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Original Article

Frontal pole–precuneus connectivity is associated with a discrepancy between self-rated and observer-rated depression severity in mood disorders: a resting-state functional magnetic resonance imaging study

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Discrepancies in self-rated and observer-rated depression severity may underlie the basis for biological heterogeneity in depressive disorders and be an important predictor of outcomes and indicators to optimize intervention strategies. However, the neural mechanisms underlying this discrepancy have been understudied. This study aimed to examine the brain networks that represent the neural basis of the discrepancy between self-rated and observer-rated depression severity using resting-state functional MRI. To examine the discrepancy between self-rated and observer-rated depression severity, self- and observer-ratings discrepancy (SOD) was defined, and the higher and lower SOD groups were selected from depressed patients as participants showing extreme deviation. Resting-state functional MRI analysis was performed to examine regions with significant differences in functional connectivity in the two groups. The results showed that, in the higher SOD group compared to the lower SOD group, there was increased functional connectivity between the frontal pole and precuneus, both of which are subregions of the default mode network that have been reported to be associated with ruminative and self-referential thinking. These results provide insight into the association of brain circuitry with discrepancies between self- and observer-rated depression severity and may lead to more treatment-oriented diagnostic reclassification in the future.

Key words: self-rated depression; observer-rated depression; discrepancy; frontal pole; precuneus.

Introduction

Depression is the leading cause of mental health–related disease, affecting an estimated 300 million people worldwide (Patel et al. 2016), with a 12-mo prevalence rate generally ~6% (Kessler and Bromet 2013), and the lifetime risk is three times higher (15% to 18%) (Bromet et al. 2011). Depression is a chronic disease, with half of the patients experience relapsing (World Health Organization 2001), and the frequency and severity of episodes tends to increase over time. It leads to a reduced quality of life (Üstün et al. 2004) and a significant burden of disease in terms of personal and economic losses (Vos et al. 2013). Depression is the third leading cause of the global burden of disease as assessed by disability-adjusted life-years, the leading cause in middle- and high-income countries, and is projected to rise to the second leading cause of the global burden of disease by 2030 (World Health Organization 2008).

There is often a discrepancy between the subjective symptoms of depression and symptoms perceived by the evaluating psychiatrist (Möller and von Zerssen 1995; Richter et al. 1998; Bagby et al. 2004). Subjective symptoms should not be disregarded as being nonobjective, as they can have a significant impact on a patient's quality of life and are an important factor of functional and personal recovery (Demyttenaere et al. 2015; Richardson and Barkham 2020). Several demographic and personality factors have been identified as explaining the discrepancy between self-rated and observer-rated depression severity. Patients whose self-rated depressive symptoms are disproportionately severe compared with their observer-rated depression severity have been found to have higher scores for phobic anxiety (Corruble et al. 1999), characteristics of non-endogenous or neurotic depression (Rush et al. 1987; Domken et al. 1994), higher neuroticism (Enns et al. 2000; Duberstein and Heisel, 2007),

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lower extraversion (Enns et al. 2000), lower agreement (Corruble et al. 1999; Enns et al. 2000), lower self-esteem (Domken et al. 1994), and comorbid borderline personality disorder (Stanley and Wilson 2004). Such patients exhibit symptoms for prolonged periods, take longer to recover from depression (Rane et al. 2010; Dunlop et al. 2011), and are associated with increased risk of committing suicide (Tsujii et al. 2014). These epidemiological findings suggest that some biological heterogeneity may underlie the variation in the discrepancy between subjective and objective symptoms among patients with mood disorders. Therefore, elucidating the neural basis of the subjective–objective discrepancy is an important research topic to better understand and to develop interventions tailored for individual patients with mood disorders.

Various assessment scales have been used to quantify self-rated and observer-rated depression severity. The Beck Depression Inventory (BDI) (Beck et al. 1996), a self-rated depression severity score, and the Hamilton Depression Rating Scale (HAMD) (Hamilton 1960), an observer-rated scale, are among the most used ones to assess depression severity. Although both measures have shown to have sufficient reliability and validity (Rush 2007), the correlation between them varies widely from study to study, with Pearson's coefficients ranging from 0.20 to 0.89 (Möller and von Zerssen 1995; Richter et al. 1998; Bagby et al. 2004). The variability in correlation coefficient may be due to the fact that they assess different components of depression, with the BDI focusing on depressive cognition (Uher et al. 2008), while the HAMD putting more stress on somatic symptoms, such as sleep and eating disturbance. Since depression is a generic label for patients with highly heterogeneous pathogenetic background, the concordance and discrepancy between self-rated and observer-rated depression severity could be useful as an indicator for subtyping depression.

However, few studies have directly investigated the neural underpinnings that lead to the discrepancy between self-rated and observer-rated depression severities. The only neuroimaging study to date on the discrepancy between self-rated and observer-rated depression severity is the near-infrared spectroscopy (NIRS) study, which reported that the task-related elevation of oxygenated hemoglobin concentration in the frontal pole (FP) and dorsolateral prefrontal cortex was higher among patients who reported disproportionately severe self-rated depression symptoms compared with those without such discrepancy (Akashi et al. 2015). Because Brodmann Area 10 (BA10), which almost overlaps FP, has been reported to be involved in self-referential processing and ruminative thinking, as well as in pondering one's distant future (Okuda et al. 2003; D'Argembeau et al. 2008), this finding suggests subjective–objective discrepancy in depressive symptoms are partially caused by increased self-referential processing and ruminative thinking. NIRS can only record blood oxygenation changes on the cortical surface of the brain, making it difficult to investigate the function of deeper brain regions. To the best of our knowledge, no studies have been conducted on the neural basis of the discrepancy between self-rated and observer-rated depression severity using functional magnetic resonance imaging (MRI) (fMRI), which can detect the neural activity throughout the brain with higher spatial resolution.

The orbitofrontal cortex (OFC) is also a region that has been reported to be associated with ruminative thinking (Jacob et al. 2020), self-referential thinking (Wang et al. 2023), and negative affect (Tozzi et al. 2021a). However, it is so far unclear whether the OFC is related to discrepancy between self-rated and observer-rated severity of depressive disorder.

In addition, the default mode network (DMN) comprises a set of brain regions whose activity increase at rest and exhibit synchronous resting-state neural oscillation (Shulman et al. 1997; Raichle et al. 2001; Fox et al. 2005). The DMN is involved in the regulation of attention and cognition (Pearson et al. 2011; Leech and Sharp 2014). The DMN has been reported to be activated in depressed patients (Sheline et al. 2010; Veer et al. 2010). The DMN is related to an integration of the self-referential processes (Hamilton et al. 2015), and increasing levels of DMN dominance are associated with higher levels of maladaptive, depressive rumination in major depressive disorder (Hamilton et al. 2011). The medial frontal cortex (MedFC) is a hub of the DMN, and its temporal dynamics reliably predict rumination scores (Gao et al. 2023). This symptomatology is predominant among a subtype of depression whose cognitive symptoms are more severe than somatic symptoms. However, the association between the function of DMN and the discrepancy between self-rated and observer-rated depression severity remains unclear.

In this context, we hypothesized that the FP, OFC, and DMN, especially the MedFC, are associated with the subjective–objective discrepancy in depressive subjects. Specifically, given that the positive association between functional connectivity (FC) in these regions and rumination (Chou et al. 2023) and activated DMN in rumination (Zhou et al. 2020) were reported, we hypothesized a possibility that the group with higher subjective–objective discrepancy may have elevated FC in these brain areas. This study aimed to test our hypothesis to investigate the neural substrates underlying the subjective–objective discrepancy using resting-state fMRI (rsfMRI).

Material and methods

Participants

A total of 124 patients with mood disorders were recruited for this study. We included depressed patients who met the criteria for major depressive disorder, dysthymic disorder, bipolar I disorder, or bipolar II disorder using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders (SCID-I) (Takahashi et al. 2010; First et al. 2012). We excluded patients with neurological diseases, including dementia, traumatic brain injury with loss of consciousness for >5 min, and low premorbid intelligence quotient (<70) as estimated using the Japanese Adult Reading Test (JART) 25-item version (Matsuoka and Kim 2006; Matsuoka et al. 2006; Hirata-Mogi et al. 2016) and manic symptoms as estimated using the Young Mania Rating Scale (Young et al. 1978; Inada et al. 2012) (score of ≥3). This study was approved by the Ethics Committee of the University of Tokyo Hospital (certification no. 630, 3150, 3202, 3349). After a thorough explanation of the purpose of the study, written informed consent was obtained from all participants, and this study was conducted following the tenets of the Declaration of Helsinki.

Clinical assessment

Observer-rated depressive symptoms were evaluated using the 17-item version of the HAMD (HAMD17) (Hamilton 1960; Tabuse et al. 2007; Williams et al. 2008), and self-rated depressive symptoms were evaluated using the BDI, 2nd edition (BDI-II) (Beck et al. 1996; Kojima et al. 2002; Kojima and Furukawa 2003) or the Center for Epidemiologic Studies Depression (CES-D) Scale (Ls 1977; Shima et al. 1985; Shima 1998). The self-rated depression scale was changed from CES-D to BDI-II during the study period to accommodate other research; the CES-D was considered a

possible replacement because it is a highly correlated self-rated scale developed with BDI as a reference. In addition, the Japanese version of the modified Global Assessment of Functioning (mGAF) (Eguchi et al. 2015) was evaluated. For participants taking psychotropic medications, we recorded medication information by calculating the equivalent values of imipramine for antidepressants, chlorpromazine for antipsychotics, and diazepam for anxiolytics (Inada and Inagaki 2015; Inagaki and Inada 2017).

Definition of a discrepancy between self-rated and observer-rated depression severity

To quantify the discrepancy between self-rated and observer-rated depression severities, HAMD17 was used as an observer-rated scale, and BDI-II and CES-D as self-rated scales, and these were z-scored to make them comparable. To examine the discrepancy between self-rated and observer-rated depression severities, the self- and observer-ratings discrepancy (SOD) was defined as the difference of the z-score of the self-rated depression scale minus the z-score of the observer-rated depression scale. The self-rated symptom predominant group (higher SOD) with discrepancy > 0.2 ($n = 47$) and the observer-rated symptom predominant group (lower SOD) with discrepancy < -0.2 ($n = 46$) were selected as participants showing extreme deviation.

MRI data acquisition

T1-weighted images and rsfMRI data were acquired during the same scanning session using a GE Discovery MR750w 3.0-T scanner and a 24-channel head coil (General Electric, Waukesha, WI, USA) at the University of Tokyo Hospital. For T1-weighted images, the scanning parameters were set as follows: slice thickness, 1.2 mm; repetition time (TR), 7.7 ms; echo time (TE), 3.1 ms; voxel size, 1 mm × 1 mm × 1.2 mm; flip angle,11°; field of view (FOV), 260 mm × 260 mm × 240 mm, and the spoiled gradient recalled echo pulse sequence was used for acquisition. Resting-state functional images were acquired using a gradient-echo echo planar imaging (EPI) pulse sequence for 10 min with the following parameters: 244 volumes; slice thickness, 3.2 mm; TR/TE, 2,500/30 ms; voxel size, 3.3 mm × 3.3 mm × 3.3 mm; flip angle, 80°; FOV, 212 mm × 212 mm × 212 mm; phase-encoding direction, posterior-to-anterior (PA). During the scan, participants were instructed to open their eyes and gaze at the cross-firm viewpoint on the screen seen through the mirror without thinking about anything specific.

Resting-state functional imaging preprocessing

MRI data were preprocessed and analyzed using MATLAB 2019b (MathWorks, Natick, MA, USA), SPM12 (Wellcome Department of Cognitive Neurology, London, UK), and CONN toolbox version 19.b (Whitfield-Gabrieli and Nieto-Castanon 2012). The first ten time-point scans were removed to allow the fMRI signal to reach a steady state. Slice temporal differences were corrected based on slice order using the CONN toolbox running in MATLAB and segmented into gray matter, white matter, and cerebrospinal fluid by matching structural data with the SPM12 unified segmentation and normalization procedure (Ashburner and Friston 2005). Data were repositioned and normalized according to the standard Montreal Neurological Institute EPI template. Spatial distortion was corrected by field mapping using the CONN toolbox, minimizing physiological noise factors and motion effects using the CompCor algorithm (Behzadi et al. 2007). Scrubbing was performed using the artifact detection tool (ART), with outlier scans identified as those with framewise displacement above 2 mm and/or global signal change >9 SD. Finally, band-pass filter denoising was performed at 0.008 to 0.09 Hz, and a Gaussian filter kernel with full width at half maximum of 8 mm was applied to spatially smooth the image.

Statistical analysis

Based on our hypothesis and previous findings, as indicated in the Introduction section, seed-based rsfMRI analysis was performed using the FP, OFC, and MedFC as seed regions. The Harvard–Oxford cortical atlas of the CONN toolbox was used to set seed regions. Pearson's correlation coefficients between the time-series blood oxygen level dependent (BOLD) signal of the seed and the time-series BOLD signal of each voxel were calculated and transformed into normally distributed z-scores by Fisher transform. Subsequently, seed-to-voxel FC maps were created. Differences in FC between the higher ($n = 47$) and lower ($n = 46$) SOD groups were examined for each seed region using t-tests including age and sex as covariates. We extracted significant cluster regions at the level of false discovery rate corrected $P < 0.05$ for clusters obtained by thresholding individual voxels at uncorrected $P < 0.001$.

Furthermore, it was necessary to explore in more detail whether such differences can be seen even across the lower SOD group, the close-to-zero SOD group, and higher SOD group. We thus examined the association in all patients ($n = 124$), also including those not showing extreme discrepancy, between SOD and the FC which differed between the lower and higher SOD groups, controlling for age and sex. In this analysis, we included a FC value at the peak voxel of the significant cluster found in the above analysis.

Results

Demographic and clinical characteristics of the study groups

The differences in the clinical backgrounds of the study participants are presented in Table 1. There were no significant differences in age, sex, duration of education, duration of illness, modified GAF-symptom (mGAF-S), modified GAF-functioning (mGAF-F), diagnosis of bipolar disorder, or medication use between the groups with higher SOD ($n = 47$) and lower SOD ($n = 46$). The mGAF-S and mGAF-F are indices in which the items and anchor points of the GAF are divided into "symptoms" and "social functioning" as an assessment of overall functioning in life, and the descriptions of the items are more detailed (Eguchi et al. 2015). The JART was significantly higher in the group with higher SOD levels ($P = 0.03$).

rsfMRI analysis of the discrepancy between self- and observer-rated depression severity

The brain regions that showed significantly greater FC differences in higher SOD ($n = 47$) than in lower SOD ($n = 46$) for FP, OFC, and MedFC seeds are shown in Table 2. There were no regions in which lower SODs showed a significantly greater FC than those with higher SODs.

A significant region of elevated FC seeded in the right FP was found in the precuneus, and a significant region of elevated FC seeded in the left FP was found in the precuneus and posterior cingulate cortex (PCC) in the higher SOD group compared to the lower SOD group (Fig. 1a, b). There were no regions where higher SODs showed significantly more elevated OFC- or MedFC-seeded FC than regions with lower SODs.

The right FP–precuneus FC (rho = 0.31, $P = 0.002$) and left FP–precuneus FC (rho = 0.33, $P = 0.001$) were significantly positively correlated with SOD in all subjects (Fig. 1c, d).

Table 1. Demographic and clinical characteristics of the participants.

	Patients with depression ($n = 93$)				
	Higher SOD ($n = 47$)		Lower SOD ($n = 46$)		
	Average	SD	Average	SD	*P* value
Age (yr)	38.0	10.4	38.0	13.4	0.67[a]
Females (*N*)	27		18		0.17[b]
SCID-I diagnosis					0.69[b]
MDD	29		29		
Dysthymic disorder	2		1		
Bipolar I disorder	10		7		
Bipolar II disorder	6		9		
Years of education	15.0	1.9	14.8	1.9	0.54[a]
Duration of illness (yr)	7.9	7.2	8.1	5.5	0.98[a]
mGAF-S	47.5	11.8	47.4	9.4	0.62[a]
mGAF-F	48.6	11.0	47.2	9.1	0.36[a]
JART25	20.2	3.5	18.6	4.9	0.03[a]
HAMD17	9.6	5.3	13.9	7.0	<0.001[a]
BDI-II ($n = 58$)	29.4	10.2	21.1	9.6	<0.001[a]
CES-D ($n = 35$)	34.8	9.1	21.0	9.0	<0.001[a]
Medication dose (mg/d)					
Antidepressants (IMP equivalent)	96.1	115.1	130.0	136.2	0.31[c]
Antipsychotics (CP equivalent)	99.6	193.4	63.3	128.3	0.29[c]
Anxiolytics (DZP equivalent)	11.3	12.1	8.1	8.8	0.14[c]

[a]Student's *t*-test [b]Pearson's chi-square test [c]Mann–Whitney *U* test. *Abbreviations*: SCID-I, Structured Clinical Interview for Diagnostic and Statistical Manualof Mental Disorders, Fourth Edition Axis I Disorders; MDD, major depressive disorder; mGAF-S, modified Global Assessment of Functioning-symptom; mGAF-F, modified Global Assessment of Functioning-functioning; JART, Japanese Adult Reading Test; HAMD, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory, 2nd edition; CES-D, Center for Epidemiologic Studies Depression Scale; IMP, imipramine; CP, chlorpromazine; DZP, diazepam.

Table 2. Brain regions that showed significantly greater FC differences in higher SOD than in lower SOD.

Seed	MNI coordinates (x, y, z)	Cluster size	Brain area	p-FDR	*T* value
Right FP	−02, −64, +36	254	Precuneus	1.84×10^{-2}	3.97
Left FP	+14, −56, +24	887	Precuneus/PCC	6.0×10^{-6}	4.67
OFC	...				
MedFC	...				

Abbreviations: MNI, Montreal Neurological Institute; FDR, false discovery rate; FP, frontal pole; OFC, orbitofrontal cortex; MedFC, medial frontal cortex; PCC, posterior cingulate cortex.

Discussion

In this study, we found an elevated FC between the right FP and the precuneus and between the left FP and the precuneus in the group with higher SOD, and the SOD was correlated bilaterally with FP–precuneus FCs.

It has been reported that the discrepancy between self-rated and observer-rated depression severity is greater in non-endogenous depression and dysthymic disorder than in endogenous depression (Rush et al. 1987), associated with personality disorders and stronger anxiety symptoms (Rane et al. 2010), and tends to be less extroverted and harmonious (Enns et al. 2000). Neuroticism and introversion have also been reported to be associated with the discrepancy between self-rated and observer-rated depression severity, introverts tend to overestimate the psychological symptoms of depression (Schneibel et al. 2012), and neuroticism is associated with ruminative thinking and psychological defense (Carter et al. 2010). The group that showed a discrepancy between self-rated and observer-rated depression severity in this study may also have cognitive biases as neurotic tendencies.

The FP, which was found to be related to the discrepancy between self-rated and observer-rated depression severity in this study, is a region that approximately matches BA10 and is known to play an important role in a variety of human-specific higher cognitive functions (Duncan 2010; Kovach et al. 2012; Waskom et al. 2014). The medial region of BA10 is involved in shifting attention to the future by thinking about the details of future events (Okuda et al. 2003; Addis et al. 2007; D'Argembeau et al. 2008) and may be involved in self-referential processing and ruminative thinking, leading to thought patterns specific to depression. The FP has also been suggested to be involved in cognitive functions, particularly in process, goal, and subgoal selection (Fletcher and Henson 2001), and, together with the precuneus, shown to be related to metacognitive abilities, the ability to introspect perception and memory (Fleming et al. 2010; Fleming et al. 2012; McCurdy et al. 2013; Fleming et al. 2014; Sinanaj et al. 2015).

The precuneus has been reported to play a central role in a wide range of highly integrated tasks such as visuospatial imagery, episodic memory retrieval, self-processing operations, and transformation of self-perspective (Cavanna and Trimble 2006). The precuneus, together with the PCC, anterior cingulate cortex, MedFC, and bilateral parietal junctions, constitutes the DMN (Shulman et al. 1997; Fox et al. 2005) and has been implicated in the regulation of attention and cognition (Pearson et al. 2011; Leech and Sharp 2014). The precuneus and PCC have been reported to have increased activity in a number of tasks,

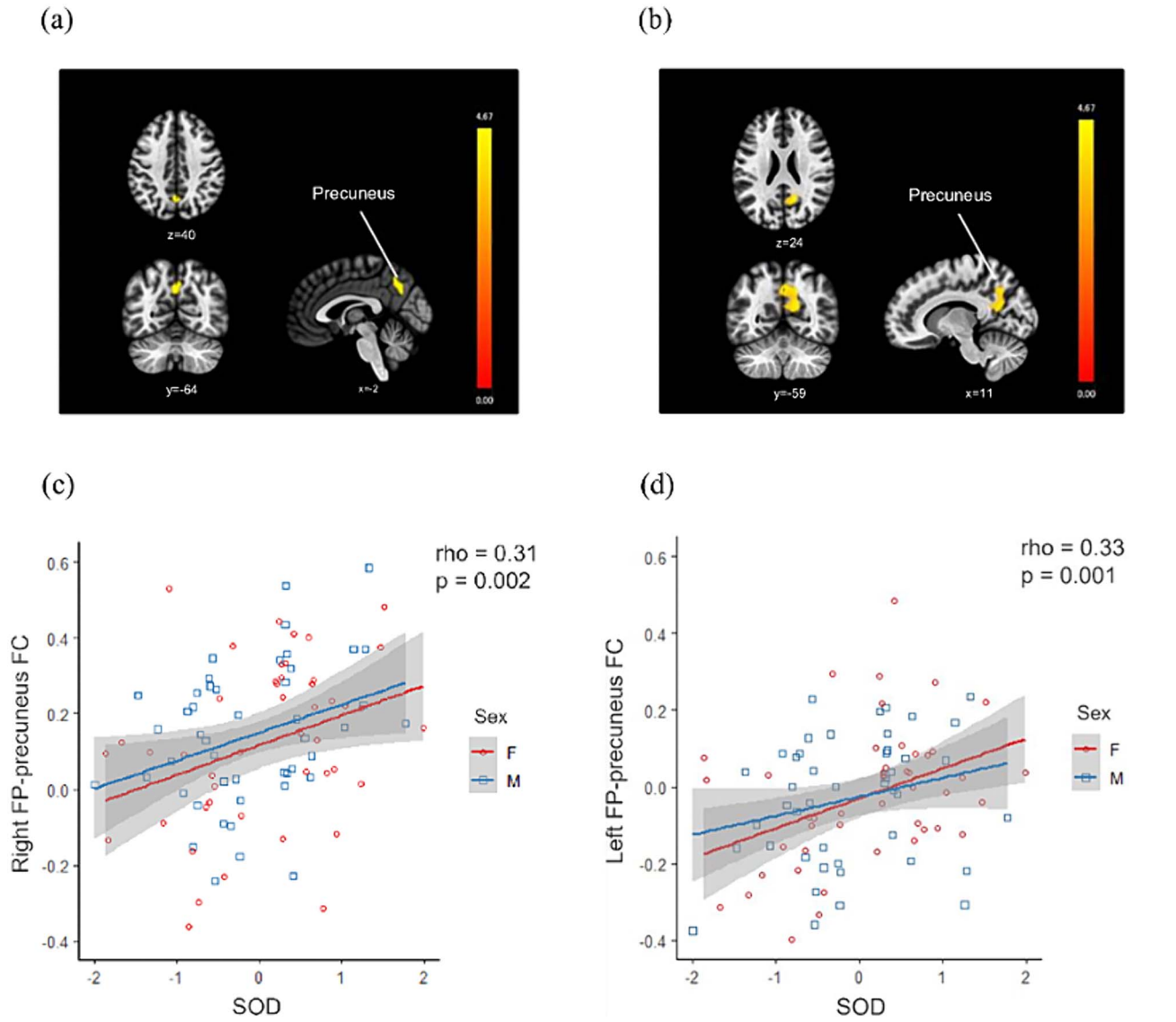

Fig. 1. Association of SOD with a FP-seeded FC. (a, b) Brain regions showing significantly elevated (a) right and (b) left FP-seeded FC in the higher SOD group compared to the lower SOD group are depicted. The vertical bars represent *t*-values. (c, d) Relationships in all patients between SOD and these FCs are described. *Abbreviations*: SOD, self- and observer-ratings discrepancy; FP, frontal pole; FC, functional connectivity.

including autobiographical memory retrieval (Maddock et al. 2001; Lundstrom et al. 2005), reward outcome monitoring (Hayden et al. 2008), and emotional stimulus processing (Maddock et al. 2003; Cavanna and Trimble 2006). The regional homogeneity of rsfMRI of the precuneus has also been reported to be altered in patients with depression due to cognitive bias in believing that negative thoughts will actualize (Jones and Bhattacharya 2014; Peng et al. 2015), which is associated with ruminative self-referential processing (Jones and Bhattacharya 2014). In addition, severe changes in FC between the precuneus and prefrontal cortex have been reported to occur in depression (Wang et al. 2014; Peng et al. 2015). The precuneus has also been suggested to be associated with subjective well-being, and subjective well-being scores have been reported to decrease with increased activity in the precuneus (Sato et al. 2019).

Regarding the FC between the precuneus and the prefrontal cortex, it has been reported that FC between the precuneus and OFC is increased in depressed patients (Cheng et al. 2018a), while FC between the precuneus and MedFC adjacent to the FP is decreased in relation to severity in depressed patients with anhedonia (Rzepa and McCabe 2018). The PCC is considered a core component of the DMN, which is known to have close neuroanatomical connections with the FP (Mansouri et al. 2015) and involved in future planning (Addis et al. 2007), emotional decision-making (Andrews-Hanna et al. 2010), and self-referencing (Gusnard et al. 2001). It has also been reported that depressed patients have increased FC between the PCC and OFC (Cheng et al. 2018b) and elevated FC between the PCC and middle frontal gyrus (Zhang et al. 2015). In this study, we also found an elevated FC between the FP and PCC in the group with the higher subjective discrepancy, suggesting that the enhancement of anxiety and negative cognition associated with excessive self-reference and future thinking may have affected the discrepancy between self-rated and observer-rated depression severities.

The FP and precuneus, between which FC was elevated in the group with a higher subjective discrepancy in this study, are both subregions of the DMN. Increased activity in the prefrontal cortex in patients with depression has been reported to be caused by

impaired cognitive processes due to poor inhibition of the DMN (Lemogne et al. 2012). The DMN is also a region reported to be activated by ruminative thinking (Berman and Jonides 2011), self-referential memory, and negative autobiographical memory (Kross et al. 2009; Nejad et al. 2013). Overall, the changes in FP–precuneus functional connectivity observed in this study suggest that they may be related with neurotic cognitive tendencies that increase anxiety through excessive self-reference and ruminative thinking.

Furthermore, we revealed that the lower SOD group was likely to exhibit a negative value of the FP–precuneus FC, while the higher SOD group tended to have a positive value. Recent meta-analytic studies have reported the lower activation in the precuneus in patients with depressive symptoms (Tozzi et al. 2021b; Xue et al. 2023). The FP is a key brain region for metacognitive judgment on non-experience (Miyamoto et al. 2018). It is suggested that patients in the lower SOD group may have impaired metacognition for their own depressive symptoms through disconnection between the FP and precuneus, while the higher SOD group may have such metacognition through the synchronized neural activity between the FP and precuneus even when the precuneus activity is decreased.

These results validate, although not completely, our initial hypothesis that the prefrontal cortex and DMN are related to the subjective–objective discrepancy in depressed patients.

Limitations

There are some limitations to this study. First, the self-rated depression scale was changed from the CES-D ($n = 52$, $n = 17$ [higher SOD], $n = 18$ [lower SOD]) to BDI-II ($n = 72$, $n = 30$ [higher SOD], $n = 28$ [lower SOD]) for consistency with other research projects. Because the CES-D was developed based on BDI-II, the similarity between the two indices is likely to be high, but a unified analysis of the indices will be considered in the future.

Second, the depressed participants in the study included multiple diagnostic groups based on the operational diagnosis: major depressive disorder, dysthymic disorder, bipolar I disorder, and bipolar II disorder. This study focused on the discrepancy between self-rated and observer-rated depression severity rather than on differences between diagnostic groups. We confirmed no significant difference in diagnostic groups between higher and lower SOD groups, which suggests that the difference in FC between diagnostic groups was, if any, negligible for our results. In this study, the participant numbers of some diagnostic groups were too small to conduct diagnosis-specific analyses for the discrepancy. However, it would be ideal to perform diagnosis-specific analyses if the number of participants is large enough.

Third, comparing the higher and lower SOD groups, both of which are abnormal, is likely to lead to difficulties in interpreting the results because it lacks a control group. We revealed a positive association in all patients, including those not showing extreme discrepancies, between the bilateral FP–precuneus FC and SOD. This implies that, compared to those with similar levels of severity in subjective and objective symptoms, this FC may be decreased in the lower SOD group and increased in the higher SOD group, respectively. However, our main results regarding the increase in this FC in the higher SOD group compared to the lower SOD group should be interpreted carefully.

Fourth, we hypothesized that the FP, OFC, and DMN, especially the MedFC, are associated with the subjective–objective discrepancy in depressive subjects because previous studies have reported these regions' roles in rumination and self-referential processing. We thus performed seed-based rsfMRI analysis using the FP, OFC, and MedFC as seed regions. However, other brain regions may also be related to rumination and self-referential processing, possibly in connection with the FP, OFC, or MedFC. Although testing this prediction is beyond the scope of this study, future studies are expected to reveal the whole-brain network associated with the subjective–objective discrepancy.

Fifth, there was a concern about the EPI image distortion due to the phase-encoding polarity in this study. Anterior-to-posterior (AP) EPI images are likely to exhibit great signal loss in the prefrontal area (especially the orbitofrontal cortex), while PA EPI images including our data are not likely to show great signal loss in the frontal gyrus (Wang et al. 2021). In addition, spatial distortion was corrected using fieldmaps. However, our results regarding the FP-seeded FC should be cautiously interpreted.

Conclusions

In this study, we found elevated FC between the FP–precuneus in the group with higher SOD. These were positively correlated with SOD, and the regions of elevation and correlation were found independently on the left and right sides. The findings of this study may provide insights into the association between the discrepancy between self-rated and observer-rated depression severity and brain circuits, which may lead to a more treatment-directed reclassification of the diagnosis in the future.

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Author contributions

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