Triple Network Model–Based Functional Dysconnectivity in Young People With Major Affective Disorders With or Without Current Suicidal Ideation

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Abstract

Background: The association between functional dysconnectivity in the triple networks—the default mode network (DMN), salience network (SN), and frontoparietal network (FPN)—and current suicidal ideation (CSI) in young people with major affective disorders remains unclear.

Methods: This study included 158 young people (mean age: ~18 years) with major affective disorders (101 with CSI and 57 without CSI) and 64 age- and sex-matched healthy control individuals. Both major depressive disorder and bipolar disorder were diagnosed according to the *DSM-5* criteria. CSI was defined by a Montgomery–Åsberg Depression Rating Scale suicide item score of ≥2. All participants underwent resting-state functional connectivity magnetic resonance imaging. Seed-based connectivity analyses were performed, with adjustment for diagnosis and prior suicide attempts.

Results: Compared with the non-CSI group, the CSI group exhibited hyperconnectivity between the anterior insula (SN) and hippocampus as well as between the posterior parietal cortex (FPN) and rectus gyrus (DMN) and hypoconnectivity between the amygdala (SN) and cerebellum crus II. Both the CSI and non-CSI groups exhibited increased functional connectivity between the posterior parietal cortex and emotional perception-related regions, specifically, the superior and middle temporal gyri, compared with healthy control individuals.

Discussion: Suicidality is associated with extensive and pronounced functional dysconnectivity in the SN, FPN, and DMN in young people with major affective disorders.

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Globally, suicide rates have increased by 60% over the last 50 years, with more than 1 million lives lost since 2020.[1,2] According to the World Health Organization, the highest age-standardized incidence of suicide in US young people (preadolescents, adolescents, and young adults) was 15.5 per 100,000 boys. The rate of suicide in girls increased by 6.7% from 2007 to 2017, whereas that in boys increased by 3.8% from 2009 to 2020.[2] In Taiwan, suicide is currently the second leading cause of death among individuals aged 15–24 years.[1,3] The incidence of suicide doubled within 2 decades, increasing from 4.0 per 100,000 individuals in 2000 to 10.7 per 100,000 individuals in 2022.[1,3] The increasing suicide rate among young people worldwide may be driven by a complex interplay of biopsychosocial adversities that remains incompletely understood.

Suicidal ideation is defined by the National Institute of Mental Health as "thinking about, considering, or planning suicide."[4] Epidemiologic data indicated that approximately 20% of high school students in the US have seriously contemplated suicide, positioning adolescents as the age group with the highest prevalence of suicidal ideation.[4] A Taiwan study involving 2,835 college students found that 9% of male and 12% of female participants reported at least 1 suicide attempt (SA) within the preceding year.[5] The Taiwan Ministry of Health and Welfare reported that up to 30% of young people who were recruited in the youth mental health support program experienced current suicidal thoughts.[6]

Functional dysconnectivity in the triple networks—the default mode network (DMN), salience network (SN), and frontoparietal network (FPN)—has been implicated in the pathomechanisms underlying

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Clinical Points

- Current suicidal ideation was related to hyperconnectivity between the salience network and hippocampus, as well as between frontoparietal and default mode networks.
- Current suicidal ideation was associated with the hypoconnectivity between the salience network and cerebellum crus II.
- Youth with current suicidal ideation exhibited extensive and pronounced functional dysconnectivity in the triple networks compared to those without.

suicidality in adults.[7,8] The DMN contributes to inwardly directed cognition and ruminative processing; the FPN regulates working memory, executive functions, and cognitive control; and the SN integrates attentional processes by evaluating internal and external stimuli to guide behavioral responses.[7,8] However, because brain development is incomplete in young individuals, very few neuroimaging studies have investigated functional dysconnectivity in the triple networks among young people with current suicidal ideation (CSI).[9–11] Ren et al conducted resting-state functional connectivity (FC) magnetic resonance imaging (MRI) in 61 patients with depression (age: ~25 years) with CSI or a recent SA and 35 patients with depression without CSI.[9] The researchers discovered that FCs in the FPN were significantly higher in patients with CSI or recent SA than in patients without CSI and healthy control individuals.[9] The Texas Resilience Against Depression Study, which involved 43 young people aged ~19.3 years, including 16 with CSI, reported that CSI was particularly associated with DMN dysfunction.[10] Chin Fatt et al[11] associated a greater CSI severity with lower FCs between limbic regions (eg, the amygdala) and the DMN and FPN. Ho et al analyzed network FC coherence in 28 young people with depression with CSI (CSI group), 21 with depression without CSI (non-CSI group), and 21 healthy young people; the researchers observed that only the CSI group exhibited reduced network FC coherence in the anterior DMN (medial prefrontal cortex–seeded) and SN (anterior insula–seeded) compared with the findings in the control group.[12] A resting-state FC MRI study involving 102 college students found that participants with high suicidality had a markedly lower FC between the right frontal pole and the bilateral inferior frontal cortex than did those with low suicidality.[13] However, a major limitation of the aforementioned studies was a lack of adjustment for previous SAs during the investigation of the association between CSI and functional dysconnectivity. This limitation complicated efforts toward determining the direct contribution of CSI to network dysfunction.

In this study, we analyzed the effect of CSI, defined by a Montgomery–Åsberg Depression Rating Scale (MADRS) item 10 score of ≥2 (weary of life; only fleeting suicidal thoughts),[14] on FCs in the triple networks—the DMN, SN, and FPN—in young people with major affective disorders. The statistical model was adjusted for a history of SAs. We hypothesized that young people with major affective disorders with CSI would exhibit more widespread and pronounced functional dysconnectivity in the triple networks than would those with major affective disorders without CSI and healthy individuals.

METHODS

Participants

In this study, we included 158 youths aged between 14 and 24 years with major affective disorders—namely, bipolar disorder and major depressive disorder—and 64 healthy youths for neuroimaging analysis. Patients were divided into the two subgroups based on the presence of CSI: the CSI and non-CSI groups. CSI was defined according to MADRS item 10 scores ≥2.[14] Those who scored 1 on MADRS item 10 were excluded from the present study owing to the ambiguity of suicidal symptoms. Patients were diagnosed with either bipolar disorder or major depressive disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria. We excluded patients with a lifetime history of schizophrenia, alcohol and substance use disorders, neurodevelopmental disorders, and organic mental disorders. All patients continued their medications during MRI and cognitive examinations. Exclusion criteria for healthy controls included any current or past psychiatric disorders. The Institutional Review Board of Taipei Veterans General Hospital approved this study and conducted it in accordance with the Declaration of Helsinki. All participants and their parents of adolescents gave their written informed consent.

Image Acquisition

High-resolution anatomical and resting-state functional MRI data were acquired on a 3-Tesla scanner (GE Healthcare Life Sciences, Little Chalfont, UK) equipped with a quadrature head coil at Taipei Veterans General Hospital. Whole-brain T1-weighted structural images were collected via a 3D magnetization-prepared rapid acquisition gradient echo sequence using the following parameters: repetition time (TR) = 12.2 ms, echo time (TE) = 5.2 ms, flip angle = 12°, 168 axial slices, field of view = 256 × 256 mm, matrix size = 256 × 256, and slice thickness = 1 mm. Resting-state functional images were obtained using a T2*-weighted gradient-echo, echo-planar imaging sequence (TR = 2500 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.5 × 3.5 × 3.5 mm, 43 axial slices). Each participant underwent 200 functional volumes while

keeping their eyes closed, maintaining a neutral mental state, and refraining from movement or sleep.

Image Data Preprocessing

Data preprocessing was performed using the CONN toolbox.[15] First, realignment and unwarping were conducted in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) by coregistering all scans to the first volume of the first session using a 6-parameter rigid-body transformation, followed by B-spline interpolation to address motion artifacts. Slice-timing correction was then performed with sinc interpolation to compensate for interleaved bottom-up acquisition. Potential outlier volumes were identified using Artifact Detection Tools,[16] defining outliers as scans with framewise displacement exceeding 0.9 mm or global blood oxygen level-dependent (BOLD) signal changes exceeding 5 SDs. A mean BOLD image was subsequently generated for each participant by averaging all non-outlier scans. Both functional and anatomical images were normalized to Montreal Neurological Institute (MNI) space and segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF) tissue classes via the unified segmentation and normalization algorithm in SPM12. This direct normalization method[17] employed the default IXI-549 tissue probability map template.[18,19] Functional data were then resampled to 2 mm isotropic voxels and spatially smoothed with an 8 mm full width at half maximum Gaussian kernel. A standard denoising pipeline[20] including regression of nuisance variables from WM and CSF time series, motion parameters and their first-order derivatives, outlier volumes, session effects and their first-order derivatives, and linear trends within each functional run. This procedure was followed by bandpass filtering of the BOLD time series in the 0.009–0.08 Hz range.

Seed-Based Connectivity

To examine the specific associations between CSI and triple network-based FCs, seed-based connectivity (SBC) analyses with the adjustment of sex, age, diagnosis, and SA history were conducted to map FC patterns with specific regions of interest (ROIs) from well-established resting-state networks. The selected ROIs included (1) the DMN, including medial prefrontal cortex, bilateral lateral parietal cortex, posterior cingulate cortex; (2) the SN, including anterior cingulate cortex (ACC), bilateral AI, bilateral rostral prefrontal cortex, bilateral supramarginal gyrus, and bilateral amygdala; and (3) the FPN, including bilateral dorsolateral prefrontal cortex and bilateral posterior parietal cortex (PPC). Fisher-transformed bivariate correlation coefficients were estimated using a weighted general linear model (GLM)[20] framework between each seed and every voxel in the brain, resulting in voxel-wise connectivity maps for each participant and seed. Finally, additional SBC analyses with further adjustments for nonsuicidal depressive symptoms (total MADRS scores minus MADRS item 10 scores) were performed to elucidate the independent effect of CSI on the triple network FCs.

Statistical Analysis

All statistical analyses were carried out using SPSS Version 25 (IBM Corp., Armonk, NY). One-way analysis of variance was used to assess group differences in continuous demographic and clinical variables, whereas Fisher χ^2 tests were used for categorical variables. A 2-tailed P value <.05 was deemed statistically significant. Group-level comparisons of SBC were performed via a GLM, controlling for age, sex, diagnosis, and SA history as covariates. Cluster-level inferences were derived using parametric statistics based on Gaussian random field theory,[21] employing a voxel-level threshold of $P < .005$ and a false discovery rate (FDR)–corrected threshold of $P < .05$. Pearson correlation coefficients were calculated to assess the associations between MADRS item 10 scores and peak voxel FC z values across all participants, with statistical significance set at $\alpha = .05$.

Data Availability

The datasets generated and analyzed during this study are not publicly available due to ethical regulations governing clinical trials in Taiwan. However, they can be obtained from the corresponding author upon reasonable request.

RESULTS

In all, 158 youths with major affective disorders, including 70 with bipolar disorder and 88 with major depressive disorder, were enrolled in the present study, without differences in age and sex (Table 1). Of youths with major affective disorders, 57 (36.1%) youths were classified as the non-CSI group, and 101 (63.9%) as the CSI group (Table 1). The CSI group was younger ($P < .001$) and scored higher in the MADRS ($P < .001$) compared to the non-CSI group (Table 1). The distribution of sex and diagnosis did not differ between the CSI and non-CSI groups (all $P > .05$), as shown in Table 1. The use of antidepressants was higher in the CSI group ($P = .032$), while the use of mood stabilizers was higher in the non-CSI group ($P = .001$) (Table 1). The use of atypical antipsychotics and the history of SAs did not differ between the CSI and non-CSI groups (all $P > .05$) (Table 1).

Table 2 and Figures 1–3 reveal the results of the SBC analyses, indicating significant group (CSI youths vs non-CSI youths vs healthy youths) differences in FC among several key brain regions. Table 2 and Figure 1 illustrate that youths with CSI showed increased FC between the

Table 1.

Demographic and Clinical Characteristics Between Groups

	Youths with major affective disorders (n = 158)	Control group (N = 64)	*P* value	Youths with major affective disorders (n = 158)		*P* value
				CSI group (N = 101)	Non-CSI group (N = 57)	
Age, mean (SD), y	18.8 (3.15)	17.9 (3.02)	.053	17.8 (3.02)	20.6 (2.58)	<.001
Sex, n (%)			.070			.721
Female	119 (75.3)	40 (62.5)		77 (76.2)	42 (73.7)	
Male	39 (24.7)	24 (37.5)		24 (23.8)	15 (26.3)	
Diagnosis, n (%)						.113
Bipolar disorder	70 (44.3)			40 (39.6)	30 (52.6)	
Major depressive disorder	88 (55.7)			61 (60.4)	27 (47.4)	
Psychotropic medications, n (%)						
Antidepressants	103 (65.2)			72 (71.3)	31 (54.4)	.032
Mood stabilizers	27 (17.1)			10 (9.9)	17 (29.8)	.001
Atypical antipsychotics	90 (57.0)			62 (61.4)	28 (49.1)	.135
Clinical symptoms						
Total MADRS scores, mean (SD)	21.9 (9.90)			26.93 (6.69)	13.05 (8.34)	<.001
MADRS suicidal item (item 10) scores, n (%)						<.001
0 (without current suicidal ideation)	57 (36.1)			0 (0.0)	57 (100.0)	
≥2 (with current suicidal ideation)	101 (63.9)			101 (100.0)	0 (0.0)	
2	49 (31.0)			49 (48.5)	0 (0.0)	
3	28 (17.7)			28 (27.7)	0 (0.0)	
≥4	24 (15.2)			24 (23.8)	0 (0.0)	
History of suicide attempt, n (%)	47 (29.7)			35 (34.7)	12 (21.1)	.073

Abbreviations: CSI = current suicidal ideation, MADRS = Montgomery-Åsberg Depression Rating Scale, SD = standard deviation.

left AI and the right hippocampus compared with the non-CSI group (peak MNI coordinate: 20, −16, −14; cluster size: 580; $P = .018$, FDR-corrected). Table 2 and Figure 2 demonstrate the FC differences seeded from the bilateral PPC. The CSI group exhibited increased FC between the left PPC and multiple regions compared with healthy youths, including the right superior temporal gyrus (STG) (68, −24, 2; cluster size: 580; $P = .013$) and the left middle temporal gyrus (MTG) (-58, −16, −14; cluster size: 503). Additionally, the CSI group showed greater FC between the left PPC and the right rectus gyrus (6, 14, -20; cluster size: 477) compared with the non-CSI group (Table 2; Figure 2). Both CSI and non-CSI groups demonstrated increased FC between the right PPC and the right STG (58, -10, -6; cluster size: 349; $P = .009$) compared with healthy youths (Table 2; Figure 2). Table 2 and Figure 3 showed that the CSI group exhibited decreased FC between the left amygdala and the right cerebellum crus II (2, −82, −34; cluster size: 1022; $P < .001$) compared with both the non-CSI group and healthy youths.

Supplementary Figure 1 shows significant relationships between MADRS item 10 scores and identified FCs among the study cohort. Panel A demonstrates a positive correlation between MADRS item 10 scores and FC between the left AI and right hippocampus ($r = 0.26$, $P < .001$), indicating enhanced connectivity with increasing suicidal ideation severity (Supplementary Figure 1A). Panel B shows a positive correlation between MADRS item 10 scores and FC between the left PPC and right rectus ($r = 0.27$, $P < .001$) (Supplementary Figure 1B). Panel C reveals a negative correlation between MADRS item 10 scores and FC between the left amygdala and right cerebellum crus II ($r = −0.27$, $P < .001$), indicating reduced connectivity with increasing suicidal ideation severity (Supplementary Figure 1C). The findings from the dimensional analyses were consistent with our findings from the categorical analyses (Table 2; Figures 1, 2, and 3).

Supplementary Figures 1 and 2 present SBC analyses additionally adjusted for nonsuicidal depressive symptoms. The significant between-group differences in FCs between the left AI and right hippocampus, and between the left amygdala and right cerebellar crus II, persisted after this adjustment. However, the between-group differences in bilateral PPC–seeded FCs were no longer significant after adjusting for nonsuicidal depressive symptoms.

DISCUSSION

Our findings support the hypothesis that young people with major affective disorders with CSI would exhibit more widespread and pronounced functional dysconnectivity in the SN, FPN, and DMN than would those with major affective disorders without CSI and healthy young people. Specifically, the CSI group exhibited the largest increase in FC between the bilateral PPC (FPN) and the right STG as well as between the left

Table 2.

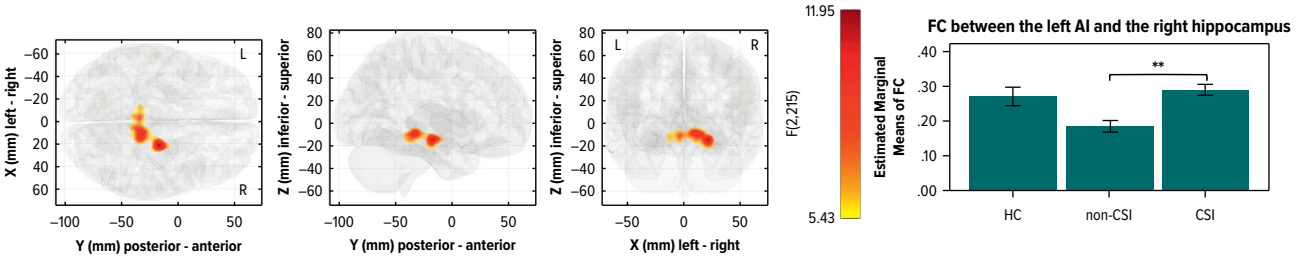
Seeds Showing Significant Functional Connectivity Differences Between Patients With and Without Current Suicidal Ideation and Controls

Seed region	AAL	Peak MNI coordinate			Cluster size	Cluster *P* value (FDR corrected)	Post hoc
		x	y	z			
L. AI	R. hippocampus	20	–16	–14	580	.018	CSI > nCSI
L. PPC	R. STG	68	–24	2	580	.013	CSI > HC
	L. MTG	–58	–16	–14	503		CSI > HC; nCSI > HC
	R. rectus	6	14	–20	477		CSI > nCSI
R. PPC	R. STG	58	–10	–6	349	.009	CSI > HC; nCSI > HC
L. amygdala	R. cereb. crus II	2	–82	–34	1022	< .001	CSI < HC; CSI < nCSI

Abbreviations: AI = anterior insula, cereb = cerebellum, AAL = automated anatomical labeling, CSI = patients with current suicidal ideation, FDR = false discovery rate, HC = healthy controls, L = left, MNI = Montreal Neurological Institute, MTG = middle temporal gyrus, nCSI = patients without current suicidal ideation, PPC = posterior parietal cortex, R = right, STG = superior temporal gyrus.

Figure 1.

Functional Connectivity Differences Seeded from the Left Anterior Insula Across Groups[a]



[a]Significant functional connectivity differences were observed with seed regions in the left anterior insula, controlling for sex, age, diagnosis, and history of suicide attempts as covariates. Results were corrected for multiple comparisons using the false discovery rate (FDR) method. The color bar represents the *F* value associated with the contrast. Bar charts on the right illustrate group differences in functional connectivity between the seed region and peak voxel, as determined by post hoc analyses (Bonferroni corrected). Error bars represent standard error of the mean.

**$P < .01$.

Abbreviations: AI = anterior insula, CSI = patients with current suicidal ideation, FC = functional connectivity, HC = healthy controls, non-CSI = patients without current suicidal ideation.

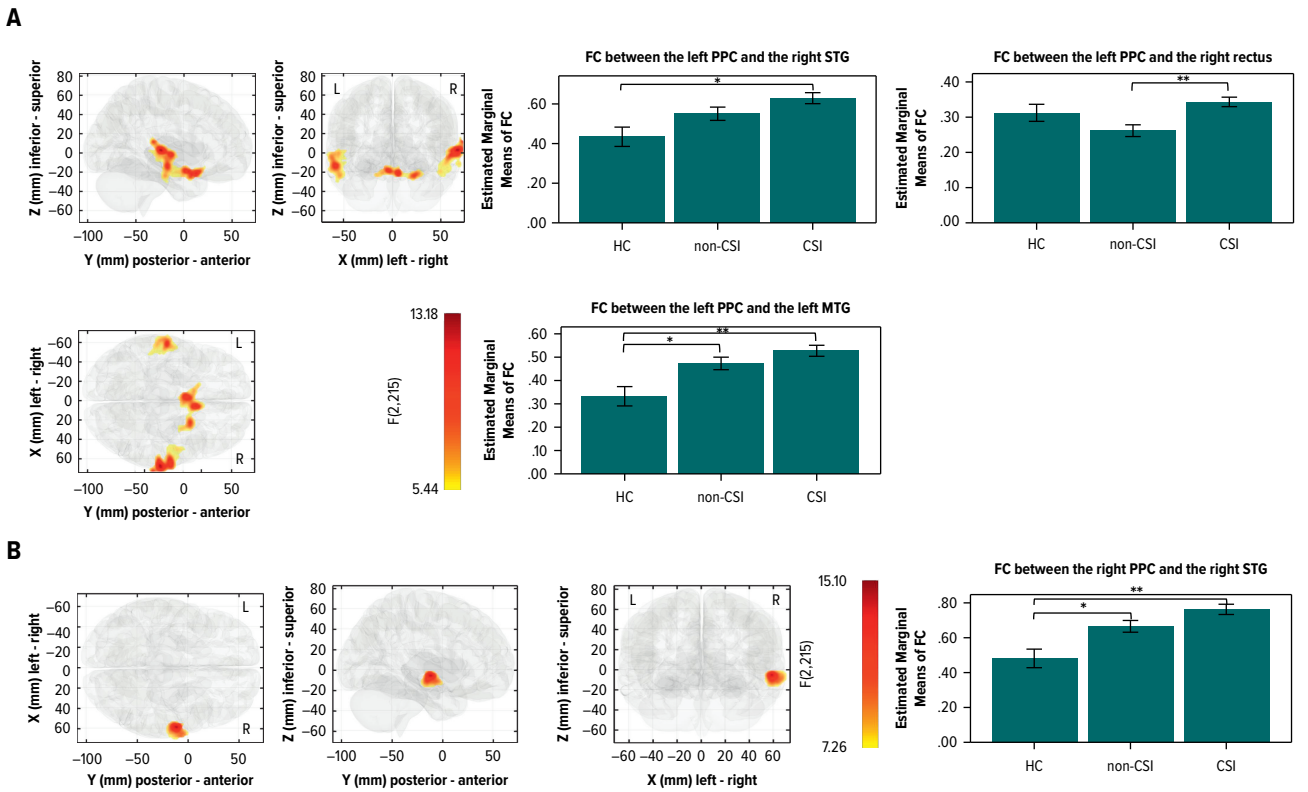
PPC and both the left MTG and the right rectus gyrus (DMN). Furthermore, compared with the non-CSI group, the CSI group exhibited increased FC between the left AI (SN) and the right hippocampus as well as reduced FC between the left amygdala (SN) and the right cerebellum crus II. After adjusting for nonsuicidal depressive symptoms, between-group differences in left AI- and left amygdala-seeded FCs remained significant, whereas those in bilateral PPC-seeded connectivity were no longer significant.

Key differences in FCs between the CSI and non-CSI groups were as follows: the CSI group exhibited a higher FC between the left AI (SN) and the right hippocampus, a higher FC between the left PPC (FPN) and the right rectus gyrus (DMN), and a lower FC between the left amygdala (SN) and the right cerebellum crus II than did the non-CSI group. These findings highlighted pronounced functional dysconnectivity in the CSI group, not only in the triple networks (SN, FPN, and DMN) but also in the memory (hippocampus) and cerebellar networks. A magnetoencephalography study involving 27 patients with major depressive disorder indicated that suicidality was particularly associated with functional dysconnectivity in the left hippocampus, left AI, and bilateral dorsolateral prefrontal cortex.[22] Li et al found that a reduction in suicidal symptoms after 90,000 pulses of intermittent theta-burst stimulation on the subgenual ACC (measured using the Beck Scale for Suicidal Ideation) was associated with reduced FC between the insula and hippocampus in adults with major depressive disorder and CSI.[23] This finding aligns with our result of increased FC between the left AI and the right hippocampus in young people with CSI. Chen et al observed a higher FC in the bilateral hippocampus in adults with depression and CSI than in those without CSI.[24]

Despite its location at the most medial margin of the inferior frontal lobe and its role as a DMN component, the

Figure 2.

Functional Connectivity Differences Seeded from the Bilateral Posterior Parietal Cortex Across Groups[a]



[a]Significant functional connectivity differences were observed with seed regions in the (**A**) left posterior parietal cortex and (**B**) right posterior parietal cortex, controlling for sex, age, diagnosis, and history of suicide attempts as covariates. Results were corrected for multiple comparisons using the false discovery rate (FDR) method. The color bar represents the *F* value associated with the contrast. Bar charts on the right illustrate group differences in functional connectivity between the seed region and peak voxel, as determined by post hoc analyses (Bonferroni corrected). Error bars represent standard error of the mean.

*$P < .05$, **$P < .01$.

Abbreviations: CSI = patients with current suicidal ideation, FC = functional connectivity, HC = healthy controls, MTG = middle temporal gyrus, non-CSI = patients without current suicidal ideation, PPC = posterior parietal cortex, STG = superior temporal gyrus.

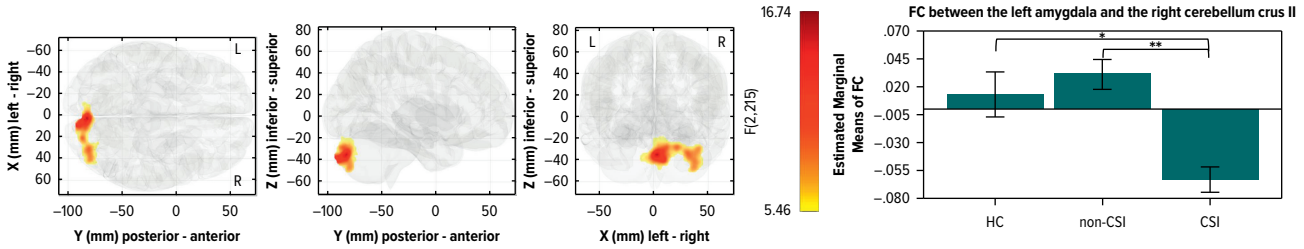
rectus gyrus has received relatively little attention in suicidality research.[25,26] Although its exact function remains unclear, a growing body of evidence suggests that it integrates multiple brain functions, such as emotion and reward processing, decision-making and cognitive control, and social functioning.[27,28] Yang et al reported that patients with a history of SAs exhibited a higher FC between the right inferior frontal orbital cortex and the left rectus gyrus than did those without a history of SAs.[25] Even after adjusting for a history of SAs, we found that young people with CSI exhibited a higher FC between the left PPC and the right rectus gyrus than did those without CSI; this finding may suggest that functional dysconnectivity between the FPN and the DMN contributes to not only previous SAs but also CSI.

Studies have implicated the cerebellum in the pathomechanisms underlying major affective disorders and suicidality.[29–31] Overwalle et al[29] demonstrated that the cerebellum crus II is specialized for social mentalization and emotional self-experiences.[29] Dysfunction in this region—for example, reduced FC with the amygdala (as observed in our study)—may align with the interpersonal theory of suicide, which posits that thwarted belongingness and perceived burdensomeness contribute to suicidal symptoms.[32] A structural MRI study reported that young adults with depression with CSI (mean age: ~27 years) had a significantly lower gray matter volume in the left cerebellum crus I/II than did those without CSI.[30] To the best of our knowledge, the present study is the first to provide evidence implicating reduced FC between the amygdala and the cerebellum crus II in the pathomechanism underlying youth suicidality.

We discovered that regardless of CSI, young people with major affective disorders exhibited common patterns of functional dysconnectivity, such as a higher FC between the left PPC (FPN) and the left MTG as well as between the right PPC and the right STG compared with the findings in healthy young people. Abnormal FCs in the STG and MTG may impair emotional information

Figure 3.

Functional Connectivity Differences Seeded from the Left Amygdala Across Groups[a]



[a]Significant functional connectivity differences were observed with seed regions in the left amygdala, controlling for sex, age, diagnosis, and history of suicide attempts as covariates. Results were corrected for multiple comparisons using the false discovery rate (FDR) method. The color bar represents the *F* value associated with the contrast. Bar charts on the right illustrate group differences in functional connectivity between the seed region and peak voxel, as determined by post hoc analyses (Bonferroni corrected). Error bars represent standard error of the mean.

*$P < .05$, ** $P < .01$.

Abbreviations: CSI = patients with current suicidal ideation, FC = functional connectivity, HC = healthy controls, non-CSI = patients without current suicidal ideation.

processing, particularly emotional perception, potentially increasing sensitivity to negative stimuli.[33–35] Using resting-state functional MRI to evaluate the regional homogeneity index, Sun et al demonstrated that patients with major depressive disorder exhibited higher regional homogeneity levels in the left STG and right MTG than did control individuals.[34] Liu et al reported that young adults (~30 years old) with first-episode major depressive disorder exhibited higher fractional amplitudes of low-frequency fluctuations in the right subgenual ACC and right MTG than did healthy adults.[35] A meta-analysis of data from 1141 youths and adults with major depressive disorder and 1242 healthy individuals indicated hyperactivity in the STG and MTG of patients, particularly youths, with depression.[36] Jankowski et al[37] associated negative self-perceptions and negative information processing biases, which are common symptoms of youth depression, with disrupted FC in the ACC, lateral temporal, and lateral parietal regions. This finding aligns with our finding of increased FC between the PPC and the STG and MTG in the CSI and non-CSI groups.

Finally, we further elucidated an independent effect of CSI in the triple network FCs after adjusting for nonsuicidal depressive symptoms in the SBC analyses. We found that the functional dysconnectivity seeded by the SN (both AI and amygdala) remained significant, while the dysconnectivity seeded by the FPN (bilateral PPC) did not. Our findings may suggest an independent relationship between CSI and SN dysfunction and a more crucial role for FPN dysfunction in nonsuicidal depressive symptoms. A 6-month follow-up resting-state FC MRI study of 40 adolescents with depression and CSI revealed that only an increase in SN, but not DMN and FPN, coherence was associated with subsequent reductions in suicidal ideation.[38] Sobczak et al[39] further identified that the AI-seeded functional dysconnectivity served as a neuromarker of suicide risk in euthymic patients with bipolar disorder. Evidence suggested that further studies would be required to elucidate whether the SN-targeted treatment strategies may be specifically beneficial for CSI.[8,38]

Our study has several limitations. First, all young people with major affective disorders continued their usual medications during MRI examinations, which was ethically justified given their high suicide risks. Previous studies have shown that the uses of psychotropic medications, including antidepressants, mood stabilizers, and atypical antipsychotics, may impact the FCs. For example, Li et al[40] demonstrated that antidepressant treatment decreased the FCs between the FPN and visual and subcortical regions, as well as between the DMN and subcortical regions. A longitudinal study involving 26 patients with bipolar disorder revealed that lithium was linked to decreases in mean connectivity in a network centered on the amygdala and left superior frontal cortex.[41] Neufeld et al indicated that olanzapine may stabilize FCs, particularly between the secondary visual network and the rest of the brain.[42] To validate our findings, future studies involving drug-free patients with and without CSI may be conducted under strictly controlled and clinically safe conditions. Second, we categorized young people with varying levels of CSI severity (MADRS item 10 scores ranging from 2 [fleeting suicidal thoughts] to ≥4 [suicidal thoughts are common, and suicide is considered a possible solution]) into a single group. Further investigation is required to determine whether different CSI severity levels are associated with different FC patterns in the triple networks. Finally, the cross-sectional design of this study precluded causal inferences from being made regarding the relationship between CSI and functional dysconnectivity in the triple networks.

In conclusion, hyperconnectivity between the PPC (FPN) and emotional perception-related regions, specifically the STG and MTG, was observed in young

people with major affective disorders, regardless of CSI. Furthermore, compared with young people without CSI, those with CSI exhibited increased FC between the left AI (SN) and the right hippocampus and between the left PPC (FPN) and the right rectus gyrus (DMN). Young people with CSI also exhibited hypoconnectivity between the left amygdala (SN) and the left cerebellum crus II. Our findings suggest that widespread and pronounced functional dysconnectivity in the SN, FPN, and DMN is associated with suicidality in young people with major affective disorders.

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Author Contributions: M-H Chen and Hsu designed the study; Cheng, Tu, and L-F Chen analyzed the neuroimaging data; M-H Chen, Huang, and Cheng drafted the manuscript; L-C Chen, and Bai enrolled the candidate patients and performed the literature reviews; all authors reviewed the final manuscript and agreed to its publication.

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Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Triple Network Model–Based Functional Dysconnectivity in Young People With Major Affective Disorders With or Without Current Suicidal Ideation

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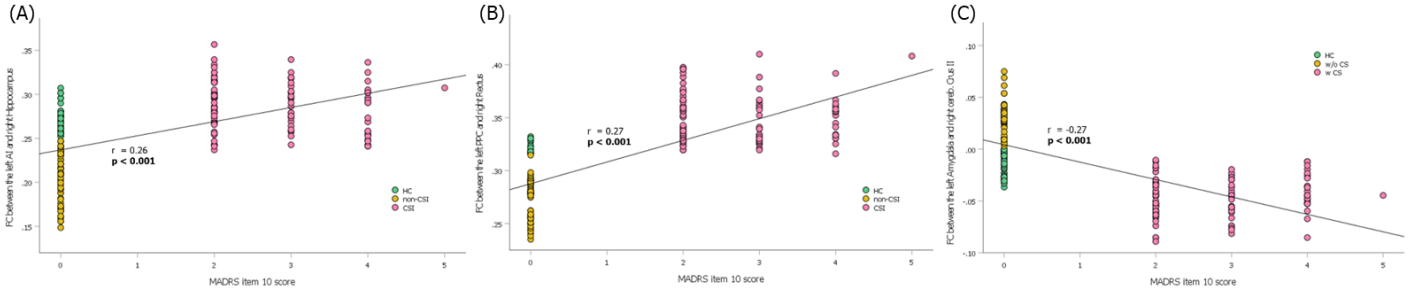
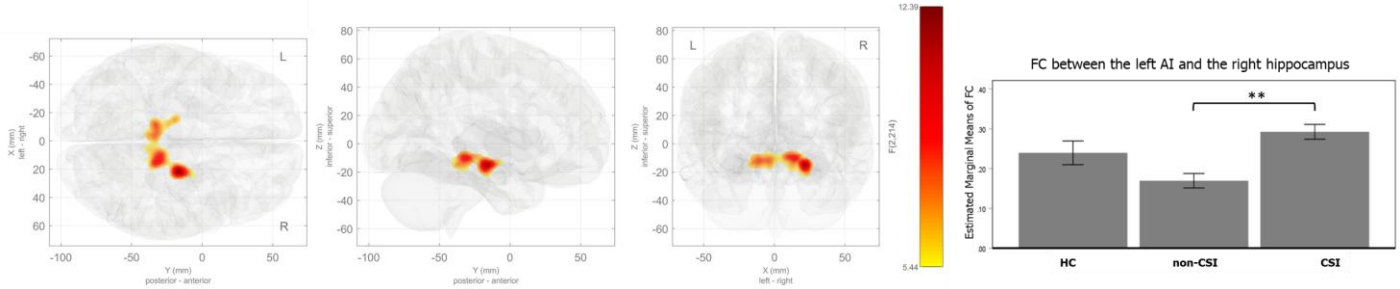
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Figure 1. Associations between suicidality severity and functional connectivity. Scatterplots depict the correlations between Montgomery–Åsberg Depression Rating Scale (MADRS) item 10 scores and functional connectivity values across all participants (n = 222). (A) Left anterior insula (salience network) to right hippocampus (r = 0.26, p < 0.001). (B) Left posterior parietal cortex (frontoparietal network) to right rectus (r = 0.27, p < 0.001). (C) Left amygdala (salience network) to right cerebellum Crus II (r = –0.27, p < 0.001). HC = healthy controls; non-CSI = patients without current suicidal ideation; CSI = patients with current suicidal ideation.

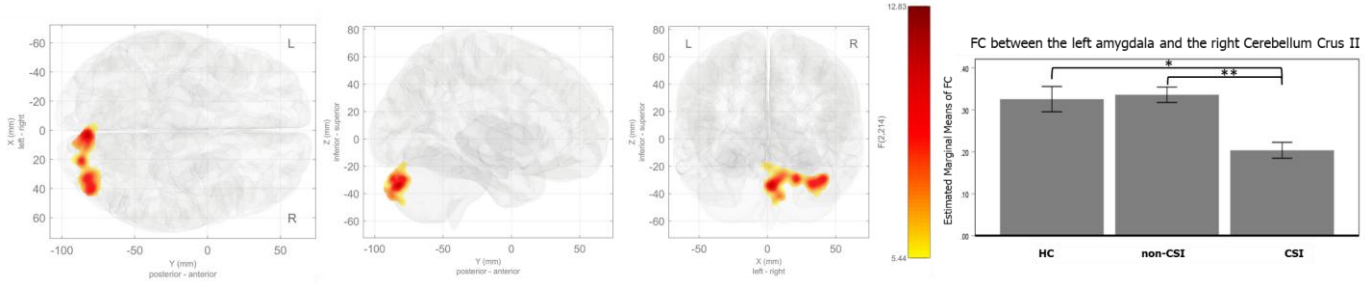


Supplementary Figure 2. Functional Connectivity Differences Seeded from the Left Anterior Insula Across Groups. Significant functional connectivity differences were observed with seed regions in the left anterior insula, controlling for sex, age, diagnosis, history of suicide attempts, and the non-suicidal depressive symptoms scores of MADRS as covariates. Results were corrected for multiple comparisons using the false discovery rate (FDR) method. The color bar represents the F-value associated with the contrast. Bar charts on the right illustrate group differences in functional connectivity between the seed region and peak voxel, as determined by post hoc analyses (Bonferroni corrected). Error bars represent standard error of the mean.



** p < 0.01
HC: healthy controls; non-CSI: patients without current suicidal ideation; CSI: patients with current suicidal ideation; AI: anterior insula; FC: functional connectivity.

Supplementary Figure 3. Functional Connectivity Differences Seeded from the Left Amygdala Across Groups. Significant functional connectivity differences were observed with seed regions in the left amygdala, controlling for sex, age, diagnosis, history of suicide attempts, and the non-suicidal depressive symptoms scores of MADRS as covariates. Results were corrected for multiple comparisons using the false discovery rate (FDR) method. The color bar represents the F-value associated with the contrast. Bar charts on the right illustrate group differences in functional connectivity between the seed region and peak voxel, as determined by post hoc analyses (Bonferroni corrected). Error bars represent standard error of the mean.



* p < .05, ** p < .01
HC: healthy controls; non-CSI: patients without current suicidal ideation; CSI: patients with current suicidal ideation; FC: functional connectivity.