ratio and global functioning scale: role, and positively correlated with positive psychotic symptoms severity. In addition, group effect of resting state FC of left amygdala and right precentral gyrus and right superior parietal lobe and right superior frontal gyrus showed trend level. To our knowledge, this is the first study to examine the resting-state functional connectivity related to cognitive reappraisal in the early phases of psychosis including FEP and CHR. Taken together, our results suggest that the alteration in the resting-state FC network regions related to cognitive reappraisal is evident at the earliest stages of psychosis.

Altered left fronto-parietal connectivity is related to impaired cognitive reappraisal and negative emotionality

Among the cognitive control regions including dorsomedial, dorsolateral, ventrolateral prefrontal cortex, and posterior parietal lobe (23), altered patterns of functional connectivity between left SPL and left IFG in FEP group was reported. Also, this connectivity was negatively correlated with reappraisal success ratio. These results imply that the more increased left fronto-parietal connectivity, the more

compromised cognitive reappraisal ability in FEP patients. Specifically, left SPL connectivity was significantly altered. SPL region, which is one of the region included in dorsal fronto-parietal attention system, is considered to assist cognitive reappraisal by holding the reappraisal in mind through modulating selective attentional process and working memory (21, 23). IFG, which showed connectivity with SPL in this study, is suggested to mediate the interaction between the dorsal and ventral attention system (45, 46). Dorsal attention system is a top-down control system, which involves intraparietal sulcus/superior parietal lobe and frontal eye field, regulating attention voluntarily while ventral attention system responds to unexpected stimuli from the bottom-up process (30, 47, 48). Specific attentional process is promoted by successful interplay between these dorsal and ventral attentional systems (48). Considering altered left SPL-left IFG connectivity was correlated with impaired cognitive reappraisal ability in FEP, it could be inferred that the decreased cognitive reappraisal ability might be due to altered intrinsic network related to selective attentional process. There would be two possibilities explaining this result. One would be selective attentional process related to cognitive reappraisal is compromised in FEP patients, making them hard to adopt cognitive reappraisal as emotion regulation strategy. Another possible explanation is that there could be a tendency to use other emotion regulation strategies such as distraction rather than cognitive reappraisal (49), leading to reappraisal success ratio to exhibit inverse relation to left SPL-left IFG connectivity. In either case, this result reflects the intrinsic network associated with selective attention contributing to cognitive reappraisal is altered in FEP. As the intrinsic network involved in dorsal and ventral attention system is altered, it is possible that selective attention ability to hold certain cognitive reappraisal strategy is disrupted and the ability to control arousal induced

by unexpected unpleasant stimuli is impaired leading to insufficient cognitive control of prefrontal cortex over amygdala and insular regions causing inadequate cognitive reappraisal. This finding is in line with previous studies reporting frontoparietal network activated during task using attention was altered in schizophrenia, which caused cognitive impairment (50, 51). However, the seeds in other prefrontal cortex did not show any significant in the resting state. Future task fMRI studies are needed to examine which regions are actively involved when performing cognitive reappraisal task.

Also, it was demonstrated that negative emotions are more prominent in FEP and CHR groups in the neural condition. Especially, in FEP, the negative emotionality in neutral condition was associated with altered fronto-parietal connectivity. This result implies that FEP patient and CHR individuals tend to perceive more negatively even in the neutral condition compared to HC.

Altered left fronto-parietal connectivity is related to more severe positive symptoms

Along with our initial hypothesis, altered fronto-parietal FC in patients with FEP showed positive correlation with PANSS positive symptoms. This finding suggests that left SPL and left IFG connectivity, which reflects impaired cognitive reappraisal, is associated with positive psychotic symptoms. Insufficient cognitive reappraisal may lead to inability to handle negative emotion efficiently, which would increase negative emotionality (18, 19, 52), contributing to formation of positive symptoms in the early stages of psychosis. Additionally, we performed an exploratory analysis in CHR individuals, which showed no correlation between Left SPL-left IFG

connectivity and SOPS positive score. This might be because effect size contributed by cognitive reappraisal was not large enough since the symptom formation was influenced by other heterogenous factors in CHR individuals who were in the very early stages of disorder.

Altered left fronto-parietal connectivity is related to lower general functioning

In FEP group, Left SPL-Left IFG connectivity showed significant and trend level of negative correlation with role functioning and social functioning, respectively. These findings imply that fronto-parietal connectivity might be differentially associated with global functioning in FEP patients and controls. Insufficient usage of cognitive reappraisal may lead to incapability of implementing social behavior, causing decreased social and role functioning (10). In addition, in CHR individuals, the fronto-parietal connectivity showed trend level of association with social functioning. These results suggest that fronto-parietal connectivity might be utilized as a neuroimaging biomarker as a potential target for intervention aimed at enhancing cognitive reappraisal leading to social and role functioning.

Trend level of group effect of amygdala-precentral gyrus and right fronto-parietal functional connectivity

Amygdala based FC showed trend level of group effect. In the exploratory post-hoc analysis, hypoconnectivity between left amygdala and right precentral gyrus in CHR individuals compared to FEP and HC groups was observed. Previously, presence of distinct amygdala-somatosensory/premotor cortex neural network was reported in

healthy individuals (53). In the study, Toschi et al. suggested that movement control and action planning could be compromised by emotional disturbance (53). CHR group showed hypoconnectivity while FEP group showed relative hyperconnectivity, which might suggest that functional compensation occurred as to offset the impaired emotional disturbance during the prodromal stage of schizophrenia. Also, the pattern of hypoconnectivity in CHR group and relative hyperconnectivity in FEP group was observed in the right superior parietal lobe and right superior frontal gyrus functional connectivity. This alteration might reflect another part of altered fronto-parietal connectivity, although a previous study reported intrinsic left fronto-parietal network connectivity and its laterality might be a candidate for underlying neural substrate of schizophrenia (54). However, since these results were only in the trend level and did not show any correlation with behavioral data, the clinical significance of the findings should be further evaluated by future studies.

Limitation

There are several limitations of the study. First, since this study is based on resting state fMRI data, it does not reflect the activity of the brain region when cognitive reappraisal occurs. However, considering resting-state functional connectivity give substantial information regarding intrinsic brain network organization (55), which may shape task-based neural activity (26, 28, 29, 31), we could be enlightened enough to be able to understand the disturbed functional network involved in impaired cognitive reappraisal in early psychosis stage. Also, since previous reports showed resting state fMRI data correlated with task fMRI data in healthy subjects and schizophrenia patients (26, 28, 29, 56), it might be able to gain insights regarding the task related functional connectivity based on altered resting state functional connectivity associated with impaired cognitive reappraisal in our study although it is yet to be determined in future studies. Second, because only cognitive reappraisal was measured among several emotion regulation strategies (57, 58), it would be difficult to ascertain which emotion regulation strategies are utilized more in FEP and CHR group compared to HC group. In the future studies, it is necessary to include various emotion regulation strategies to reveal how the dispositional usage of the strategies in FEP and CHR is reflected in the functional connectivity. Third, all FEP patients were taking antipsychotic medications, which might have influenced the results of the resting state functional connectivity although one study has reported that resting-state functional connectivity was not affected by antipsychotics in schizophrenia patients (59). Since only FEP patients took antipsychotics except 2 CHR individuals, the results could be distorted if antipsychotics usage was adjusted. Thus, we did not adjust antipsychotics dosage when comparing resting state

connectivity. Among FEP patients, the left SPL-left IFG connectivity did not show any correlation with olanzapine equivalent dosage (r = -0.082, p = 0.633). However, this result merit caution in the interpretation of the results. Lastly, it is hard to differentiate whether the current result is the consequence of damage or compensation in the neural network. It would be useful to clarify whether the aberrant functional connectivity related to disturbed emotion regulation progresses through a longitudinal study including more participants from the early stages of psychosis.

Implication

To our knowledge, this is the first to study cognitive reappraisal in both FEP patients and CHR individuals by seed-based resting-state functional connectivity. This study showed that aberrant fronto-parietal connectivity would be one of the neurobiological bases for impaired emotional regulation in psychosis. These results suggest that fronto-parietal connectivity might be utilized as a biomarker as a potential target for therapeutic intervention. Based on this study, it is possible to create an intervention model by focusing on implementing impaired emotion regulation ability on symptom formation during the early phases of psychosis. The intervention should include cognitive-behavioral therapeutic approach that can enhance emotion regulation ability including cognitive reappraisal strategy. Through this, it would be possible to ameliorate the newly formed psychotic symptoms in CHR individuals and FEP patients.

Conclusion

The study suggested that the aberrant intrinsic fronto-parietal connectivity reflecting impaired emotion regulation, especially cognitive reappraisal, was correlated with newly formed psychotic symptom in the early stages of psychosis. Since correlation analysis was performed in the study, we cannot delineate whether the altered fronto-parietal connectivity caused the impaired cognitive reappraisal. However, from a clinical perspective, the aberrant fronto-parietal connectivity might be used as a potential indicator of impaired emotion regulation, necessitating enhancement of cognitive reappraisal ability by cognitive rehabilitation and emotional training in a subset of individuals of schizophrenia. Through this, it might be possible to reduce the severity of positive symptoms in the early stages of the disorder.

Potential Conflicts of Interest

Nothing to report.

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초 록

배경 및 목적: 정신증의 초기단계에서 인지적 재평가와 같은 감정 조절 능력의 손상이 잘 알려져 있었음에도 그 생물학적 기반을 밝히는 연구는 부족하다. 이 연구에서는 휴지기 기능적 뇌영상 연구를 통해 인지적 재평가와 관련된 뇌신경학적 기반을 규명하고자 한다.

방법: 본 연구는 36명의 초발 정신증, 32명의 임상적 고위험군, 48명의 건강한 대조군의 휴지기 기능적 뇌영상을 기반으로 한다. 초발 정신증 및 임상적 고위험군의 감정 조절 능력, 특히 인지적 재해석 연관 뇌영역을 시드로 사용하여 전뇌 기능 연결성 분석을 진행하였고, 이 연결성이 인지적 재해석 성공률 비율, 양성 증상 중등도 및 사회적 기능과 상관관계가 있는지 분석하였다.

결과: 초발 정신증 환자는 건강한 대조군에 비해서 왼쪽 위마루소엽과 아래전두이랑 사이의 휴지기 기능성 연결성이 증가한 것으로 나타났다. 또한 초발 정신증 환자군에서 변인을 통제한 이후에도 위마루소엽-아래전두이랑 사이의 기능적 연결성이 높을수록 인지적 재해석 성공률 비율이 낮아지고, 더 많은 양성 정신병적 증상을 경험하며, 사회적 기능이 떨어지는 것을 확인했다.

결론: 본 연구의 결과는 정신증의 발현 초기단계에서부터 감정 조절 장애를 반영하는 전두엽-두정엽 연결성의 내인적 손상이 있음을 시사한다. 손상된 감정 조절 능력은 양성 증상의 증가와 전반적 기능의 감소와 관련이 있었다. 이 연구는 감정 조절 능력 손상의 생물학적

표지자를 발굴하여, 이를 초발 정신증과 임상적 고위험군과 같은 초기 정신증 대상자에서 새롭게 형성되는 정신병 증상을 개선하기 위한 객관적인 지표로 활용할 수 있음을 제시했다.

주요어: 휴지기 기능적 연결성, 인지적 재해석, 감정 조절 능력, 초발 정신증, 임상적 고위험군, 조현병

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Association of resting-state functional connectivity with cognitive reappraisal, positive symptom, and general functioning in first-episode psychosis

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