Frontothalamic Circuit Abnormalities in Patients With Bipolar Depression and Suicide Attempts

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ABSTRACT

Objective: Suicide is the leading cause of premature death among patients with bipolar disorder (BD), so it is imperative to identify biological or psychometric markers for suicide risk. Previous functional neuroimaging studies of the general BD population have focused on abnormalities within cortical-subcortical circuits. The aim of the current study was to examine potential cortico-subcortical circuit abnormalities predictive of suicide attempt in patients with BD.

Methods: We examined functional connectivity (FC) based on 5 regions of interest: bilateral anterior cingulate cortex (ACC), medial frontal cortex, inferior frontal cortex, amygdala, and thalamus, by resting-state functional magnetic resonance imaging (rs-fMRI) in 65 participants, including patients with BD and suicide attempts (SA group; n = 24), patients with BD and no suicide attempts (NSA group; n = 15), and healthy control subjects (HC group; n = 26). Patients met *DSM-5* criteria for bipolar I disorder with current major depressive episode.

Results: The total patient group (SA+NSA) exhibited significantly lower FC between bilateral thalamus and frontal cortex ($F = 35.11$, $P < .01$), and this deficit was most severe in the SA group. In addition, patients demonstrated significantly reduced FC values between bilateral inferior frontal gyrus and both inferior temporal gyrus ($F = 20.68$, $P < .01$) and fusiform gyrus ($F = 20.98$, $P < .01$), but FC was stronger in the SA group than the NSA group. Both patient groups also exhibited reduced FC based on these seeds including bilateral amygdala, medial frontal cortex, and ACC, but without significant differences between the SA and NSA groups.

Conclusions: The results suggest that reduced FC within specific frontothalamic circuits may increase the vulnerability for suicidal behavior in patients with BD. These FC abnormalities might provide potential predictors of suicide attempt in BD.

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Bipolar disorder (BD) is a severe mental illness strongly associated with suicidal behavior. Indeed, suicide is a leading cause of death in this patient group, and a recent review concluded that the risk of suicide among BD patients was up to 20–30 times greater than that for the general population.[1–4] Approximately 25%–60% of BD patients attempt suicide during their illness, and ~4%–19% die by suicide.[5] Suicide attempt is currently the strongest predictor of further suicide attempts and suicide.[6] In addition, there is evidence that suicide in BD patients may be more violent and lethal.[7] However, the pathophysiologic mechanisms that motivate suicide are unclear, so it is currently difficult to accurately predict suicide attempt and completion based solely on BD clinical features.[8]

Depression is the predominant mood state associated with suicide in bipolar disorder.[9] Bipolar disorder patients with suicide attempts are hospitalized more frequently for depression than BD patients without suicide attempts,[10] and previous severe depression is highly predictive of later suicidal behavior.[11,12] Patients with more severe depressive phases are also more likely to attempt suicide.[13,14]

Strong association of suicidal behavior with depression suggests that treatment with antidepressants might reduce suicidal risk, though most studies have yielded inconsistent evidence.[15] Some patients with BD can worsen clinically and increased risk of suicidal behavior when given an antidepressant.[16,17] Lithium is the only known antisuicidal treatment with evidence from randomized controlled studies of a reduction in the risk of suicide of more than 50%.[18] However, the benefits of lithium are restricted by adverse effects and a low therapeutic index.[19] Given these findings, pathophysiologic mechanisms underlying suicidality in BD might be distinct from those underlying depressive symptoms of BD.

Several previous studies of patients with BD and suicide attempt have demonstrated morphometric and functional abnormalities in key nodes of cortical-subcortical circuits, such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC),[20] caudate nucleus, putamen, thalamus, and nucleus accumbens.[21] Under normal conditions, these circuits mediate reciprocal communication between cortical and subcortical regions[22] critical for normal emotional regulation and cognitive function. In this experiment, we used

Clinical Points

- Bipolar disorder (BD) is a severe mental illness strongly associated with suicidal behavior. The pathophysiologic mechanisms underlying suicidality in BD might be distinct from those underlying depressive symptoms of BD.
- The authors suggest that the abnormally weak functional connectivity between thalamus and frontal cortex may disrupt affective and cognitive functions and confer a heightened vulnerability for suicidal behavior.

resting-state functional magnetic resonance imaging (rs-fMRI) to examine spontaneous neural activity in patients with bipolar depression and suicide attempts, patients with bipolar depression and no suicide attempts, and matched healthy control (HC) subjects. Given that extreme affective instability and cognitive deficits are major trait-related risk factors for suicide in bipolar disorder,[23,24] we chose to measure whole brain connectivity to these cortical and subcortical regions implicated in emotion generation, emotion regulation, and cognitive control, including bilateral ACC, medial frontal cortex, inferior frontal cortex, amygdala, and thalamus.

METHODS

Participants

A total of 39 patients with bipolar I disorder currently experiencing a major depressive episode were recruited from the psychiatric inpatient unit of Anhui Mental Health Center between May 1, 2019, and June 20, 2021. All patients met *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria for bipolar depression and were diagnosed by 2 qualified psychiatrists using the Structured Clinical Interview for *DSM-5* (SCID).[25,26] Patients were divided into 2 groups, 24 with suicide attempts (SA group) and 15 with no suicide attempts (NSA group). Suicide attempts were defined as self-injurious acts committed in the person's lifetime that involved at least some intent to die. The clinical severity of depressive symptoms was assessed using the Hamilton Depression Scale (HDRS).[27] Inclusion criteria were confirmed BD diagnosis (above) and HDRS score ≥ 20 on the day of fMRI. Exclusion criteria were as follows: (1) electroconvulsive therapy in the previous 3 months; (2) lifetime diagnosis of substance abuse, schizophrenia, or schizoaffective disorder; (3) previous or current neurologic illness; (4) head motion exceeding 2 mm in translation or 2° rotation during the fMRI scans; and (5) other contraindications for MRI.

We also recruited 26 healthy participants meeting the same criteria as patients except for BD diagnosis as the HC group. The study was conducted in accordance with the recommendations of Human Brain Imaging Collection, Anhui Medical University Ethics Committee, and the protocol was approved by the Anhui Medical University Ethics Committee. All subjects volunteered to participate in the study and provided written informed consent after receiving a full written and verbal explanation of study aims and procedures.

MRI Data Acquisition

Structural and functional magnetic resonance images were acquired from all participants using a 3-T scanner (Discovery GE750w at University of Science and Technology of China). During rs-fMRI scanning, participants were instructed to keep their eyes closed without falling asleep and to avoid thinking of anything in particular. Functional images, each consisting of 217 echo-planar volumes, were acquired using the following parameters: repetition time = 2,400 ms, echo time = 30 ms, flip angle = 90°, matrix size = 64 × 64, field of view = 192 × 192 mm^2, slice thickness = 3 mm, and 46 continuous slices (1 voxel = 3 × 3 × 3 mm^3). High spatial resolution T1-weighted anatomic images consisting of 188 slices were acquired in the sagittal orientation using the following parameters: repetition time (TR) = 8.16 ms, echo time = 3.18 ms, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1 mm, flip angle = 12°, and field of view = 256 × 256 mm^2.

Resting-State fMRI Data Preprocessing

The rs-fMRI data were preprocessed using the Data Processing Assistant for Resting-State Functional MR Imaging toolkit,[28] a software package based on Statistical Parametric Mapping (www.fil.ion.ucl.ac.uk/spm) and the Resting State Functional MR Imaging Toolkit[29] (http://www.restfmri.net).

The first 10 volumes were deleted to allow signal equilibration. After slice timing correction, the time series was realigned to the first volume for head motion correction. After realignment, data with head movement exceeding 2 mm of translation or 2° of rotation in any direction were discarded. Structural T1-images were transformed to Montreal Neurologic Institute (MNI) space using Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra (DARTEL). Functional images were then transformed to MNI space based on the transformation matrix for structural images and linear trends were removed. Nuisance signals, such as those from 24 Friston motion parameters, white matter, and cerebrospinal fluid, were regressed out. All functional images were then smoothed with a 4-mm isotropic Gaussian kernel and bandpass filtered (0.01–0.10 Hz). Subsequently, scrubbing was conducted to remove time points with high motion (defined as framewise displacement > 0.5), as well as 1 time point prior to and 2 time points following each high-motion time point.[30]

Functional Connectivity Analysis

To identify changes in cortico-subcortical circuits associated with suicidality in BD, FC analyses were conducted using the following regions of interest (ROIs) as seeds: bilateral ACC, medial frontal cortex, inferior frontal cortex, amygdala, and thalamus. The bilateral ACC, inferior frontal cortex, medial frontal cortex, amygdala, and thalamus

Table 1. Demographic and Clinical Information of the Study Population

	BD and suicide attempts	BD and no suicide attempts	Healthy controls	Statistic	*P* value
Demographic					
Age, mean (SD), y	33.5 (12.1)	29.8 (10.9)	34.2 (11.3)	$F=0.654$	.523
Sex				$\chi^2=0.588$	.745
Male	9	6	8		
Female	16	8	18		
Education years, mean (SD)	10.8 (3.4)	12.5 (3.5)	11.8 (4.0)	$F=1.251$	.292
Clinical					
Duration of illness, mean (SD), y	8.32 (1.45)	7.28 (1.77)		$t=0.439$	.663
HDRS, mean (SD)	26.9 (7.0)	27.3 (6.3)		$t=1.011$	.319
Suicide ideation (HDRS item), mean (SD)	2.64 (0.14)	2.21 (0.21)		$t=1.730$	.092
Framewise displacement, mean (SD)	0.05 (0.03)	0.04 (0.02)	0.05 (0.02)	$F=0.740$	.48
Medication					
Medication load index, mean (SD)	2.24 (0.12)	2.35 (0.17)	NA	$t=-0.575$	.569
Medication, n of participants					
SSRIs	10	6	0		
SNRIs	2	1	0		
Antipsychotics	18	12	0		
Anticonvulsants[a]	18	8	0		
Lithium	8	6	0		

[a]Anticonvulsants consisted mainly of benzodiazepines and valproate.
Abbreviations: BD = bipolar disorder, NA = not applicable, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

seeds were identified using Wake Forest University Pickatlas software (WFU Pickatlas, version 3.0.5).[31] The signal time courses of each voxel within these ROIs were extracted, and Pearson correlation coefficients were calculated for all other voxels. These correlation values were then transformed to Fisher *z* scores and used to construct FC maps for each individual and group.

Correlation Analyses Between rs-fMRI and Disease Severity

To examine the relationships between cortical-subcortical circuit strength and clinical symptom severity, we calculated correlations between regional FC values (above) and HDRS scores controlling for sex, age, and years of education.

Statistical Analysis

Group means from normally distributed datasets were compared by 1-way analysis of covariance (ANCOVA) and group means from skewed datasets by the Mann-Whitney *U* test. Sex ratio was compared by the χ^2 test. Functional connectivity maps of each seed region were compared among groups using a voxel-based, 1-way ANCOVA with sex, age, years of education, and antipsychotic medication dose as covariates, followed by post hoc 2-sample *t* tests using Statistical Parametric Mapping (SPM)12 (https://www.fil.ion.ucl.ac.uk/spm). To control for multiple comparisons, statistical maps were thresholded using the Gaussian random field correction with a voxel-level threshold of $P<.001$ and cluster-level threshold of $P<.05$. If significant by ANCOVA, post hoc 2-sample *t* tests were performed to compare FC values within voxel clusters between groups. Furthermore, we also calculated whole brain connectivity based on these ROIs using antidepressant dose as a covariate (Supplementary Figures 1–5).

RESULTS

Demographic and Clinical Characteristics of the Study Population

The study population was composed of 39 BD patients, 24 with suicide attempts (SA group) and 15 with no suicide attempts (NSA group), and 26 HCs. Table 1 summarizes the demographic and clinical characteristics of the study population. There was no significant group difference in mean age, sex ratio, and years of education. As expected, HDRS scores were significantly higher in the combined patient group (SA+NSA) than the HC group, confirming current depressive symptoms. All patients were currently taking medication, and all antipsychotics prescribed were second generation. Medication load is described in Supplementary Table 1. The two patient groups did not differ in disease duration or the proportions currently receiving antipsychotic, lithium, antiepileptic drug, antidepressant drug, and benzodiazepine treatments. There were also no significant differences in mean framewise displacement as calculated by the method of Power et al.[30]

Weaker Functional Connectivity to the Bilateral Thalamus in BD Patients With Suicide Attempt

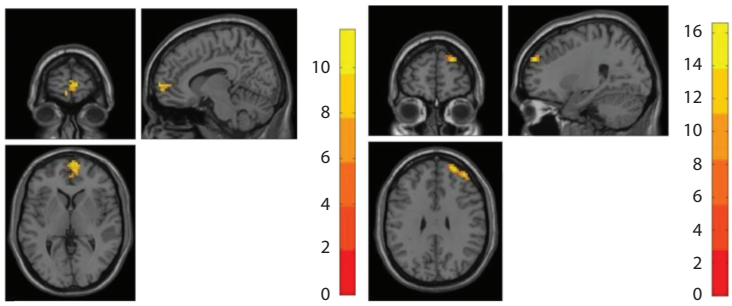
Functional connectivity of the bilateral thalamus with medial frontal gyrus and superior frontal gyrus was significantly reduced in both patient groups compared to the HC group and was lower in the SA group than the NSA group ($F=35.11$, $P<.01$) (Figure 1).

Stronger Functional Connectivity to the Bilateral Inferior Frontal Gyrus in BD Patients With Suicide Attempt

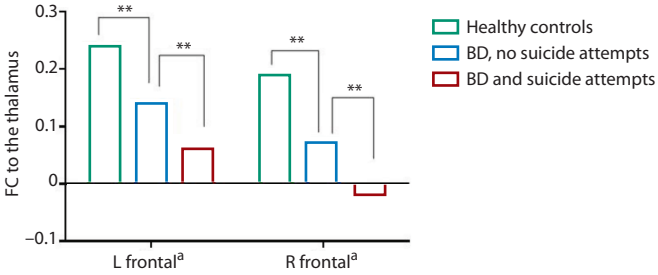
Functional connectivity of the bilateral inferior frontal gyrus with inferior temporal gyrus ($F=20.68$, $P<.01$) and

Figure 1. Whole-Brain Changes in Functional Connectivity to the Bilateral Thalamus Across 3 Groups

A. The left and right thalamus demonstrated decreased functional connectivity to the frontal clusters across groups. The color bar indicates *F* statistic magnitude.



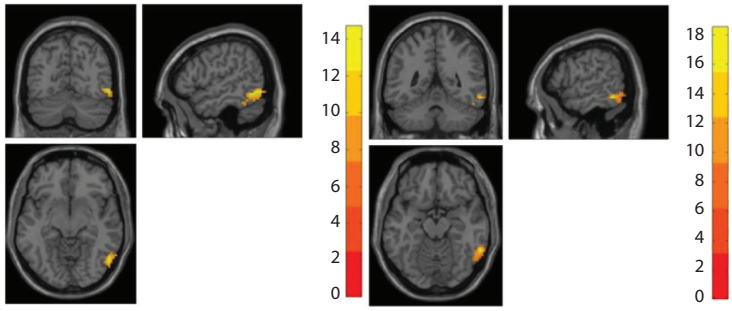
B. Bar chart shows the average Fisher *Z* transformed functional connectivity values between the bilateral thalamus region of interest and the frontal cluster among the subjects within each group.



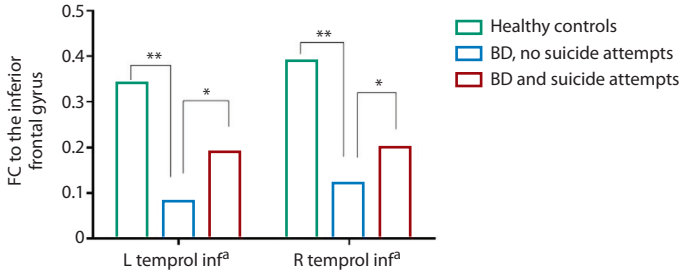
[a]Represents functional connectivity based on the left (L) and right (R) thalamus.
**$P < .01$.
Abbreviations: BD = bipolar disorder, FC = functional connectivity.

Figure 2. Whole-Brain Changes in Functional Connectivity to the Bilateral Inferior Frontal Gyrus Across Groups

A. The bilateral frontal inferior gyrus demonstrated increased functional connectivity to the inferior temporal gyrus in BD with suicide attempts compared to BD with no suicide attempts and decreased functional connectivity to the inferior temporal gyrus in BD compared to healthy controls.



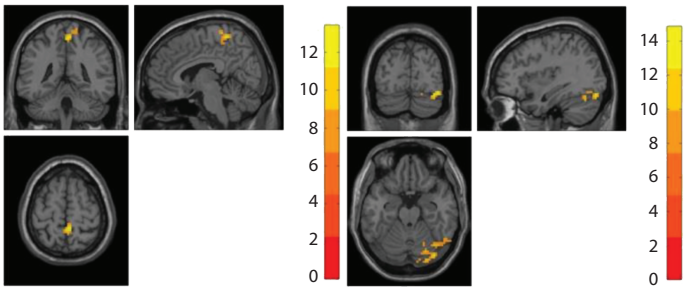
B. Bar chart shows the average Fisher *Z* transformed functional connectivity values between the bilateral inferior frontal gyrus and the inferior temporal gyrus among the subjects within each group.



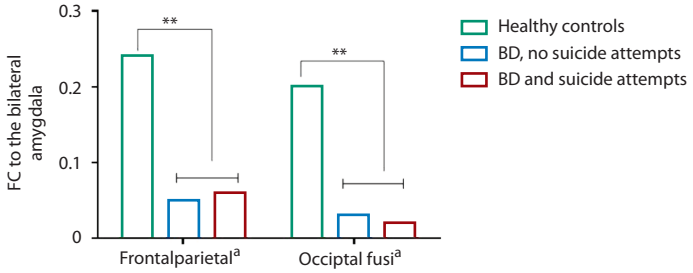
[a]Represents functional connectivity based on the left (L) and right (R) frontal inferior gyrus. "Temprol inf" refers to areas including the inferior temporal gyrus and fusiform gyrus.
*$P < .05$, **$P < .01$.
Abbreviations: BD = bipolar disorder, FC = functional connectivity.

Figure 3. Whole-Brain Changes in Functional Connectivity to the Bilateral Amygdala Across Groups

A. The bilateral amygdala demonstrated decreased functional connectivity to the frontalparietal and fusiform gyrus clusters in BD compared to healthy controls. The color bar indicates *F* statistic magnitude.



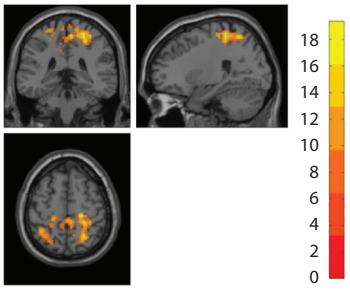
B. Bar chart shows the average Fisher *Z* transformed functional connectivity values between the bilateral amygdala ROI and frontalparietal and fusiform gyrus clusters among the subjects within each group.



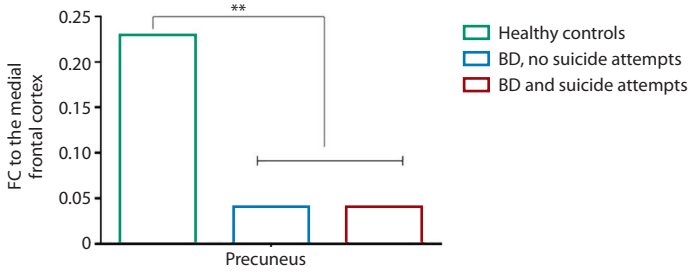
[a]The center of frontalparietal cluster is 6, –42, 63 in Montreal Neurologic Institute (MNI) coordinates. The center of occipital fusi cluster is 36, –81, – 21 in MNI coordinates.
**$P < .01$.
Abbreviations: BD = bipolar disorder, FC = functional connectivity, ROI = region of interest.

Figure 4. Whole-Brain Changes in Functional Connectivity to the Bilateral Medial Frontal Cortex Across Groups

A. The bilateral medial frontal cortex ROI demonstrated decreased functional connectivity to the precuneus clusters in BD compared to healthy controls. The color bar indicates *F* statistic magnitude.



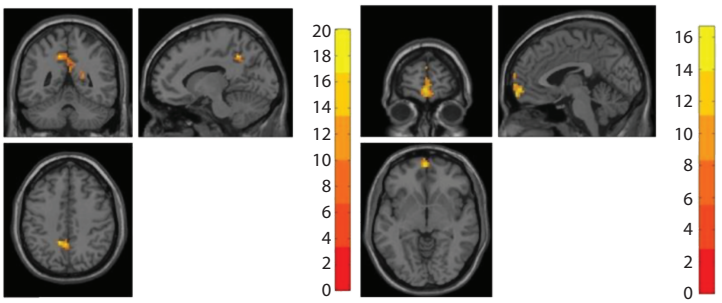
B. Bar chart shows the average Fisher *Z* transformed functional connectivity values between the bilateral medial frontal cortex ROI and precuneus among the subjects within each group.



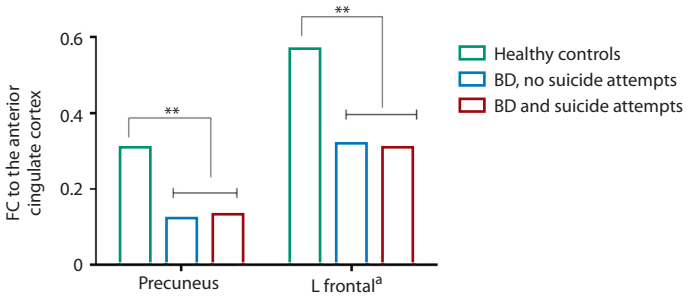
**$P < .01$.
Abbreviations: BD = bipolar disorder, FC = functional connectivity, ROI = region of interest.

Figure 5. Whole-Brain Changes in Functional Connectivity to the Bilateral Anterior Cingulate Cortex Across Groups

A. The bilateral anterior cingulate cortex ROI demonstrated decreased functional connectivity to the precuneus and frontal clusters in BD compared to healthy controls. The color bar indicates *F* statistic magnitude.



B. Bar chart shows the average Fisher *Z* transformed functional connectivity values between the bilateral anterior cingulate cortex ROI and the clusters within precuneus and frontal cortex among the subjects within each group.



[a]Represents the functional connectivity based on the left anterior cingulate cortex.
**$P < .01$.
Abbreviations: BD = bipolar disorder, FC = functional connectivity.

fusiform gyrus ($F = 20.98$, $P < .01$) was also significantly reduced in patients compared to controls, but in contrast to bilateral thalamus pathways, FC in these pathways was stronger in the SA group than the NSA group (Figure 2).

Nonspecific BD-related FC Changes With Bilateral Amygdala, Medial Frontal Cortex, and Anterior Cingulate Cortex

We also observed significant differences in FC with the bilateral amygdala ($F = 25.64$, $P < .01$), ACC ($F = 25.41$, $P < .01$), and medial frontal cortex ($F = 32.51$, $P < .01$) among groups, and post hoc *t* tests indicated significant differences between the total patient group and HC group but no difference between the SA and NSA groups (Figures 3–5).

Associations Between FC Changes and Disease Severity

There was no significant correlation between FC strength and HDRS scores ($P > .05$, false discovery rate–corrected).

DISCUSSION

This rs-fMRI study revealed significantly lower FC of the bilateral thalamus with frontal cortex in BD patients compared to matched controls and even weaker FC in patients with previous suicide attempt (SA) compared to patients without previous suicide attempt (NSA). Patients also demonstrated weaker FC of bilateral inferior frontal gyrus with inferior temporal gyrus and fusiform gyrus, but, in this case, FC was stronger in those with suicide attempt. Finally, patients exhibited weaker FC to the bilateral amygdala, medial frontal cortex, and ACC, but without significant difference between those with or without suicide attempt. Thus, increases and decreases in FC within specific cortical-subcortical circuits may promote suicidality in BD.

Consistent with our primary finding of weakened FC of bilateral thalamus with frontal cortex in BD patients with suicide attempt, previous studies have reported structural and metabolic abnormalities in the thalamus associated with depressive symptomatology[32–34] and suicide.[35–37] The thalamus receives strong dopaminergic projections that are critical for mood regulation.[38] The frontothalamic pathway is also crucial for cognition and emotional processing. Thalamic abnormalities are known to be involved in the pathophysiology of suicidal behaviors, and reduced thalamic volume has been reported in psychotic disorder patients with suicide attempts.[35,39] Moreover, the numbers of frontothalamic circuit fibers projecting to medial frontal cortex and OFC were significantly reduced in suicidal patients with depression compared to depressed patients without suicidal ideation or attempt.[37] Local decreased activity in prefrontal cortex was found in a cohort of

individuals with depression who had completed suicide.[23] The thalamus also has one of the highest levels of serotonin transporter (SERT) expression in the human brain.[40] These SERTs regulate serotonergic transmission by transporting serotonin from the extracellular space into the neuron, and SERT capacity has a major influence on emotional behavior and brain connectivity[41] by modulating information flow between the limbic system and cerebral cortex.[42] Thus, serotonergic signaling in the thalamus participates in critical higher brain functions such as executive function[43,44] and mood regulation.[45–48] We suggested that the abnormally weak FC between thalamus and frontal cortex may disrupt affective and cognitive functions and confer a heightened vulnerability for suicidal behavior.

Impulsivity is a cardinal feature of BD[49,50] and is especially severe among patients who complete or attempt suicide.[49–52] The inferior frontal gyrus (IFG) is involved in the modulation of behavioral inhibition,[53,54] and we found a significant decrease in FC of the bilateral IFG with the inferior temporal gyrus (ITG) and fusiform gyrus among patients. However, FC strength in the SA group was intermediate between the NSA and HC groups. We speculated that this stronger FC of the IFG with ITG and fusiform gyrus may facilitate suicidal acts among BD patients by increasing impulsivity. A previous study reported increased regional brain activity in the ITG of depressed patients with suicide attempts.[55] Moreover, the ITG was identified as one of the top 10 regions for predicting suicide in depressed patients.[56] The ITG is involved in a putative output system that regulates visceral functions connected to emotions,[57] so abnormalities in the ITG may cause emotional disturbances, which in turn could increase suicide risk among BD patients.

We found that both patient groups exhibited weaker FC among bilateral amygdala, medial frontal cortex, and ACC, regions strongly implicated in the BD depressive state but not specifically in suicide vulnerability. The amygdala is involved in the regulation of emotion and in learning associations between stimuli with emotional salience and neutral stimuli. Consistent with these functions, multiple human neuroimaging studies have confirmed amygdalar hyperactivity in patients with depression.[58,59] The amygdala is activated quickly in response to unpleasant or hostile stimuli.[60–62] There are also widespread alterations in the frontal gray matter, including the medial frontal cortex and paracentral lobule, in subjects with emotional bias and attention deficits.[63–65] Anatomic and function changes in the medial frontal cortex are also crucial to the pathophysiology of depression. Functional studies have found abnormal activity in the medial frontal cortex during both emotional tasks and the resting state[66–68] that were correlated with clinical features of depression, such as emotional bias, apathy, loss of motivation in the context of both positive and negative incentives,[69,70] disrupted emotional processing, and increased rumination. The ACC also contributes to executive function[71] and processing of top-down activation through connections with prefrontal cortex, parietal cortex, and the motor system.[72] Aberrant brain connectivity and local activity in the ACC and precuneus may disturb default-mode network function, resulting in abnormal emotional regulation.[72,73] Taken together, these widespread abnormalities in the default mode network are likely critical to the pathogenesis of depression and closely associated with clinical manifestations such as emotional bias, cognitive deficits, and rumination.

Our study had several limitations. First, the sample size was relatively small, so the results require validation in a larger cohort. Second, this was a cross-sectional study without longitudinal observations, precluding conclusions on causality. Third, variations in ongoing pharmacotherapy may account for differences between patient groups (although there were no differences in the proportions receiving different drug classes). Nonetheless, this complication is unavoidable given the ethical considerations of keeping patients medication-free. Further studies using a prospective design and well-matched patient cohorts are required to address these issues. Fourth, our results were inconsistent with some of the previous research, possibly because of the heterogeneity of subjects, such as those with acute suicide behavior[74] or unipolar depression.[75] Fifth, in order to reduce sample heterogeneity, we excluded participants with any substance abuse. Because of this, generalizability of our results could be limited.

CONCLUSION

Bipolar patients with previous suicide attempts exhibited significantly weaker FC of the bilateral thalamus with the frontal cortex compared to patients without suicide attempts. These cortical-subcortical circuit alterations may increase the vulnerability for suicidal behavior in BD patients and thereby provide predictive biomarkers. Future longitudinal studies are needed to understand the neural correlates of suicidal behavior in BD patients and identify unique predictors of suicide risk.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

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Supplementary Material

Article Title: Frontothalamic Circuit Abnormalities in Patients With Bipolar Depression and Suicide Attempts

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List of Supplementary Material for the article

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Supplementary Content

1. As described in the previous articles[1, 2], for measuring total medication load in BD patients we used a strategy in which each medication was coded as absent = 0, low = 1 (equal or lower average dose), or high = 2 (greater than average dose) with reference to the midpoint of the Physician's Desk Reference recommended daily dose range. We calculated a composite measure of total medication load for each individual, reflecting dose and variety of different medications taken, by summing all individual medications. (see Table 1 in Results).

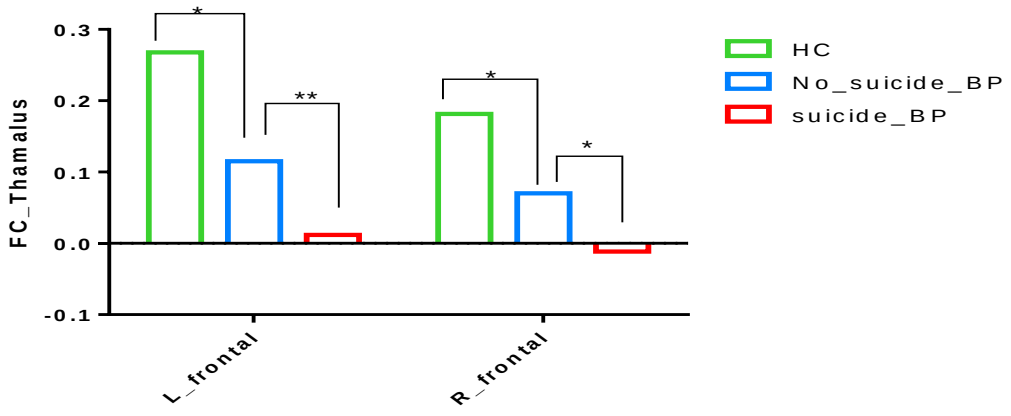
2. The names and dosages of the drugs taken by each patient were detailed in the table below.

Supplementary Table 1. Names and Dosages of Drugs Taken by Each Patient

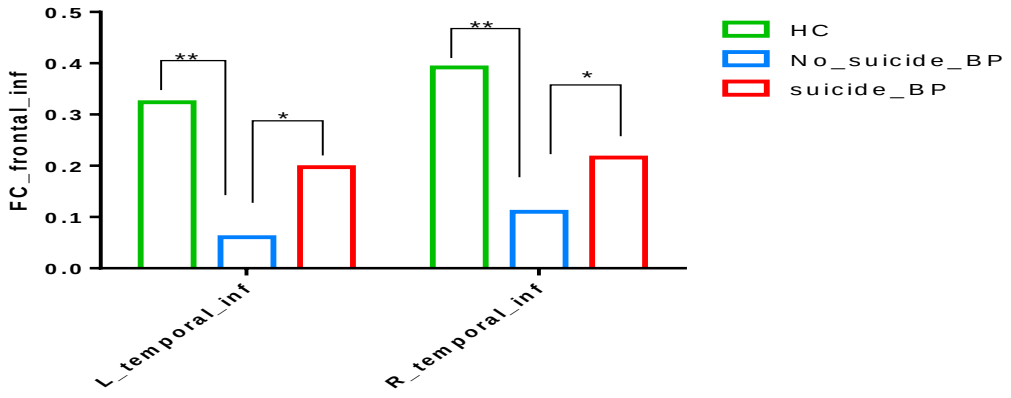
BPD_SA	Antidepressants	dosage(mg)	Antipsychotics	dosage(mg)	anticonvulsants	dosage(mg)	Lithium	dosage(mg)
PT1001	Sertraline	50	quetiapine	300	valproate	200		
							lithium	
PT1003	Duloxetine	50	aripiprazole	10			carbonate	500
PT1005			quetiapine	200	valproate	300		
PT1006					valproate	400		
PT1007	Sertraline	50	aripiprazole	10	valproate	200		
PT1009	escitalopram	10	quetiapine	100	valproate	300		
							lithium	
PT1010					valproate	200	carbonate	250
PT1012			quetiapine	200	valproate	300		
							lithium	
PT1015	Sertraline	75			valproate	200	carbonate	500
							lithium	
PT1017	Sertraline	50	quetiapine	300			carbonate	250
PT1019			aripiprazole	15	valproate	300		
PT1020	Sertraline	50			valproate	200		
							lithium	
PT1022	fluoxetine	20	olanzapine	5			carbonate	250
PT1023			quetiapine	200	valproate	150		
							lithium	
PT1025			aripiprazole	20			carbonate	500
PT1027	Duloxetine	40			valproate	300		
PT1028	Sertraline	50	quetiapine	250				
PT1030	escitalopram	10	quetiapine	200	valproate	200		
							lithium	
PT1031			olanzapine	5			carbonate	250
PT1032			quetiapine	150	valproate	300		
PT1033					valproate	500		
PT1035	Sertraline	50			valproate	300		
PT1036			quetiapine	200	valproate	200		
PT1038			aripiprazole	10	valproate	300		
							lithium	
PT1039			quetiapine	300			carbonate	500

BPD_NSA	Antidepressants	dosage(mg)	Antipsychotics	dosage(mg)	anticonvulsants	dosage(mg)	Lithium	dosage
							lithium	
PT1002	Sertraline	50			valproate	300	carbonate	250
PT1004	Duloxetine	40	aripiprazole	10	valproate	200		
							lithium	
PT1008			quetiapine	200			carbonate	500
PT1011			quetiapine	200	valproate	200		
							lithium	
PT1013	escitalopram	10	quetiapine	300			carbonate	250
PT1014			aripiprazole	15	valproate	300		
							lithium	
PT1016			quetiapine	150			carbonate	250
PT1018	Fluoxetine	20	olanzapine	5	valproate	200		
							lithium	
PT1021			aripiprazole	10			carbonate	500
PT1024			quetiapine	150	valproate	300		
PT1026	Sertraline	50	aripiprazole	10				
PT1029					valproate	300		
							lithium	
PT1034	escitalopram	10	aripiprazole	20			carbonate	250
PT1037	Sertraline	50	quetiapine	200	valproate	200		

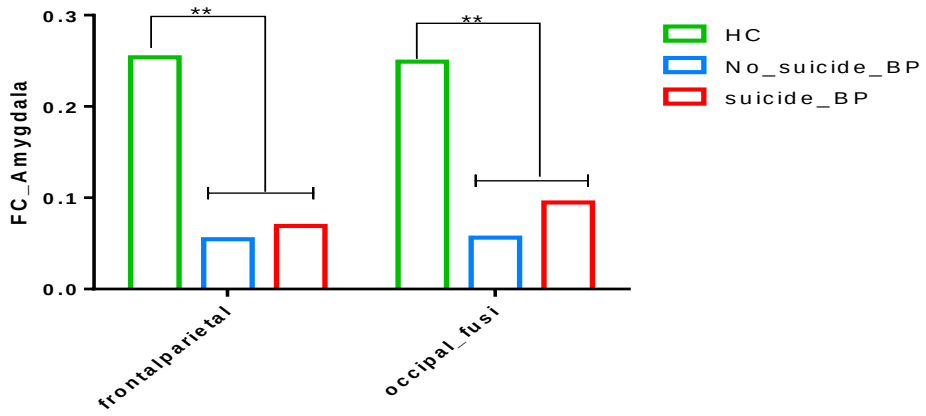
2.Furthermore, we recalculated the whole brain connectivity based on these ROIs using antidepressant dose as a covariate. After this processing, the results for the whole brain connectivity based on these ROIs are still similar with the previous. (see below)



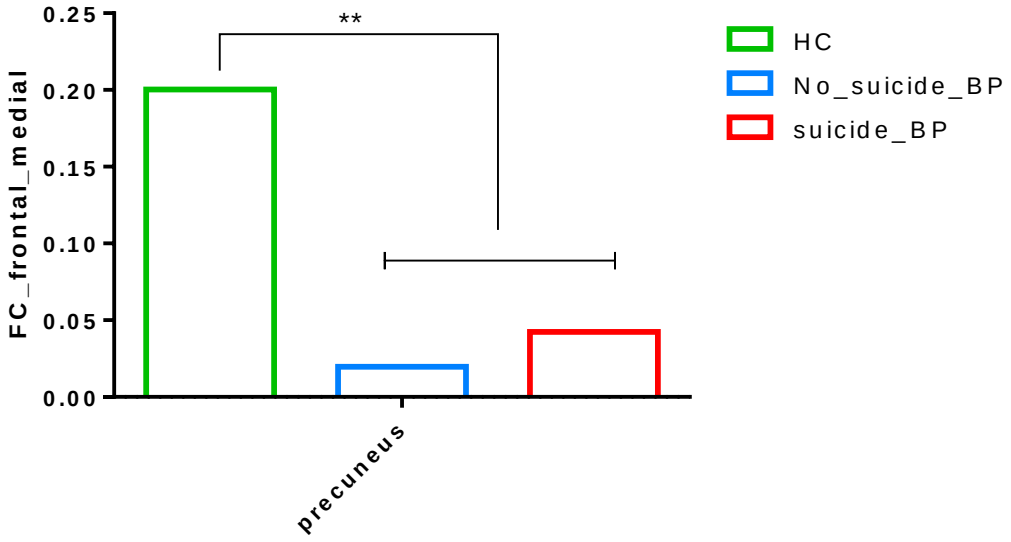
Supplementary Figure 1. A bar chart of the average Fisher's Z transformed functional connectivity values between the bilateral thalamus ROI and the frontal cortex among the subjects within each group.



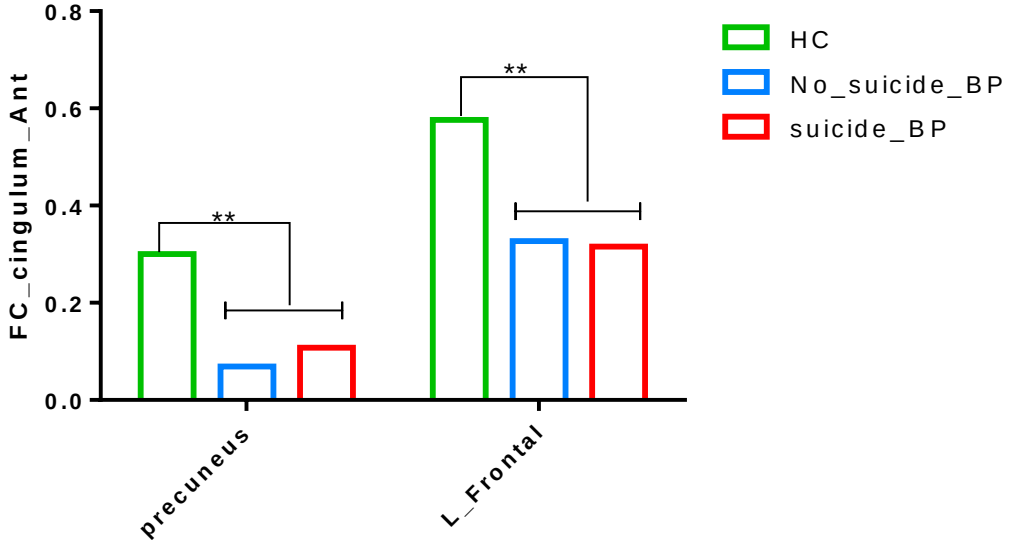
Supplementary Figure 2. A bar chart of the average Fisher's Z transformed functional connectivity values between the the bilateral frontal inferior gyrus and the temporal inferior gyrus among the subjects within each group. * <0.05, **<0.01



Supplementary Figure 3. A bar chart of the average Fisher's Z transformed functional connectivity values between the bilateral amygdala ROI and the clusters within frontalparietal and fusiform gyrus among the subjects within each group.



Supplementary Figure 4. A bar chart of the average Fisher's Z transformed functional connectivity values between the bilateral medial frontal cortex ROI and precuneus among the subjects within each group.



Supplementary Figure 5. A bar chart of the average Fisher's Z transformed functional connectivity values between the bilateral anterior cingulate cortex ROI and the clusters within precuneus and frontal cortex among the subjects within each group.

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