



Frontopolar cortex activation associated with pessimistic future-thinking in adults with major depressive disorder

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ABSTRACT

Background: Pessimistic thinking about the future is one of the cardinal symptoms of major depressive disorder (MDD) and is an important domain of cognitive functioning associated with hopelessness. Neuroimaging studies have shown that the frontopolar cortex (Brodmann area [BA] 10) is involved in thinking about the future and demonstrated that patients with MDD have dysfunctions in BA10. However, the relationship between pessimistic thinking about the future and brain activity is unclear. Hence, we aimed to compare brain activity during future-thinking between patients with MDD and healthy individuals.

Methods: We assessed 23 patients with current MDD and 23 healthy individuals. Participants were instructed to imagine the future or to recall the past using the future-thinking paradigm with four distinct temporal conditions (distant future, near future, distant past, and near past) during functional MRI. Resting-state functional MRI was also performed to explore the functional connectivity of BA10.

Results: Compared with healthy individuals, patients with MDD had greater negative thinking about the distant future and exhibited increased activation in the medial BA10 when imagining the distant future, following small-volume correction focusing on the frontopolar a priori region of interest (family-wise error correction $p < 0.05$). Increased positive functional correlation between the right BA10 seed region and the posterior cingulate cortex was also observed.

Conclusion: Patients with MDD who show greater pessimistic thinking about the distant future demonstrate increased activation in the frontopolar cortex. These findings are consistent with the hypothesis that frontopolar cortical dysfunction plays a key role in the hopelessness that manifests in patients with MDD.

Non-standard abbreviations

MDD	Major depressive disorder
BA10	Brodmann area [BA] 10
GRID-HAMD	GRID-Hamilton Depression Rating Scale
BDI-II	Beck Depression Inventory-II
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
RTs	reaction times
ANOVA	analyses of variance
ROI	region of interest
SVC	small-volume correction
FEW	family-wise error
CBT	cognitive behavioral therapy
PCC	posterior cingulate cortex
fMRI	functional MRI

1. Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder, with an estimated 300 million people affected globally (World Health Organization, 2018). Patients with MDD tend to show pessimistic thinking about the future due to reduced ability to imagine a positive future, which predisposes them toward hopelessness (MacLeod et al., 1998). Further, patients with MDD have specific irrational and pessimistic thoughts about future opportunities and prospects with respect to self, but not with respect to others; these negative cognitive biases produce the depressive mood and hopelessness that are characteristic of depression, rather than vice versa (Abramson et al., 1978;

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Beck, 1963). In accordance with Beck's cognitive theory of depression, a recent systematic review of the empirical literature indicates that patients with MDD have a less concrete style of processing (i.e., abstract thinking) and reduced ability to imagine possible futures (Hallford et al., 2018). In the context of cognitive behavioral therapy, the ability to imagine possible futures is implicated as a central goal of therapy, which includes planning and predicting events and outcomes and completing between-session assignments associated with prospective memory (Altgassen et al., 2015). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and International Classification of Disease (ICD-10) list pessimistic thinking about the future as one of the cardinal symptoms of MDD. However, despite its clinical significance, little has been reported on the neurobiological underpinnings of pessimistic thinking about the future in MDD patients.

Neuroimaging studies have shown that the medial frontopolar cortex, located in the medial area of anterior prefrontal cortex (Brodmann area [BA] 10), plays a key role in future-thinking in healthy individuals (Benoit et al., 2011). Although the anterior prefrontal cortex is commonly activated during imagination of future and past events (Schacter et al., 2007), some studies regarding differences in regional brain activation between thinking of the future and thinking of the past have shown that medial BA10 is associated with thinking about future events, rather than thinking about past events (Addis et al., 2007; Okuda et al., 2003). It has been proposed that BA10 serve as an integrative center for higher-order emotional, cognitive, and social processes (Burgess et al., 2007; Gilbert et al., 2010). Further, BA10 has been associated with representational perspectives regarding the complex and long-term consequences of social behavior (Krueger et al., 2007; Wood and Grafman, 2003) and feelings of guilt (Moll et al., 2008). In studies involving non-human primates, BA10 was found to be associated with aspects of executive control of goal-directed behavior, such as monitoring current goals (Mansouri et al., 2017). Other findings from the published literature show that BA10 contributes to behavioral disturbances related to self-referential processing (Johnson et al., 2009; Kupfer et al., 2012; Yoshimura et al., 2014), ruminative self-focus (Jones et al., 2017), and self-blaming feelings (Green et al., 2012) in patients with MDD, which may contribute to hopelessness (Abramson et al., 1978).

Despite these findings, studies of brain activity related to future-thinking in MDD remain scarce. Hach and colleagues (Hach et al., 2014) reported that during future-thinking, patients with MDD showed decreased activity in the medial temporal lobe and the medial parietal cortex, accompanied by increased activity in the frontopolar cortex. However, that study did not examine the relationship between the level of frontopolar cortex (BA10) activity and the pervasiveness of pessimistic future-thinking, or the role of the temporal distance of future-thinking. Other studies have shown that the frontopolar cortex (BA10) is more closely associated with distant future-thinking than with near future-thinking (D'Argembeau et al., 2008; Okuda et al., 2003).

A meta-analysis study of resting-state functional connectivity showed that MDD was characterized by hyperconnectivity between the prefrontal cortex and posterior cingulate cortex (PCC) at rest (Kaiser et al., 2015). PCC is a core component of the "default mode" network at rest, and is related to planning for the future (Addis et al., 2007; Stawarczyk and D'Argembeau, 2015), affective decision-making (Andrews-Hanna et al., 2010), and self-reference (Gusnard et al., 2001). The mechanism by which alteration of resting-state connectivity from the frontopolar cortex affects future-thinking, however, remains unclear.

We therefore aimed to evaluate task-related brain activity during future-thinking and resting-state brain activity in the medial frontopolar cortex (BA10) by examining functional brain differences between patients with MDD and healthy individuals. We investigated the correlations between the level of brain activity and the intensity of pessimistic thinking about the future to elucidate the neural mechanisms underpinning the future-thinking process. We hypothesized that

compared to healthy individuals, patients with MDD would show pessimistic future-thinking associated with altered brain function in medial the frontopolar cortex (BA10) both during the task and at rest.

2. Material and methods

2.1. Participants

The participants were assessed at a university teaching hospital located in Tokyo between July 2015 and October 2017. During their usual consultations, treating psychiatrists provided a brochure with information about the study; they then invited patients to participate. If a patient showed interest in the study and provided contact details to the research team, a face-to-face appointment was scheduled with a study psychiatrist. All experimental procedures received prior approval by the Institutional Review Board (Keio University IRB reference no. 20150070). Each participant provided written informed consent and underwent a comprehensive assessment by a study psychiatrist for eligibility. Patients were eligible for inclusion in the study if they were aged 20–70 years and had MDD (either single or recurrent episodes) based on the Structured Clinical Interview for DSM-IV diagnosis (SCID) (First et al., 2007), conducted by study psychiatrists who received extensive training in the administration of semi-structured interviews (NK and AN). All patients also met the operational criterion of a total score of 16 or greater on the 17-item GRID-Hamilton Depression Rating Scale (GRID-HAMD) (Tabuse et al., 2007; Williams et al., 2008), and experienced at least moderate-level depression symptoms. GRID-HAMD was used by the assessors (psychiatrists and licensed clinical psychologists) to assess objective depressive symptoms; notably, the assessors had received extensive GRID-HAMD training and had achieved excellent inter-rater reliability (ICC = 0.94–0.98). Exclusion criteria were a primary DSM-IV axis I diagnosis other than MDD, lifetime manic or psychotic episodes, alcohol or substance use disorder, antisocial personality disorder, serious and imminent suicidal ideation, organic brain lesions or major cognitive deficits, serious or unstable medical illnesses, and general MRI exclusions. We used advertisements to recruit age-, gender-, and education-matched healthy individuals from local communities. Healthy individuals were eligible for inclusion in the study if they were free of any current or past psychiatric or neurological disorders or substance abuse disorders, and none were taking psychotropic medications. Twenty-four individuals were screened for inclusion as healthy subjects; one was excluded due to potential current psychiatric disorder, as evaluated by the SCID. We evaluated all participants' subjective depression severity using the self-reported Beck Depression Inventory-II (BDI-II) (Beck et al., 1996; Kojima et al., 2002) and Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Fujisawa et al., 2010; Rush et al., 2003) assessments. We screened and assessed 30 patients for eligibility; we excluded five who had HAMD scores of < 16, or who had a primary DSM-IV axis I diagnosis other than MDD. Twenty-five patients and 23 healthy individuals participated in this study ($n = 48$ in total). Of the 48 participants, one patient had claustrophobia, and another had a giant arachnoid cyst. One healthy control participant fell asleep during resting-fMRI and was re-scanned. Resting-state fMRI images were unavailable for one participant. Therefore, 46 participants had task MRIs of adequate quality for analysis and 45 participants had resting-state fMRIs of sufficient quality. A summary of demographic and clinical features is shown in Table 1.

2.2. Task description and procedure

Based on the Future Thinking Implicit Relations Assessment Procedure developed by Kosnes and colleagues (Kosnes et al., 2013), we used a modified version of the future-thinking task contextualized and adapted to Japanese culture. The future-thinking task used an event design composed of four temporal conditions (distant future, near

Table 1
Demographic and clinical comparison of patients with major depression and healthy individuals.

Characteristic	Healthy individuals (N = 23)		Patients with MDD (N = 23)		Analysis		
	Mean	SD	Mean	SD	t	df	p
Demographic characteristics							
Age (years)	40.0	11.3	36.7	9.7	-1.1	44	0.29
Education (years)	16.3	2.7	15.8	2.0	-0.69	44	0.50
	N	%	N	%	χ^2	df	p
Male Gender	9	39.1	7	30.4	0.38	1	0.54
Unemployed	0	0	1	4.3	1.02	1	0.31
Marital status							
Married	16	69.6	12	52.2	3.7	2	0.16
Separated, divorced, widowed	0	0	1	4.3	3.7	2	0.16
Single	7	30.4	10	43.5	3.7	2	0.16
Cohabiting	18	78.3	20	87.0	0.6	1	0.44
Smoking habit	14	60.1	17	73.9	0.17	1	0.69
Alcohol habit	4	17.4	3	13.0	0.89	1	0.35
Psychological characteristics							
	N	%	N	%	χ^2	df	p
Previous hospitalization	-	-	2	8.7	-	-	-
Previous suicide attempts	0	0	1	4.3	-	-	-
Self-reported childhood abuse	1	4.3	0	0.0	-	-	-
Self-reported experience of childhood bullying	1	4.3	6	26.0	-	-	-
Family history of psychiatric disorders (first-degree)	7	30.4	8	34.8	0.1	1	0.75
Specifiers of index episode (DSM-IV)							
	N	%	N	%			
Chronic (≥ 2 years from index episode)			0	0			
Melancholic features			10	43.5			
Atypical features			0	0			
Comorbid DSM-IV Axis I diagnoses							
Panic disorder (with agoraphobia)			1	4.3			
Social anxiety disorder			1	4.3			
Obsessive-compulsive disorder			1	4.3			
Generalized anxiety disorder			1	4.3			
Dysthymic disorder			0	0			
	Mean	SD	Mean	SD	t	df	p
Total number of depression episodes	-	-	1.9	1.0	-	-	-
Duration of index depression episode (months)	-	-	45.6	54.0	-	-	-
DDD of antidepressant medications prescribed	-	-	0.91	0.5	-	-	-
Number of antidepressant medications prescribed (current)	-	-	1.0	0.6	-	-	-
			N	%			
No medication	-	-	3	13.0	-	-	-
1 medication	-	-	16	69.6	-	-	-
≥ 2 medications	-	-	4	17.4	-	-	-
Types of antidepressant medications prescribed							
			N	%			
SSRI			12	52.2			
SNRI			5	21.7			
NaSSA			5	21.7			
TCA			1	4.3			
Benzodiazepines prescribed			13	56.5			
Antipsychotics prescribed			3	13.0			
Mood stabilizer medications prescribed			2	8.7			
	Mean	SD	Mean	SD	t	df	p
GRID-HAMD score	-	-	21.3	5.2	-	-	-
BDI-II score	4.7	4.2	30.6	8.8	12.7	44	< 0.001
QIDS-SR score	2.3	1.9	14.0	3.6	14.5	44	< 0.001
Each QIDS item ≥ 2							
			N	%			
1. Sleep-onset insomnia			13	56.5			
2. Mid-nocturnal insomnia			10	43.5			
3. Early morning insomnia			13	56.5			
4. Hypersomnia			6	26.1			
5. Sad mood			7	30.4			
6. Decreased appetite			7	30.4			
7. Increased appetite			1	4.3			
8. Decreased weight within the past 2 weeks			5	21.7			
9. Increased weight within the past 2 weeks			2	8.7			
10. Concentration/decision-making			12	52.2			
11. Outlook of self			15	65.2			
12. Suicidal ideation			6	26.1			

(continued on next page)

Table 1 (continued)

Characteristic	Healthy individuals (N = 23)		Patients with MDD (N = 23)		Analysis		
	Mean	SD	Mean	SD	t	df	p
Demographic characteristics							
13. Involvement			15	65.2			
14. Energy/fatigability			14	60.9			
15. Psychomotor slowing			5	21.7			
16. Psychomotor agitation			5	21.7			

Note: Previous axis I Disorder were not assessed. Abbreviations: MDD = major depressive disorder, DDD = defined daily dose, GRID-HAMD = 17-item GRID-Hamilton Depression Rating Scale, BDI-II = Beck Depression Inventory-II, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitor, NaSSA = Noradrenergic and Specific Serotonergic Antidepressant, TCA = tricyclic antidepressant.

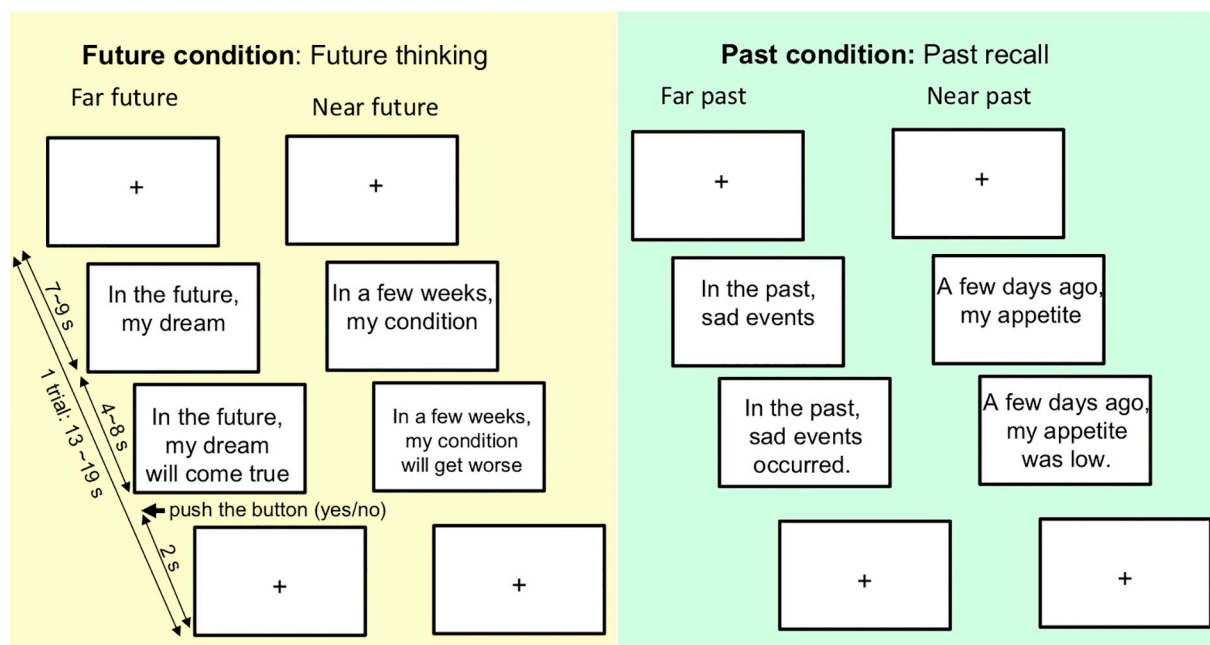


Fig. 1. Future-thinking task. Example trials for four different conditions are shown. Participants were asked to imagine the future or recall the past when the slide presented the temporal words. Once the sentence was complete, participants pushed a button to indicate a response of yes or no.

future, distant past, and near past) (Fig. 1). We used the past conditions as the comparison target to evaluate whether the difference in BA10 activity would occur in the future condition, rather than in the past condition. Furthermore, we assessed differences in positive and negative valences in both the future and past conditions, in order to evaluate pathological alteration in MDD. After presenting a fixation slide, each trial began with the first slide that contained a written description of the temporal words “in the future” as a distant future condition, “in a few weeks” as a near future condition, “in the past” as a distant past condition, or “a few weeks ago” as a near past condition; the written description was presented simultaneously with its main context on the screen (e.g., “your dream” or “sad things”). Participants were instructed to imagine distant or near future events, or to recall distant or near past events, while the first slide was presented for 4–8 s (e.g., in response to the first presentation of “in the future, dreams,” a participant might think “in the future, I wonder whether my dreams will come true...they must come true”). The distant future was defined at least 3 years after the scanning day, whereas the near future corresponded to the period from the next few days to the next few weeks (with a maximum of 4 weeks), as in a prior study (D’Argembeau et al., 2008; Okuda et al., 2003). The definitions were similar for the past conditions. Each trial consisted of the following sequence of events up to the second slide,

which included a full sentence (e.g., “in the future, your dream will come true,” or “in the past, sad things happened”). In Japanese, the final phrase defines whether the sentence is affirmative or negative. To yield the latter, auxiliary verbs are attached to the end of the sentence. After the second slide was presented, participants were asked to judge whether the full sentence was congruent with what they were thinking after presentation of the first slide. The subjects pushed a button to respond “yes” or “no,” which was followed by a fixation screen that was presented for 7 to 9 s. The task consisted of 64 trials, with 16 trials for each condition (Appendix Table A1). Each run lasted between 10.8 and 12.5 min, depending on the time taken by participants to identify each event and to press a button in response. The trials were presented in a random order for each participant.

The main sentence components for the task were selected based on contents covering cardinal symptoms of major depression (e.g., mood, appetite, and sleep) and high concordance rate (> 85%) for interpretation of main sentences among 36 psychiatrists. The content validity and construct validity were confirmed by a panel of expert clinical psychiatrists, neuropsychiatrists, and neuropsychologists. We also confirmed that neither positive nor negative valences were significant between temporal conditions (*p*-value = 0.21, one-way ANOVA). The test-retest reliability of the task was also excellent (*p*-value < 0.001,

$r = 0.98$, Pearson correlation).

All stimuli were presented in black text on a light white background and projected on a screen viewed by participants on a mirror incorporated into the head coil. SuperLab software (version 5.0; Cedrus Corp., San Pedro, CA, USA) was used for the presentation of stimuli and for collecting the reaction times (RT) and response data. Responses were provided using an MR-compatible two-button response box connected to the control computer, which recorded the responses and reaction time.

2.3. Behavioral assessment

All participant responses (yes or no) for each trial and reaction times (RTs) during the future-thinking task in fMRI were recorded. RT was calculated from the time when the sentence was shown on the second slide to the time when the subject pushed the button to respond. The ratio of the number of responses for negative valence in each temporal distance condition was calculated to assess differences between the patient and control groups. The ratios of negative valence trials and RT data were analyzed using a repeated measures analyses of variance (ANOVA) with a between-subjects factor of group (depression patients, controls) and within-subjects factors of task (distant future, near future, distant past, near past) and valence (positive, negative). Bonferroni-corrected pairwise comparisons were performed with the threshold criterion for significance set at $p < 0.05$, in order to test the hypothesis of a greater group effect for the future-thinking task.

All demographic, clinical characteristics, and behavioral data were analyzed with SPSS (version 24.0, IBM Corp., Armonk, NY, USA). Summary scores of the raw and standard scores were computed where appropriate. Categorical data (e.g., gender) were analyzed with chi-squared tests and continuous data (e.g., age) were analyzed with t -tests, as appropriate.

2.4. MRI acquisition

Images were acquired on a 3.0-T GE Discovery MR750 MRI scanner (GE Medical Systems, Milwaukee, WI, USA) with a 32-channel receiver coil in the MRI center at Keio University hospital. Participants lay supine on a scanner bed and viewed visual stimuli front-projected onto a screen through a mirror attached to the head coil. Foam pads were used to minimize head motion.

Functional task images of blood oxygenation level-dependent (BOLD) signals were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TR = 2400 ms, TE = 28 ms, FOV = 224 mm \times 224 mm, flip angle = 90°, slice thickness = 2 mm, and gap = 1 mm). Forty-four interlaced axial slices were acquired in order to cover the whole brain. For each participant, two functional runs were conducted, each of which lasted between 10.8 and 12.5 min (between 324 and 375 volumes). The axial slices were adjusted to be parallel to the anterior commissure–posterior commissure plane. Detailed anatomical data were collected using a high-resolution T1-weighted image (three-dimensional inversion recovery spoiled gradient-recalled acquisition with the following parameters: TI = 900 ms, TR = 2070 ms, TE = 4.13 ms, flip angle = 7°). Participants also completed a 10-min eyes-open resting-state scan (240 volumes acquired) with the following parameters: TR = 2000 ms, TE = 28 ms, flip angle = 90°, and thickness = 3.1 mm. Participants were instructed to lie still, stay awake, focus on a fixation cross, and allow their minds to wander before the resting scan started. The whole session was approximately 40 min in length. If subjects fell asleep, the scan was repeated.

2.5. Task-function MRI image preprocessing

All pre-processing and analyses of imaging data were conducted using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre

for Neuroimaging, Institute of Neurology, London, UK) implemented in MATLAB (Mathworks Inc., Natick, MA, USA). The structural T1 scan was co-registered to the subject's mean EPI image. Functional scans were realigned using iterative rigid-body transformations that minimize the residual sum of squares between the first and subsequent images, and temporally corrected for slice timing. They were normalized to the Montreal Neurological Institute (MNI) EPI template (voxel size = 2 \times 2 \times 2 mm³) and spatially smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm. Global changes were also removed by proportional scaling. First-level analyses were performed to determine voxel-wise activation of each subject while participants were thinking about the future or recalling the past. An event-related model was used with four condition types: distant future, near future, distant past, and near past. Each event was modeled by a canonical hemodynamic response function (HRF) that characterized the neural response. To consider the group difference for reaction times, we added the temporal derivatives at the first-level analysis. The HRF was applied 2 s after a full sentence appeared on each trial, based on a prior study that used an imagery task with cues (Addis et al., 2007); this ensured that the cognitive process was constructive, rather than merely reading sentences. A general linear model was used for statistical parametric maps. In addition, a high-pass temporal filter with cutoff of 128 s was implemented to remove low frequency drift in the signals. The realignment parameter was used for multiple regression to control for any variance associated with motion. Subsequent second-level analyses were performed on the SPM contrast images of the first-level canonical HRF responses for group random effects using two-sample t -tests to identify the brain regions related to each temporal condition. In order to adjust for the potential effects of age, gender, and education, all analyses were performed with these variables as covariates. An uncorrected statistical threshold of $p < 0.001$ with an extent threshold of 10 voxels, and uncorrected statistical cluster-forming threshold of $p < 0.001$, were used across the whole brain. Further, region of interest (ROI) analyses, focused on the medial frontopolar cortex, were conducted using the small-volume correction (SVC) tool for the correction of multiple comparisons in SPM12; p -values were thresholded using family-wise error cluster-wise correction (p FWE < 0.05). Coordinates for the medial frontopolar ROI were taken from meta-analytic data of previous fMRI studies that were focused on episodic future-thinking ($x = -2$, $y = 58$, $z = -4$) (Stawarczyk and D'Argembeau, 2015); additionally, the sphere was set with a 14-mm radius, equal to the FWHM for smoothing. Furthermore, to assess the association between medial BA10 ROI activation and the depressive severity or pervasiveness of pessimistic thinking about the distant future, we performed Pearson correlation analysis between medial BA10 ROI activation and the BDI score or ratio of negative valence responses to the distant future. Additionally, motion parameters that may produce spurious activity differences were assessed by one-way ANOVA with a between-subjects group factor (depression patients, controls).

2.6. Resting-state fMRI analyses

Resting-state fMRI was also performed to explore functional connectivity from BA10. Resting state functional images were analyzed using the functional connectivity (CONN) toolbox version 17 (Gabrieli Lab. McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA) in Matlab. The structural T1 scan was co-registered to the subject's mean EPI image. Functional scans were first corrected for slice timing to reduce the within-scan acquisition time difference between slices, then realigned to eliminate the influence of head motion during the experiment. All participants included in this study exhibited head motion of < 1.5 mm in any of the x , y , or z directions, and < 1.5° in any angular dimension. Realigned functional images were spatially normalized to the MNI space and resampled to 2 \times 2 \times 2 mm³. Next, images were smoothed with an 8-mm FWHM isotropic Gaussian kernel. After preprocessing, the first

covariates were defined as the realignment parameters which were six rigid-body parameters that characterized the estimated subject motion; scrubbing was performed to remove offending scans for each subject and session. For second-level covariance analysis, the covariates included age, gender, and years of education. Linear regression of the confounding effects was performed with three possible confounders, such as the BOLD signal from the white matter and CSF masks (five dimensions each), any previously-defined within-subject covariates (realignment and scrubbing), and the main condition effects (condition blocks convolved with HRF to remove unwanted motion, physiological, and artefactual effects from the BOLD signal). Functional images were band-pass filtered from 0.0008 to 0.09 Hz to reduce the influence of noise. In the first-level analysis, the CONN toolbox separately computed correlation coefficients between resting-fMRI signals in a seed region and each voxel in the brain, in order to generate the parametric seed-voxel correlation map. To evaluate functional connectivity, Z maps were generated showing connectivity between ROIs, as defined by the MNI standard space gray matter atlas.

The CONN established 91 cortical ROIs and 15 subcortical ROIs, as defined by the FSL Harvard-Oxford Atlas maximum likelihood cortical atlas (HarvardOxford-cort-maxprob-thr25-1 mm.nii); it disregarded Cerebral White Matter, Cerebral Cortex, and Lateral Ventricle areas, as well as 26 cerebellar parcellation ROIs from the AAL Atlas. The CONN also set network ROIs as four Default Mode Network ROIs, three SensoriMotor ROIs, four Visual ROIs, seven Salience/Cingulo-Opercular ROIs, four Dorsal Attention ROIs, four FrontoParietal/Central Executive ROIs, four Language ROIs, and two Cerebellar ROIs; these were defined on the basis of CONN's independent component analysis of a dataset of 497 healthy control participants. The bilateral frontopolar cortex BA10 was selected as a seed ROI, based on anatomical masks provided by the CONN toolbox defined in the Montreal Neurological Institute (MNI) space. The peak voxels of right and left BA10 seed ROIs were: right, $x = 26$, $y = 52$, $z = 8$; and left, $x = -26$, $y = 52$, $z = 8$. In a second level random-effects ANOVA, connectivity maps of the left and right frontopolar cortex seeds (BA10), associated with future-thinking in all participants, were analyzed separately. The cluster-forming height threshold was set at $p < 0.001$ uncorrected. Regions that showed a group difference (patients $>$ controls or patients $<$ controls) in the frontal pole connectivity were reported if they survived a stringent cluster-level extent threshold at False Discovery Rate (FDR) correction p -value < 0.05 , which was applied over the set of target ROIs. Furthermore, we assessed the overlap of the BA10 seed ROI set by CONN and the cluster-BA10 ROI from the task-fMRI result (MDD $>$ HC in the distant future condition) with MRIcron (Chris Rorden's Neuropsychology Lab, Charleston, SC, USA).

3. Results

3.1. Behavioral measures

The group characteristics did not differ in terms of age, gender, or years of education. The mean 17-item GRID-Hamilton Depression Rating Scale total score in the MDD group was 21.3 (SD 5.2), which indicated that most patients had moderately severe depressive symptoms. The patient group showed significantly higher scores in the BDI-II and QIDS-SR assessments, which were used as subjective depression severity measurements (all p values < 0.001).

The mean ratios of negative valence responses for each temporal distance during the future-thinking task are shown in Table 2. The ratio of negative valence responses differed between the groups with temporal distance ($F = 16.9$; $df = 3176$; $p < 0.001$). The MDD group showed a significantly higher ratio of negative valence responses to the distant future ($F = 62.3$; $df = 1176$; $p < 0.001$), near future ($F = 84.0$; $df = 1176$; $p < 0.001$), and near past conditions ($F = 52.3$; $df = 1176$; $p < 0.001$).

The patients with MDD required significantly longer reaction times

to answer for the distant future ($F = 18.8$; $df = 1352$; $p < 0.001$), near future ($F = 11.7$; $df = 1352$; $p < 0.001$), and near past conditions with positive valence ($F = 9.9$; $df = 1352$; $p = 0.0018$); as well as for the distant future ($F = 6.9$; $df = 1352$; $p = 0.0092$) and distant past ($F = 5.4$; $df = 1352$; $p = 0.02$) conditions with negative valence, when compared to the controls. The group difference in reaction time was most pronounced for the positive valence responses regarding the distant future (2.43 s vs 1.46 s; $F = 18.8$, $df = 1352$; $p < 0.001$) (Table 2).

3.2. Task fMRI

The patient group exhibited significantly increased activation in the bilateral frontopolar area (BA10) and the middle temporal gyrus in the main effects of the distant future condition, when compared with healthy individuals (all p -values < 0.001 , uncorrected, two-sample t -test) (Table 3). Further, medial BA10 ($x = 0$, $y = 56$, $z = 7$) survived with the frontopolar small volume correction (p FWE corrected = 0.029) in the same comparison (Fig. 2A). Anomalous activity at the frontal pole was associated with imagining the distant future in individuals with MDD, compared with that in healthy individuals. No brain areas showed differential higher activity in the MDD group, compared with the healthy individuals, for the main effects of three other temporal conditions. Healthy individuals, compared to those with MDD, had higher activation in the cuneus for the main effects of the distant future; temporal pole for the main effects of the near future; bilateral precentral gyrus, cuneus, and postcentral gyrus for the main effects of the distant past; and precentral gyrus, bilateral calcarine cortex, angular gyrus, and postcentral gyrus for the main effects of near past conditions (all p -values < 0.001 , uncorrected, two-sample t -test).

We also assessed correlations between medial BA10 activation and clinical characteristics specific to MDD, using ROI analysis. For the distant future condition, a cluster of BA10 voxels showed the most significant changes in activation in second level analysis in the MDD group, compared to healthy individuals. This activity cluster was defined as a medial BA10 ROI. The peak voxel of this ROI was located at $x = 0$, $y = 56$, and $z = 7$ in MNI coordinates. Pearson's correlation analysis revealed that the effect size of medial BA10 ROI activation was positively associated with the ratio of negative valence trials for the future condition ($r = 0.36$, $p = 0.01$) and the BDI-II score ($r = 0.44$, $p = 0.02$) in all participants (Fig. 2B).

No significant difference was found between groups for motion parameters when compared by one-way ANOVA (all p -values $> .05$).

3.3. Frontopolar cortex functional connectivity

Fig. 3A shows regions where the groups differed in functional connectivity in the right frontopolar cortex BA10 ROI during the resting state. Based on the seed from the right BA10, the MDD group demonstrated significantly increased functional connectivity to the PCC and "default mode" network lateral parietal region when compared with healthy individuals, and decreased connectivity to the insula, inferior frontal gyrus pars opercularis, and rostral prefrontal cortex (threshold ROI-to-ROI connections; p -FDR (seed-level correction) < 0.05) (Table 4). No group difference was detected from the seed from the left BA10. Furthermore, we confirmed overlapping of the BA10 seed ROI set by CONN and the cluster-BA10 ROI from the task-fMRI result (MDD $>$ HC in the distant future condition) (Fig. 3B).

4. Discussion

The principal and most novel finding of this study is that compared with healthy individuals, patients with MDD demonstrate increased activation in the bilateral medial frontopolar cortex (BA10) when thinking about the distant future. Interestingly, the level of medial frontopolar cortex activity correlated with the pervasiveness of pessimistic future-thinking and severity of depressive symptoms. These

Table 2
Behavioral responses in the future-thinking task.

Measure	Task condition	Healthy individuals		Depression patients		Analysis		
		(n = 23)		(n = 23)		F	df	p
		Mean	SD	Mean	SD			
Ratio of negative valence trials (%)	Distant Future	6.0	1.6	54.9	7.1	62.3	1	< 0.001
	Near Future	9.2	2.3	66.0	5.3	84.0	1	< 0.001
	Distant Past	28.5	4.3	28.8	4.5	0.002	1	0.97
	Near Past	19.8	3.0	64.7	4.4	52.3	1	< 0.001
Reaction time for positive valence trials (ms)	Distant Future	1456	528	2432	898	18.8	1	< 0.001
	Near Future	1681	526	2451	756	11.7	1	< 0.001
	Distant Past	1709	630	2037	652	2.1	1	0.15
	Near Past	1636	613	2343	1155	9.9	1	0.0018
Reaction time for negative valence trials (ms)	Distant Future	2013	930	2603	824	6.9	1	0.0092
	Near Future	2161	925	2391	569	1.0	1	0.31
	Distant Past	1695	753	2220	681	5.4	1	0.02
	Near Past	1740	635	2139	534	3.1	1	0.08

Abbreviations: SD = standard deviation, ms = milliseconds. % = (number of negative valence responses/16 trials) × 100%.

Table 3
Comparison of future-thinking-related activation in patients with major depression and healthy individuals.

Contrast and Region	Hemisphere	BA	# voxels	MNI Coordinate			t	df
				x	y	z		
				Depression Patients (n = 23) > Healthy Individuals (n = 23)				
Distant Future condition								
Frontal pole cortex	L	10	25	-18	59	25	4.33	44
Frontal pole cortex ^a	R	10	21	3	56	11	3.55	44
Middle temporal gyrus	L	37	27	-42	-55	-4	4.21	44
Near Future condition								
None identified								
Distant Past condition								
None identified								
Near Past condition								
None identified								
Depression Patients (n = 23) < Healthy Individuals (n = 23)								
Distant Future condition								
None identified								
Near Future condition								
None identified								
Distant Past condition								
Precentral gyrus	R	6	318	48	-7	18	4.91	44
Precentral gyrus	L	6	91	-45	-10	28	4.81	44
Cuneus	R	18	56	15	-85	14	4.12	44
Postcentral gyrus	R	3	37	45	-19	56	4.00	44
Near Past condition								
Precentral gyrus	R	4	38	42	-13	60	4.76	44
Calcarine cortex	R	23	13	15	-73	11	4.02	44
Postcentral gyrus	L	4,6	11	-51	-13	32	3.59	44

Listed brain regions survived at p values < 0.001 uncorrected.

Abbreviations: BA = Brodmann's area, MNI = Montreal Neurological Institute, FWE = family-wise error.

^a Brain regions survived with the small volume correction at p values FWE corrected < 0.05

findings demonstrate that patients with MDD who show greater pessimistic thinking about the distant future also show increased activation in the medial frontopolar cortex.

Our findings of increased activation in medial BA10 during future-thinking confirmed prior findings that demonstrate increased activity in the frontopolar cortex during future-thinking processes in patients with MDD (Hach et al., 2014). Further, we demonstrated that patients with MDD had greater pessimistic future-thinking. This adds to a previous study that examined the influence on brain activity of imagining emotional events in the near and distant future (D'Argembeau et al., 2008). In fact, the medial frontopolar cortex is a brain region that is critical for triggering affective and emotional signals when imagining future outcomes (Schacter et al., 2017), and a region associated with thinking about outcomes rather than processes (Gerlach et al., 2014).

Thus, patients with MDD may pre-experience emotional feelings regarding pessimistic outcomes of distant future events, and have difficulty imagining the distant future. Alternatively, depressive automatic affective thought related to the "default mode" network may recruit BA10 in patients with MDD (Kaiser et al., 2015). The frontopolar cortex is a core component of the "default mode" network, a set of brain regions that have greater activity in baseline conditions than during experimental tasks. Further, our findings are consistent with prior imaging studies reporting that altered activation in the frontopolar cortex in individuals with MDD is caused by lack of "default mode" network inhibition (Lemogne et al., 2012) or by "default mode" network hyperactivation (Christoff et al., 2016). In sum, our findings suggest that patients with MDD who experience negative cognition when imagining the distant future have altered frontopolar cortex activity.

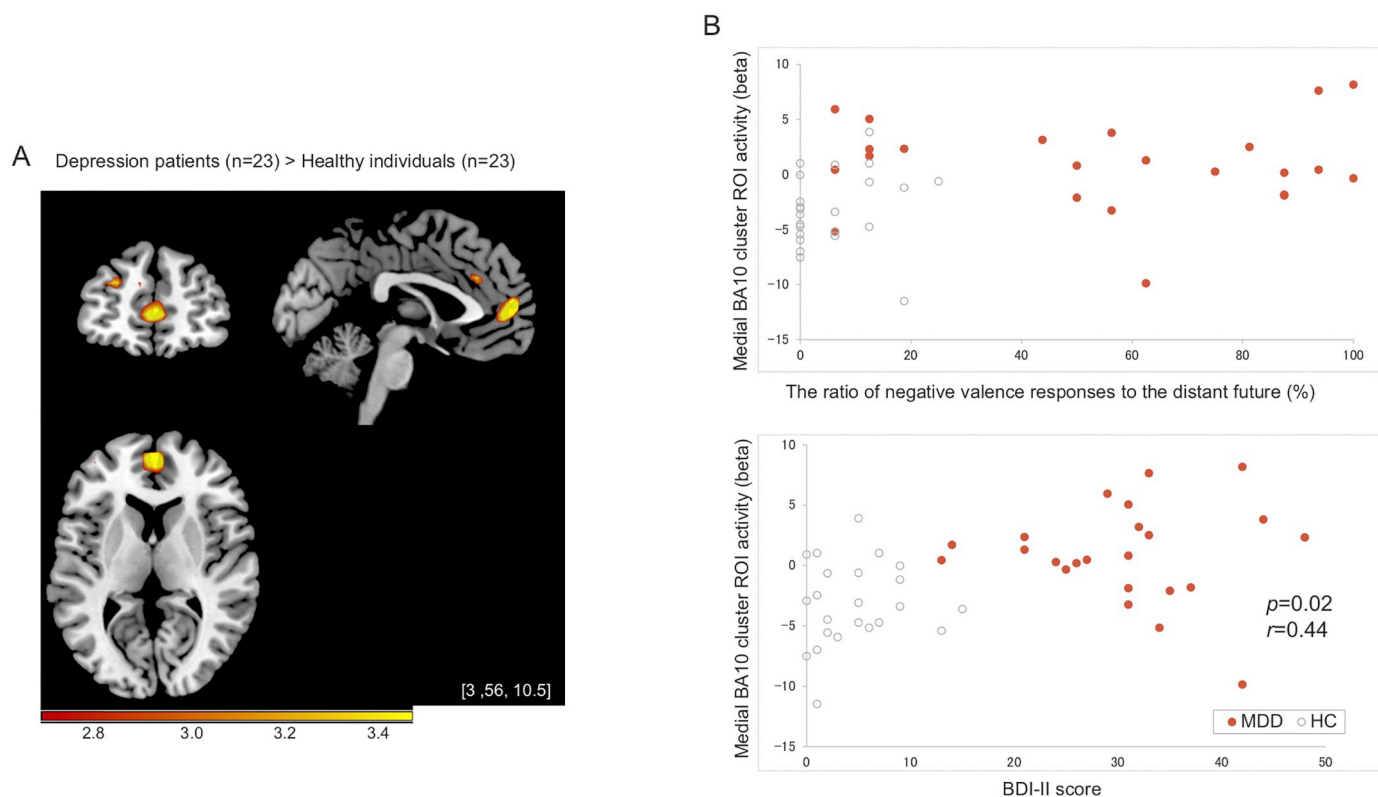


Fig. 2. Effects of depressed thinking on distant future-thinking-related brain activation.

Panel A shows a group comparison of medial frontopolar small volume correction between depression and healthy groups (FWE corrected $p < 0.05$). Panel B shows scatterplots of activation in the medial frontopolar cluster ROI, which had a significant positive correlation with the ratio of negative valence responses for the distant future conditions and BDI-II score.

Abbreviations: MDD = major depressive disorder, HC = healthy controls, BDI-II = Beck depression inventory-II, ROI = region of interest

Our findings show that medial BA10 activation accompanies distant future-thinking in depression patients. No other brain regions were implicated in other temporal conditions. Previous studies report that BA10 is associated with distant future-thinking in healthy individuals, and suggest that distant future-thinking is distinct from near future-thinking (Brosch et al., 2018; D'Argembeau et al., 2008; Okuda et al., 2003). Clinically, increased abstractness of processing (i.e. ruminative self-focus) has been shown to exacerbate negative cognitive biases that reduce the ability to imagine positive future events in depression patients (Beck et al., 1974). Perhaps patients with MDD have greater deficiencies and need greater effort to imagine the distant future as opposed to the near future, due to their abstract style of processing.

We observed that the patients with MDD showed greater negative valence responses toward the future and increased medial BA10 activation during distant future-thinking. This suggested that increased medial BA10 activation during distant future-thinking was associated with pessimistic future-thinking. This is in line with Beck's cognitive theory of depression (Beck and Alford, 2009; Beck, 1963, 2008) and with empirical studies showing that depression patients have an abstract style of processing and reduced ability to imagine a positive future (Hallford et al., 2018). These findings suggest that frontopolar cortex activity is a potential neuromarker for assessing cognitive function. In fact, mindfulness-based cognitive behavioral therapy (CBT) is reported to alter medial BA10 function (Gotink et al., 2016). Moreover, the functional connectivity between brain regions, including medial BA10, is associated with differential treatment outcomes for medications or CBT (Dunlop et al., 2017). Therefore, changes in medial BA10 activation during future-thinking may be a neuromarker of successful depression treatments such as CBT, which challenges negative dysfunctional cognition about the future.

We observed increased brain functional connectivity from a seed in

BA10 to the PCC and “default mode” network lateral parietal region in patients with MDD. The PCC is a core component of the “default mode” network, and is related to self-reference (Gusnard et al., 2001) and planning for the future (Addis et al., 2007). Our findings are consistent with a recent meta-analysis, which reported that, compared to healthy individuals, patients with MDD have increased connectivity within the “default mode” network (Kaiser et al., 2015). Furthermore, increased activation and connectivity in the frontopolar cortex at rest is associated with ruminative self-focus (Jones et al., 2017). Thus, functional alteration in BA10 when thinking about the distant future may be associated with increased BA10 functional connectivity. However, in our study, patients with MDD had decreased brain functional connectivity from the BA10 seed to the insula. The insula has been shown to participate in the salience network, which plays a central role in the detection of stimuli related to behavior and the coordination of neural resources (35). It is also noteworthy that study participants unintentionally think about the self or future during resting state fMRI (Schacter et al., 2007). This finding suggests that patients may shift attention without deep future-thinking processes during resting fMRI. Thus, the findings were briefly as follows: medial BA10 hyperactivation during distant future-thinking, increased positive functional correlation between BA10 and PCC and between BA10 and the “default mode” network lateral parietal region, and decreased positive functional correlation between BA10 and insula; taken together, these findings may reflect inflexible self-focused thoughts and distracted attention. This altered connectivity may be associated with dysfunctional cognition related to distant future-thinking in patients with MDD.

The behavioral results of the present study demonstrated that individuals with MDD had a biased pessimistic view of the future and found it difficult to think about a positive future, and especially the distant future, for themselves. Compared with healthy individuals,

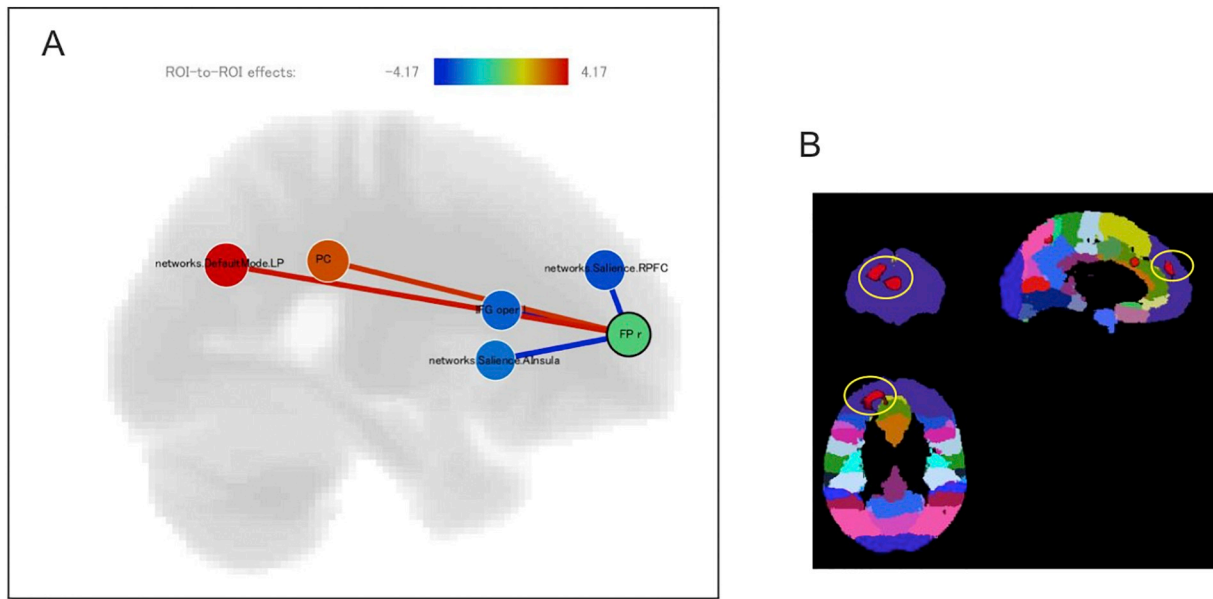


Fig. 3. Between-group functional connectivity comparison using a frontopolar cortex BA10 seed in healthy individuals and patients with major depression. Panel A shows between-group functional connectivity comparison using a frontopolar cortex BA10 seed in healthy individuals and patients with major depression. Compared to healthy individuals, patients with MDD had greater connectivity between the right frontopolar cortex BA10 seed and posterior cortex, and lower connectivity between the seed and the insula, inferior frontal gyrus pars opercularis, and rostral prefrontal cortex. Threshold ROI-to-ROI connections; p-FDR (seed-level correction) < 0.05.

Panel B shows overlap of the frontopolar BA10 seed ROI set by CONN and the BA10 clusters from task-fMRI result. The frontopolar BA10 seed ROI overlaps with BA10 clusters from the task-fMRI result (MDD > HC in distant future condition). The FSL Harvard-Oxford Atlas maximum likelihood cortical atlas (HarvardOxford-cort-maxprob-thr25-1 mm.nii) was templated. Purple area was defined as the frontopolar ROIs in CONN. The red area shows clusters in BA10 from the task-fMRI result.

Abbreviations: DMN = “default mode” network, LP = lateral parietal cortex, PC = posterior cingulate, salience N = salience network, IFG = inferior frontal gyrus, RPFC = rostral prefrontal cortex, ROI = region of interest, FDR = false discovery rate

patients with MDD had a significantly higher ratio of negative valence trials for the distant future, near future, and near past conditions; but a similar ratio for the distant past condition. These findings agree with findings from previous studies exploring cognition about the future in depression, which demonstrate that patients with MDD show more pessimistic future-thinking (Lavender and Watkins, 2004). It is also noteworthy that the group difference in reaction time between patients with MDD and healthy individuals was most prominent in the distant future condition with positive valence. Perhaps MDD patients with greater pessimistic future-thinking have a reduced ability to think positively about future events and this causes them to show longer reaction times.

The results of this study should be interpreted with caution. First, we did not control for medication and duration of depressive episodes,

which may affect brain activity or connectivity (Admon et al., 2017; Heller et al., 2013). To our knowledge, however, an association between antidepressants and medial BA10 has not been reported to date; however, further study is required. Second, participants were recruited from a university teaching hospital, thus limiting generalizability. Third, we had a relatively limited sample size. Future studies with a larger sample size are necessary for analysis of the correlation between the extent of BA10 activation and behavioral data. Fourth, a control (neutral) task was difficult to use in our future-thinking task, which was a temporal task; therefore, we could not eliminate background signal associated with the task. Fifth, our task may have a potential confounding issue because some aspects of contents (e.g. conceptual word or physical-state related words) were not controlled. Finally, the current study employed a cross-sectional design. Longitudinal studies are

Table 4

Between-group functional connectivity using a Frontopolar Cortex BA10 seed in healthy individuals and patients with major depression.

Seed: right frontopolar cortex (BA10) x,y,z = (26,52,8)	Hemisphere	MNI coordinate			Maximum T score		
		BA #	x	y	z	p-FDR	
Depression Patients (n = 23) > Healthy Individuals (n = 22)							
Positive connectivity							
DMN LP	R	39	47	-67	29	3.85	0.024
PC	L	31	1	-37	30	3.5	0.036
Negative connectivity							
Insula	L	13	-44	13	1	-4.17	0.024
IFG pars opercularis	L	44	-51	15	15	-3.82	0.024
RPFC	L	10	-32	45	27	-3.68	0.027

Threshold ROI-to-ROI connections; p-FDR (seed-level correction) < 0.05.

Abbreviations: DMN = “default mode” network, LP = lateral parietal, PC = posterior cingulate, IFG = inferior frontal gyrus, RPFC = rostral prefrontal cortex, ROI = region of interest, FWE = family-wise error.

required to determine whether individuals with greater medial BA10 activation will maintain this during depressive episodes or show alterations through treatment. Detailed analyses of task-related functional connectivity from medial BA10 also should be pursued in future studies to explore the involvement of synergetic mechanisms in future-thinking.

5. Conclusions

This study explored the functional significance of frontal pole activity related to negative cognition about the distant future in individuals with MDD. Our results suggest that patients with MDD show pessimistic future-thinking and difficulty imagining their distant future, which associates with abnormal patterns of medial frontal pole activity. To our knowledge, this is the first study to assess brain activity in the medial frontal pole during temporally distant future-thinking, and the relationship between brain function and negative bias toward the future in depression. Dysfunction of the medial frontal pole during distant future-thinking may reflect negative cognition about the future, and this may constitute a neuromarker for successful depression treatments such as CBT, which challenges negative dysfunctional cognition about the future.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2019.101877>.

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