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The neurobiology of suicide: The 'suicidal brain'

Edited by
Cicek Hocaoglu, E. Erdal Erşan and
Hilario Blasco-Fontecilla

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The neurobiology of suicide: The 'suicidal brain'

Topic editors

Cicek Hocaoglu — Recep Tayyip Erdoğan University, Türkiye
E. Erdal Erşan — Niğde Ömer Halisdemir University, Türkiye
Hilario Blasco-Fontecilla — Puerta de Hierro University Hospital

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Table of contents

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Xenia Gonda,
Semmelweis University, Hungary

*CORRESPONDENCE
Cicek Hocaoglu
✉ cicekh@gmail.com

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Editorial: The neurobiology of suicide: the 'suicidal brain'

Cicek Hocaoglu*

Department of Psychiatry, Recep Tayyip Erdogan University, Rize, Türkiye

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suicide, neurobiology, biomarker, suicidal behavior, suicidal brain

Editorial on the Research Topic
The neurobiology of suicide: the 'suicidal brain'

Suicide is a growing public health problem (1, 2). It can be seen in a wide range of people, from mentally healthy individuals who react to challenging living conditions to patients with severe mental disorders (3–5). Suicide has complex biological, social, and psychological risk factors and a multidimensional clinical presentation (6, 7). Recent studies have revealed the complexity underlying the neurobiological mechanisms of suicide (8–12). This Research Topic includes 10 studies examining the neurobiological causes of suicidal behavior. In the first article, Jiang et al. investigated the relationship between plasma inflammatory cytokine levels and changes in brain white matter (WM) integrity in patients with bipolar disorder who attempted suicide. Although no significant relationship was found between plasma inflammatory cytokines and WM integrity in the study, the increase in IL-6 levels was remarkable. The results of this study may provide a scientific basis for understanding abnormal immunological and neuroimaging changes in the possible mechanisms of suicidal behavior in patients with bipolar disorder (Jiang et al.). Secondly, Genis-Mendoza, Dionisio-García, et al. examined increased cortisol levels and number of suicide attempts and its relationship with depression. In this study, plasma cortisol levels were found to be high in individuals with depression and two or more suicide attempts. The authors stated that cortisol levels can be taken into account in people who attempt suicide and can be evaluated as a marker in the prevention of this global problem (Genis-Mendoza, Dionisio-García, et al.). In the third article, Kim et al. examined impaired oxygenation of the prefrontal cortex by functional near-infrared spectroscopy (fNIRS) during a verbal fluency task in young adults with major depressive disorder and suicidal behavior. In this study, it is noteworthy that a significantly impaired prefrontal oxygenation was obtained, especially in the right ventrolateral prefrontal cortex (VLPFC) in major depressive disorder (MDD) patients with suicidal tendencies. Impaired prefrontal oxygenation during cognitive execution may serve as a diagnostic biomarker for suicidality in young adult patients with MDD (Kim et al.). In a systematic review, Genis-Mendoza, Hernández-Díaz, et al. examined the relationship between TPH1 polymorphisms and the risk of suicidal behavior. The authors reported that the A218C polymorphism of the TPH1 gene may be a possible risk factor for suicide as a result of the study designed as an updated meta-analysis of 18.398 individuals (Genis-Mendoza, Hernández-Díaz, et al.). In the fifth article, Li X. et al. examined changes in whole-brain gray matter volumes (GMVs) before and after electroconvulsive therapy (ECT) in adolescents with MDD and suicidal ideation. The authors reported increased GMV in the right superior frontal gyrus and right superior temporal gyrus after ECT. They also reported that frontal-temporal-precuneus structure

changes may be a potential cause of depressive and suicidal symptoms in adolescents (Li X. et al.). In the sixth study, Li J. et al. examined the associations between anxiety, depression, and risk of suicidal behavior in Chinese medical school students. The authors emphasized the importance of screening for anxiety and depressive symptoms when assessing the risk of suicidal behavior and reducing anxiety in addition to depressive symptoms in treatment (Li J. et al.). In this review, Dobbertin et al. evaluated the current results of MRI studies examining the neuroimaging changes of the suicidal brain and its relevance to practice. The authors reported that there were morphological changes in brain neuroimaging studies, especially in the frontolimbic network, and there was evidence pointing to deterioration in cognitive functions (Dobbertin et al.). In the eighth article, Koseki et al. examined a pharmacovigilance approach to assess the occurrence of suicidal events induced by antiepileptic drugs using the Japanese adverse drug event report database. The increased suicidality rate after antiepileptic drug (AED) therapy is controversial. The authors suggested that young women using more than one antiepileptic drug especially should be warned about suicidal behavior in the first months of treatment (Koseki et al.). In the ninth article, Tsiouris and Flory compared the downregulation of cyclic adenosine monophosphate levels in leukocytes of hibernating black bears with the findings of cyclic adenosine monophosphate reported in major depressive disorder. It has been reported in previous studies that cyclic adenosine monophosphate (cAMP) levels in lymphoblasts and leukocytes of patients with major depressive disorder (MDD) are downregulated compared to controls. Similarities have been noted between the neurobiological changes associated with MDD in humans and many conditions associated with mammalian hibernation. The authors noted that they resemble neurobiological findings associated with hypometabolism (metabolic depression) observed during mammalian hibernation and reported during MDD (Tsiouris and Flory). In the last study, da Silva Schmidt et al. sought an answer to the question of whether glutathione could be a biomarker for suicide risk in women 18 months after birth. In this study, it was concluded that there is a relationship between low glutathione levels in the postpartum period and suicide risk. The authors noted that glutathione may be a potential biomarker or etiological factor in women at moderate to high risk of suicide (da Silva Schmidt et al.).

We would like to thank Frontiers for their interest and support in the planning of our Research Topic. We would also like to thank all the authors and referees who contributed to the preparation of the Research Topic.

The pandemic that affected our world during our Research Topic changed our lives. Then, a short time ago, an earthquake disaster that took place in our country, Turkey, increased our suffering even more. I respectfully commemorate all the souls who passed away in both life events and the significant stress created because of them. Continuing to work, produce, and contribute to science without losing hope and increasing solidarity despite all difficulties should be among our top priorities.

In conclusion, I think that the Research Topic provides an assessment of neurobiological risk factors for suicidal behavior that will play an important role in the prevention of suicide, as well as in the regulation of treatment algorithms and in the follow-up of treatment.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Altered Levels of Plasma Inflammatory Cytokines and White Matter Integrity in Bipolar Disorder Patients With Suicide Attempts

Xiaowei Jiang[1†], Yingrui Guo[2†], Linna Jia[2], Yue Zhu[2], Qikun Sun[3], Lingtao Kong[2], Feng Wu[2] and Yanqing Tang[2,4]*

[1] Brain Function Research Section, Department of Radiology, The First Affiliated Hospital of China Medical University, Shenyang, China, [2] Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, China, [3] Department of Radiation Oncology, The First Affiliated Hospital of China Medical University, Shenyang, China, [4] Department of Geriatric Medicine, The First Affiliated Hospital of China Medical University, Shenyang, China

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Takahiro A. Kato, Kyushu University, Japan

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Hisaomi Suzuki, National Hospital Organization (NHO), Japan

***Correspondence:**
Yanqing Tang
tangyanqing@cmu.edu.cn

[†]These authors have contributed equally to this work and share first authorship

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Objective: Bipolar disorder (BD) has a higher lifetime rate of suicide attempts (SA) than other psychiatric disorders. Furthermore, BD patients with SA (BD + S) are prone to a worse quality of life. However, the pathophysiology of BD + S is poorly understood. To further reveal the potential mechanisms of BD + S, abnormalities in peripheral plasma inflammatory cytokines and brain white matter (WM) in BD + S, as well as the correlation between them are investigated.

Methods: We tested the levels of TNF-α, IL-1β, and IL-6 in peripheral plasma and collected the diffusion tensor imaging (DTI) data from 14 BD + S, 24 BD patients without SA (BD-S), and 26 healthy controls (HCs). The three groups were matched by age and gender. The levels of TNF-α, IL-1β, and IL-6 were detected by Luminex multifactor detection technology, and the fractional anisotropy (FA) values were employed to depict the alterations of WM. Partial correlation analyses were conducted to detect correlations between levels of TNF-α, IL-1β, and IL-6 and changes of WM, and the relationships between severity of clinical symptoms, including scores of HAMD-17 and YMRS, and cytokine levels or FA values in all groups.

Results: For plasma inflammatory cytokines, there was no significant difference in their levels except for IL-6 among the three groups. *Post-hoc* analyses revealed that increased IL-6 level was only detected in BD + S ($p < 0.05$, Bonferroni correction). For DTI, BD + S showed specifically decreased FA in the bilateral middle cerebellar peduncle and the left superior corona radiata compared to BD-S and HCs ($p < 0.05$, Bonferroni correction). Additionally, both BD + S and BD-S groups revealed decreased FA in the bilateral body and genu of corpus callosum (CC) compared to HCs ($p < 0.05$, Bonferroni correction). No significant correlation between plasma inflammatory cytokines and WM integrity was found. In the BD + S group, we found negative correlation between the

scores of YMRS and FA values of the left middle cerebellar peduncle (r = −0.74, p = 0.035).

Conclusion: The inflammation and impaired WM integrity may provide a scientific basis to understand the potential mechanisms of BD + S.

Keywords: bipolar disorder, suicide attempts, inflammatory cytokine, diffusion tensor imaging, TNF-α, IL-1β, IL-6, white matter integrity

INTRODUCTION

Among psychiatric disorders, bipolar disorder (BD) has the highest suicide incidence (1–4). A recent meta-analysis demonstrated that the lifetime prevalence of suicide attempts (SA) in BD was 33.9% (5), which is at least 20 times higher than the general population (6). Epidemiological studies also showed that approximately 20–60% of BD patients had attempted suicide in their lifetime, and approximately 4–19% died due to suicide (7). In addition, BD patients with SA (BD + S) have a worse quality of life (8) and are peculiarly prone to poor functional outcomes (9). However, the pathophysiology of suicide in BD continues to be poorly understood.

Increasing evidence suggests an important role of cell-mediated immune activation and chronic inflammation in the pathophysiology of BD and SA. For example, previous studies consistently showed both higher TNF-α and IL-6 levels were associated with BD (10–12). Similarly, abnormally higher levels of TNF-α, IL-1β, and IL-6 were shown in the SA population (13–15). However, limited research has focused on the immune system impairment of BD + S. To our knowledge, only one study has investigated plasma inflammatory cytokines of BD + S and found increased IL-1β expression (16). The above studies provide a perspective of immunology to understand BD + S.

Another common sign of abnormalities is in white matter (WM). Studies using diffusion tensor imaging (DTI), which is the commonly used neuroimaging method to investigate the impairment of WM (17), found that BD + S exhibited lower fractional anisotropy (FA) in the uncinate fasciculus (UF), the ventral frontal cortex, and the cerebellar regions than BD without SA (BD-S) and healthy controls (HCs) (18, 19). Additionally, lower FA in the orbital frontal cortex, the middle portion of the forceps minor, and the anterior and posterior portion of the right cingulum bundle were also found in BD + S compared to BD-S (20, 21). Furthermore, BD + S showed a smaller WM volume (22) and declined FA values in the corpus callosum (CC), which may be related to suicidality (23). In addition, increased white matter hyperintensities have been consistently reported in BD + S (24–27). In summary, BD + S may have the impairment of WM microstructure.

Moreover, peripheral plasma inflammatory cytokines are closely related to the aberrant WM (28–30). They could pass the blood-brain barrier to activate microglia, which may impair brain cells, including the myelin sheath – an essential component of WM (17). Although evidence has suggested the important roles of plasma inflammatory cytokines and WM impairment in BD + S, the complicated and interwoven relationship between plasma inflammatory cytokines and WM integrity in BD + S has rarely been investigated. Therefore, we combined the plasma levels of inflammatory cytokines with the WM microstructure method to explore the immunologic and neuroimaging changes in BD + S and the relationship between them to further reveal the potential mechanisms of BD + S.

MATERIALS AND METHODS

Subjects

Sixty-four subjects aged from 15 to 47 years old were included in the study. Among them, 14 were BD + S, 24 were BD-S, and 26 were HCs; the three groups were age and gender matched. BD patients were recruited from the Department of Psychiatry, the First Affiliated Hospital of China Medical University. HCs were recruited by advertisement. All subjects were provided with written informed consent after a detailed description of the study. If they were juveniles, further consent was provided by their parents/legal guardians. The study was authorized by the Institutional Review Board of the First Affiliated Hospital of China Medical University.

For adult patients, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders (SCID-I) was used to determine whether the patients met the criteria of BD (31). For adolescent and child patients, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) was used to determine whether the patients met the criteria of BD (32). All the BD patients were free of any other Axis I and Axis II disorders. HCs did not have a history of Axis I or Axis II disorders themselves or in their first-degree relatives. The severity of clinical symptoms was evaluated by using the 17-item Hamilton Rating Scale for Depression (HAMD-17) (33) and the Young Mania Rating Scale (YMRS) (34).

In the study, SA was defined as a self-destructive act with the purpose to die at least one attempt in one's lifetime (35). A self-made scale based on the definition of SA and excluded the self-injurious behavior without suicidal purpose. The reason for exclusion of the self-injurious behavior is that it may be a confounder to obscure the potential mechanism of SA.

Assessment of diagnosis, severity of symptoms, and SA were completed by at least one researcher who had passed a consistency test for clinical assessment.

Subjects were excluded if they were on anti-inflammatory medications or had any somatic diseases which may cause potential brain structural changes such as neurological disorders, uncontrolled hypertension, uncontrolled diabetes, substance or alcohol abuse, a history of head trauma resulting in more

than 5 min of unconsciousness, or any magnetic resonance imaging (MRI) contraindications. All the subjects underwent a general physical examination which showed no evidence of ongoing infection.

Plasma Inflammatory Cytokines Analysis

Blood samples were collected between 10:00 a.m. and 2:00 p.m., with EDTA as an anticoagulant, following standard procedures. After centrifugation at 2,000 rpm for 10 min, the plasma samples were kept at −80°C for further analysis. The plasma inflammatory cytokine levels were measured by the immunoassay (Human Magnetic Luminex Assay, Human Premixed Multi-Analyte Kit, R&D Systems, Inc., Minneapolis, MN, United States). In this process, a Human magnetic premixed microparticle cocktail of antibodies (Kit Lot Number L120614) was used to magnetically label the samples.

Magnetic Resonance Imaging Acquisition

MRI data were collected by the GE Signa HDX 3.0T scanner at the Department of Radiology, the First Affiliated Hospital of China Medical University. DTI scanning was performed using the following parameters: TR/TE = 17,000/86 ms, field of view = 24 cm × 24 cm, imaging matrix = 120 × 120, slice number = 65, slice thickness = 2 mm, slice spacing = 2 mm, acquired along 26 directions (25 with b = 1,000 s/mm^2 and 1 with b = 0), and voxel size = 2 mm^3. Subjects were told to close their eyes and relax while remaining awake throughout scanning.

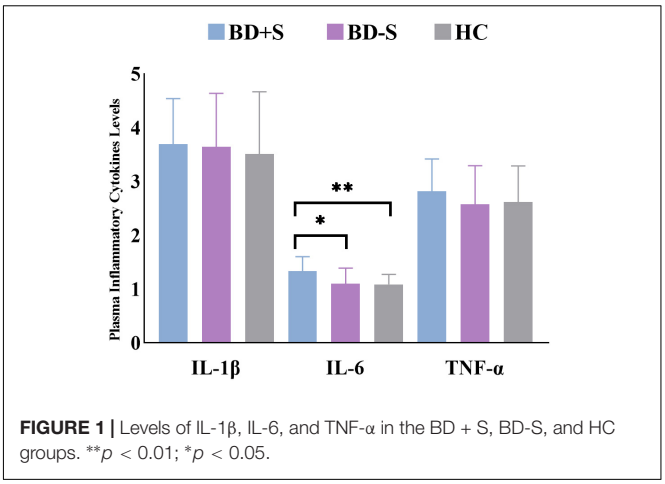

FIGURE 1 | Levels of IL-1β, IL-6, and TNF-α in the BD + S, BD-S, and HC groups. $^{**}p < 0.01$; $^{*}p < 0.05$.

Image Processing

Pipeline for Analyzing braiN Diffusion imAges software[1] was used to process DTI data. For each subject, the voxel-wise

[1]http://www.nitrc.org/projects/panda

TABLE 1 | Demographic characteristics and cytokines levels of subjects.

Variables	HC (n = 26)	BD + S (n = 14)	BD-S (n = 24)	$F/\chi^2/t$	p	*Post-hoc* comparison (Bonferroni), p		
						HC vs. BD + S	HC vs. BD-S	BD + S vs. BD-S
Characteristics								
Age, years	28.23 ± 7.69	26.79 ± 7.68	26.13 ± 1.91	0.41	0.67	1.00	1.00	1.00
Male/Female	10/16	6/8	12/12	0.68	0.71	NA	NA	NA
Education, years	15.44 ± 3.08	12.71 ± 2.58	13.54 ± 2.99	4.56	0.01*	0.02*	0.08	1.00
Duration of illness, months	NA	70.56 ± 80.64	39.71 ± 39.45	1.464	0.07	NA	NA	NA
Medication use	NA	11 (78.57%)	21 (87.50%)	0.53	0.65	NA	NA	NA
Antidepressants	NA	6 (42.86%)	14 (58.33%)	0.85	0.50	NA	NA	NA
Antipsychotics	NA	10 (71.43%)	11 (45.83%)	2.34	0.18	NA	NA	NA
Mood stabilizer	NA	9 (64.29%)	16 (66.67%)	0.02	1.00	NA	NA	NA
Disease state								
Depression	NA	4 (28.57%)	11 (45.83%)	1.10	0.29	NA	NA	NA
Mania/hypomania	NA	5 (35.71%)	3 (12.50%)	2.87	0.09	NA	NA	NA
Remission	NA	5 (35.71%)	10 (41.67%)	0.13	0.72	NA	NA	NA
Subcategories of BD								
BD-I	NA	9(64.29%)	10(41.67%)	1.81	0.18	NA	NA	NA
BD-II	NA	4(28.57%)	9(37.50%)	0.31	0.58	NA	NA	NA
Unclear	NA	1(7.14%)	5(20.83%)	1.25	0.26	NA	NA	NA
HAMD-17 scores	0.96 ± 1.54	11.39 ± 10.06	10.46 ± 10.74	10.88	0.00*	0.00*	0.00*	1.00
YMRS scores	0.04 ± 0.20	7.85 ± 9.67	5.08 ± 8.39	6.50	0.00*	0.00*	0.04*	0.73
Cytokines, pg/ml								
IL-1β	3.51 ± 1.16	3.70 ± 0.84	3.64 ± 1.00	0.81	0.45	0.75	0.69	1.00
IL-6	1.09 ± 0.19	1.34 ± 0.26	1.17 ± 0.22	6.02	0.01*	0.01*	0.53	0.047*
TNF-α	2.61 ± 0.68	2.82 ± 0.60	2.57 ± 0.72	0.87	0.43	0.83	1.00	0.87

*Data are presented as number (%) or mean ± standard deviation; BD, bipolar disorder; n, number of subjects; HC, healthy control; BD + S, BD patients with suicide attempts; BD-S, BD patients without suicide attempts; HAMD-17, 17-item Hamilton Rating Scale for Depression; YMRS, Young Manic Rating Scale; *Significant level at $p < 0.05$; NA, not applicable.*

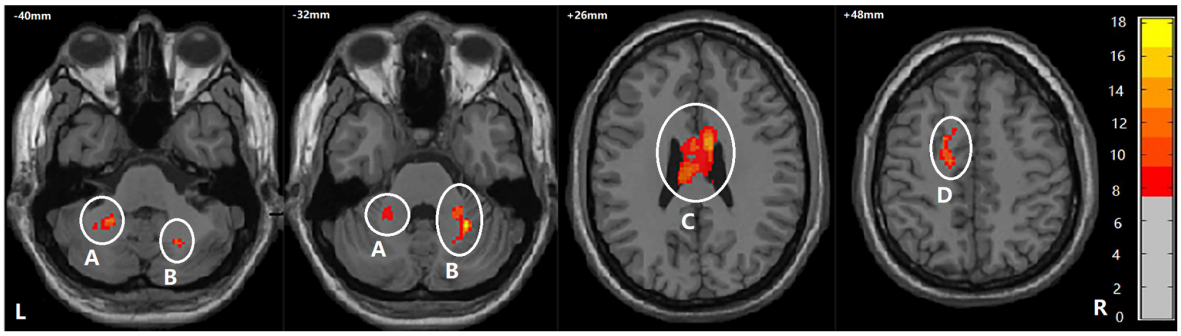

FIGURE 2 | Regions showing WM differences among the BD + S, BD-S, and HC groups. A, the left middle cerebellar peduncle; B, the right middle cerebellar peduncle; C, the bilateral body and genu of corpus callosum; D, the left superior corona radiate. The number is z-coordinate; The color bar is the range of *F*-values; L, left; R, right.

diffusion tensor matrix was first constructed in the native space. The eigenvalues and eigenvectors were then yielded by diagonalizing this matrix. Based on these three eigenvalues, each subject's voxel-wise FA map was calculated. All FA maps were non-linearly registered to the FMRIB58_FA template and normalized to the Montreal Neurological Institute (MNI) space. After that, a mean FA map was generated for all subjects. Finally, FA maps were smoothed using a Gaussian filter kernel of 6 mm full width at half maximum.

Statistical Analyses

Diffusion tensor imaging data were analyzed using SPM8.[2] We performed a one-way analysis of covariance (ANCOVA) with age and sex as covariates to examine the statistical differences in WM tracts among three groups. Statistical significance was determined by voxel $p < 0.005$ and cluster $p < 0.05$ [Gaussian random field (GRF) correction]. The FA values for each cluster with statistical differences were extracted.

We used IBM SPSS Statistics (version 22.0, Armonk, NY, United States) for Windows to analyze the demographic and clinical characteristics of subjects. The independent-samples *t*-test was utilized to compare the duration of illness between BD + S and BD-S. One-way analysis of variance (ANOVA) was used to compare age, education years, total scores of HAMD-17 and YMRS, and FA values among BD + S, BD-S, and HCs. Additionally, Chi-square tests were adopted to compare differences in gender, disease state, medication status, and subcategories of BD. We utilized ANCOVA with age and sex as covariates to examine the significant differences in plasma inflammatory cytokine levels across the three groups. Statistical significance was determined by $p < 0.05$. Partial correlation analyses with age, sex, and medication as covariates were adopted to evaluate correlations between the FA values and levels of TNF-α, IL-1β, and IL-6, and the relationships between severity of clinical symptoms, including scores of HAMD-17 and YMRS, and cytokine levels or FA values in BD + S, BD-S, and HC group, respectively.

[2]www.fil.ion.ucl.ac.uk/spm/software/spm8

RESULTS

Demographic Characteristics and Plasma Inflammatory Cytokine Levels

There were no significant differences in age, gender, and education years among BD + S, BD-S, and HCs. Duration of illness, medication status, disease state, and subcategories had no significant differences between the two subgroups of BD. The two patient subgroups showed significant higher scores of HAMD-17 and YMRS than HCs, and no significant differences were found between BD + S and BD-S (**Table 1**).

For plasma inflammatory cytokine levels, there was a significant difference in IL-6 level ($F = 6.02$, $p = 0.01$) but no significant difference in IL-1β level ($F = 0.81$, $p = 0.45$) or TNF-α level ($F = 0.87$, $p = 0.43$) among these three groups. *Post-hoc* analyses found significantly increased IL-6 level in BD + S compared to BD-S and HCs ($p < 0.05$, Bonferroni correction) (**Figure 1** and **Table 1**).

White Matter Integrity Findings

Among BD + S, BD-S, and HC groups, significant FA differences were found in the bilateral middle cerebellar peduncle, the

TABLE 2 | Differences of WM among BD + S, BD-S, and HC.

Cluster	Region	Voxels	Peak MNI coordinates			*F*-values*
			x	*y*	*z*	
A	Left middle cerebellar peduncle	122	−22	−48	−40	12.06
B	Right middle cerebellar peduncle	135	28	−50	−32	16.55
C	Bilateral body and genu of corpus callosum	701	8	2	26	11.77
D	Left superior corona radiate	112	−20	4	48	11.87

*WM, white matter; MNI, Montreal Neurological Institute; *Significant at $p < 0.005$ by GRF correction.*

bilateral body and genu of CC, and the left superior corona radiata ($p < 0.005$, GRF correction) (**Figure 2** and **Table 2**). *Post-hoc* analyses revealed that compared to BD-S and HCs, BD + S showed significantly decreased FA in the bilateral middle cerebellar peduncle and the left superior corona radiata ($p < 0.05$, Bonferroni correction). Compared to HCs, both BD + S and BD-S groups showed significantly reduced FA in the bilateral body and genu of CC ($p < 0.05$, Bonferroni correction), and there were no significant differences between the two subgroups of BD (**Figure 3**).

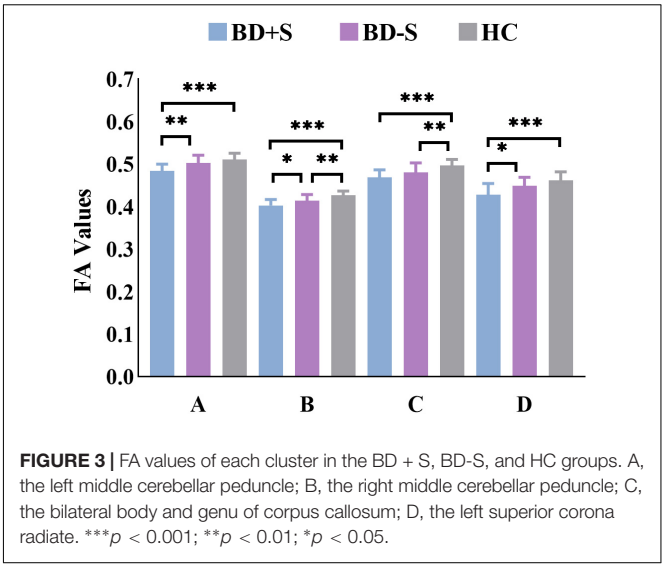

FIGURE 3 | FA values of each cluster in the BD + S, BD-S, and HC groups. A, the left middle cerebellar peduncle; B, the right middle cerebellar peduncle; C, the bilateral body and genu of corpus callosum; D, the left superior corona radiate. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

Correlation Analyses

Correlation Between the Plasma Inflammatory Cytokine Levels and the White Matter Integrity

No regions showed correlations between the plasma inflammatory cytokine levels and the FA values in all groups.

Correlation Between the Severity of Clinical Symptoms and Cytokine Levels

No correlations between the severity of clinical symptoms and cytokine levels were found in all groups.

Correlation Between the Severity of Clinical Symptoms and Fractional Anisotropy Values

In the BD + S group, we found negative correlation between the scores of YMRS and FA values of the left middle cerebellar peduncle ($r = -0.74$, $p = 0.035$) (**Figure 4**). And no correlation between the scores of HAMD-17 and FA values were found in BD + S group.

In the BD-S group, no correlations between the scores of HAMD-17 or YMRS and FA values were found.

DISCUSSION

The study explored alterations in the levels of TNF-α, IL-1β, and IL-6, as well as the WM integrity among BD + S, BD-S, and HCs. The correlations between the WM integrity and the levels of TNF-α, IL-1β, and IL-6 were also examined within each group. The findings revealed that BD + S exhibited specifically increased IL-6 levels and lower FA values in the bilateral middle cerebellar peduncle and the left superior corona radiate. Furthermore, both BD + S and BD-S showed decreased FA values in the bilateral body and genu of the corpus callosum, indicating the possible neuroimaging mechanisms of BD. However, no relationship between these plasma inflammatory cytokines and the WM integrity was found in any groups. What is more, we found that the FA values of left middle cerebellar peduncle and the score of YMRS were negatively correlated in BD + S.

Significantly elevated IL-6 level was specific to BD + S in this study. Accumulating evidence suggests that IL-6 is an important proinflammatory cytokine associated with BD (36–40) and suicide (41, 42). One study investigated a similar group found that BD patients with suicide risk had increased IL-1β levels (16). Inconsistent results were predominated in the BD patients and suicide population. For example, BD patients displayed increased levels of TNF-α and IL-1β compared to HCs (12, 16, 38, 40, 43). When comparing suicidal patients with non-suicidal ones and HCs, no significant difference in the levels of IL-6 and TNF-α was found (44). In contrast to the above studies, which focused just on BD or suicide, our research was concerned with SA in BD. Thus, these inconsistent results may be related to the heterogeneous groups. More studies investigating BD + S and BD-S are needed to confirm the results in the future. In addition, BD + S presented higher levels of IL-1β and TNF-α than BD-S and HCs, though it did not reach statistical significance. This may suggest that BD + S has a different immune pattern with BD-S and HCs, and the inflammation of BD + S is more aberrant than BD-S.

Regarding neuroimage, BD + S exhibited specifically impaired WM in the bilateral middle cerebellar peduncle and the left superior corona radiate. It is a pity that we did not find any evidence indicating that the above two brain regions are related to BD + S. The only study of BD + S reported that WM integrity impairments in the right cerebellar regions (19), which is similar with our results. This may indicate that the cerebellum plays a role in the mechanism of suicide in patients with BD. Since we did not find a direct correlation between corona radiata and BD + S, but we found indirect evidence that, internal capsule, which is anatomically connected with the corona radiata (45), is relevant to future SA in adolescents and young adults with BD (46). Although we did not find any alterations in FA values of internal capsule, we infer that the anatomical connection between corona radiata and internal capsule will lead to the functional interaction between them. Thus, corona radiata may be involved to the mechanism of BD + S through its relationship with internal capsule. Furthermore, Reich R. et al. found increased FA values of the corona radiata is positive correlated with greater impulsivity in BD + S (47), which may deepen understanding of our findings. Conversely, decreased FA values of corona radiata in BD + S was revealed in our finding. There are few studies on the WM integrity of corona radiata in BD + S. In the study of other diseases we observed increased FA values of corona radiata in patients with suicide attempts (48, 49). However, the FA values

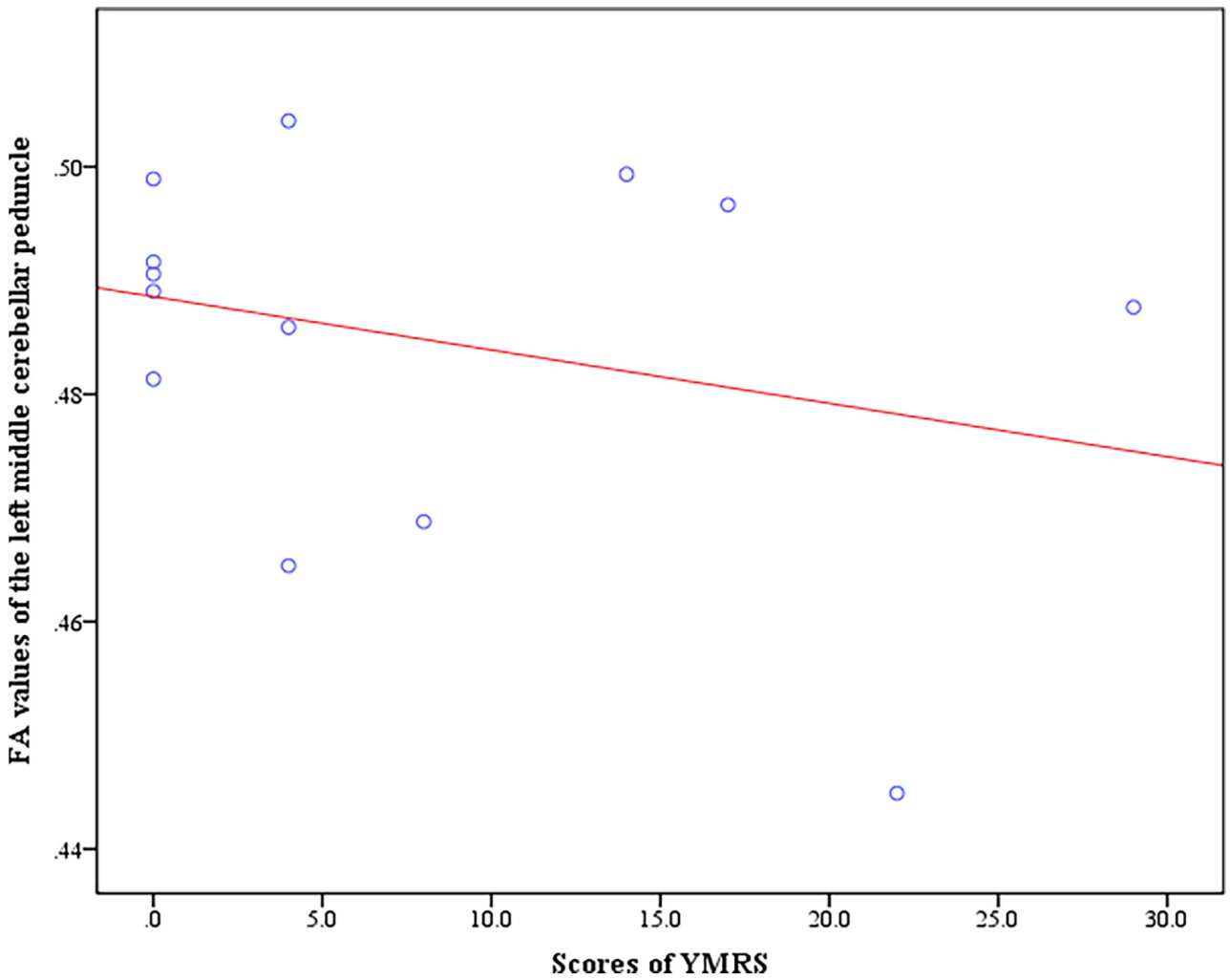

FIGURE 4 | Negative correlation between the scores of YMRS and FA values of the left middle cerebellar peduncle in BD + S group.

of corona radiata decreased in veterans with suicidal ideation (50). Therefore, the results of the FA values of corona radiata are contradictory in suicidal population, and further study is needed to confirm the role of corona radiata in BD + S.

The FA values of the bilateral body and genu of CC decreased in both BD + S and BD-S groups, indicating that the impaired bilateral body and genu of CC may be involved in the neuroimaging mechanism of BD. CC is the main interhemispheric connector that contains 300 million axons and connects most cortical regions of the brain. It is responsible for integrating motor, cognitive, sensory, and learning information between the two hemispheres (51). A growing body of literature suggests that the CC plays an important role in the pathophysiological mechanism of BD (52–54), and numerous DTI studies have demonstrated that BD patients showed impaired WM integrity in the CC compared to HCs (53, 55–58). Nery-Fernandes et al. found a reduction in the genu and isthmus area of CC in BD patients, but no difference in any subregion of CC between BD + S and BD-S (52), which corresponds to our results. Likewise, similar to the cytokine findings, we also found that the FA values decreased gradually from HC to BD-S to BD + S. Our findings may support the idea that impaired WM occur in a graded manner, i.e., BD + S > BD-S > HCs.

A relationship between the plasma inflammatory cytokines and the WM integrity was not found in the current study. By searching the literature, we found only one study investigating the relationship between WM and cytokines in BD, and the results revealed that the TNF-α level is inversely associated with WM integrity in BD-I patients (28). Nevertheless, the study did not include HCs. On the other hand, it is inconclusive whether the increased cytokine levels in the central nervous system are parallel to those in the peripheral blood (59). As a result, cytokines in peripheral blood may not reflect WM injury. Therefore, the relationship between them may not be determined. Another study, which drew a similar conclusion with ours, showed that the levels of IL-6 and TNF-α did not have a significant increase in BD patients compared to HCs (60). Relatively small number of studies limit our

interpretation of the results. Consequently, we should pay attention to BD + S and provide more evidence for the underlying mechanism of the BD + S.

BD + S displayed negative correlation between the scores of YMRS and FA values of the left middle cerebellar peduncle, indicating that the decreased FA values of the left middle cerebellar peduncle is related to manic or hypomanic symptoms of BD + S. Similarly, Olivito G. et al. demonstrated that the cerebellum, which including the middle cerebellar peduncle, plays an important role in mania and hypomania in BD patients (61). The finding is novel and hint subgroup analysis may dig deeper into the relationship between the brain and symptoms.

Limitation

We recruited BD patients of different ages, different disease states, and different medication use statuses. To explore the potential influence, we compared the FA values and IL-6 levels divided by age, state, and medication use in BD + S and BD-S groups. We found that there were no statistical differences between adolescent and adult groups, between the different states, and between the medication use and medication-free groups (**Supplementary Tables 1–6**). Therefore, age, state, and medication may have little influence on the results. However, the potential impact of these factors cannot be ignored. In addition, the study was a cross-sectional study with a small sample size, which requires a follow-up and larger sample sizes in the future.

CONCLUSION

In summary, the results suggest that BD + S may present specific and much more aberrant immunologic and neuroimaging changes compared with BD-S. It may provide a scientific basis to understand the potential mechanisms of BD + S and calls for attention to the suicide attempts of BD patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Scientific Research Ethics Committee of the First Affiliated Hospital of China Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XJ was responsible for conceptualization, investigation, data curation, writing original draft, and funding acquisition. YG performed the data processing, statistical analyses, visualization, and wrote the original draft. LJ wrote the original draft. YZ validated the results. QS acquired the data. FW and LK recruited the patients, confirmed the diagnosis, and acquired the funding. YT was responsible for conceptualization, project administration, and funding acquisition. All authors reviewed and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.861881/full#supplementary-material

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Increased Levels of Cortisol in Individuals With Suicide Attempt and Its Relation With the Number of Suicide Attempts and Depression

Alma Delia Genis-Mendoza[1,2†], Diana María Dionisio-García[3†], Thelma Beatriz Gonzalez-Castro[4], Carlos Alfonso Tovilla-Zaráte[5], Isela Esther Juárez-Rojop[3], María Lilia López-Narváez[6], Rosa Giannina Castillo-Avila[3] and Humberto Nicolini[1*]*

[1] Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, Ciudad de México, Mexico, [2] Hospital Psiquiátrico Infantil "Juan N. Navarro", Servicios de Atención Psiquiátrica, Mexico City, Mexico, [3] División Académica de Ciencias de la Salud, Universidad Juárez Autónoma de Tabasco, Villahermosa, Mexico, [4] División Académica Multidisciplinaria de Jalpa de Mendéz, Universidad Juárez Autónoma de Tabasco, Jalpa de Méndez, Mexico, [5] División Académica Multidisciplinaria de Comalcalco, Universidad Juárez Autónoma de Tabasco, Comalcalco, Mexico, [6] Secretaria de Salud de Chiapas, Hospital Chiapas Nos une "Dr. Jesús Gilberto Gómez Maza", Tuxtla Gutiérrez, Mexico

Background: Abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) have been reported in individuals with suicide behavior. The aim of the study was to evaluate cortisol levels in peripheral plasma of individuals with more than one suicide attempt.

Methods: Cortisol concentrations in peripheral plasma were measured using the ELISA technique. Suicide attempts were evaluated by the Columbia Suicide Severity Rating Scale, while depression was evaluated by the Hamilton Depression Rating Scale.

Results: We found elevated cortisol levels in the suicide attempt group when compared with healthy controls ($F = 7.26$, p-value $= 0.008$), but no statistical differences with the psychiatric diseases group ($F = 1.49$, p-value $= 0.22$). Cortisol levels were higher in individuals with depression ($F = 8.99$, $P = 0.004$) and in individuals with two or more suicide attempts ($F = 13.56$, $P < 0.001$).

Conclusions: Cortisol levels are increased in individuals who attempt suicide and higher of cortisol concentrations in plasma regard to depression and more attempts of suicide.

Keywords: suicide attempt, cortisol, HPA axis, suicide behavior, stress, suicide

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***Correspondence:**
Carlos Alfonso Tovilla-Zaráte
alfonso_tovillaz@yahoo.com.mx
Humberto Nicolini
hnicolini@inmegen.gob.mx

†These authors have contributed equally to this work and share first authorship

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INTRODUCTION

Suicide is a public health problem worldwide. In 2020, 1.5 million deaths by suicide were reported (1). Epidemiology studies indicate that an estimate of 80% of these deaths were in low and middle-income countries (2, 3).

The etiology of suicide behavior is unknown; however, it has been proposed a diathesis-stress model to explain its pathogenesis. It is believed that the diathesis may have a biological origin. The literature shows that, when stress in perceived, there are clear changes in cortisol levels (4). Therefore, the stress diathesis theory of suicide postulates that there are predisposing and precipitating risk factors of suicide attempts. Genetic, inflammation, serotoninergic systems, peripheral biomarkers as cholesterol and, the alteration of the hypothalamic-pituitary-adrenal axis

(HPA), could be participant in the biological diathesis of suicide behavior (5–7).

Some studies have addressed the association between altered levels of circulating cortisol and an increased risk of suicide behaviors (8); nonetheless, these studies have observed a variety of outcomes. For example, in a response to an experimental stressor in suicide attempters compared with non-suicidal individuals, a low baseline cortisol prior to the stressor was found in attempters (9). However, in veterans with and without suicide attempts, a no-significant association with cortisol levels and suicidal behavior was observed (10); similarly, no-significant association with cortisol levels was observed in individuals with psychiatric illnesses and suicide behavior (11, 12) also, higher cortisol levels were associated with increased suicidal severity and suicide attempts (13) moreover, increased cortisol response after dexamethasone suppression test have been presented in patients that were weary life (14) and in Due to the inconsistent results regarding the association of cortisol levels and suicide behavior, two meta-analyses have explored this association (15, 16) and their results suggest a possible role of cortisol levels in suicide behavior. Therefore, the need of more studies performed in other populations and the inclusion of healthy and psychiatric controls is imperative in order to determine the role of cortisol levels and suicide attempt. The objectives of the present study were to evaluate plasma cortisol levels in Mexican individuals with suicide attempt and to determine if cortisol levels differ between these individuals and those with psychiatric diseases and a healthy comparison group; and finally, to associate plasma cortisol levels with the characteristics of suicide attempt.

METHODS

This is a cross-sectional study conducted from January to December, 2020, in Tabasco, Mexico. This study meets the criteria established in the Declaration of Helsinki and was approved by the ethics committee of the Regional Hospital of High Specialty of Mental Health (HRAESM/DG/UWI/351/2020). All participants signed an informed consent. None of the individual included in the study received financial compensation for their participation.

Participants

Our study group comprised a total of 143 Mexican individuals, that were recruited from February 2020 to July 2021. We included three hospitals in Tabasco State: The High Specialization Regional Hospital Dr. Gustavo A. Rovirosa Pérez in Villahermosa City, The General Hospital of Comalcalco Dr. Desiderio G. Rosado Carbajal in Comalcalco City, and The Regional Hospital of High Specialty of Mental Health in Villahermosa City.

The sample was divided in 3 groups: (1) The suicide attempt group included 56 patients who had a diagnosis of suicide attempt, made by at least one psychiatrist using the evaluation of suicide behavior by the Columbia Suicide Severity Rating Scale (C-SSRS); they were all selected from admissions to the hospital emergency department. (2) The group of individuals with psychiatric diseases (excluding depression) and no-history of suicide behavior was formed by 31 patients; the psychiatric diagnoses (including schizophrenia) were made by at least one psychiatrist. (3) The healthy control group included 56 participants who reported no-history of suicide attempt or psychiatric illnesses. All the participants were volunteers; they were informed about the study, the procedure and the objectives; they all signed an informed consent form and agreed to the collection of the biological sample. The objective of including these three groups was to compare the cortisol levels in three types of population, since literature indicates variations among them.

Data Collection

Demographic characteristics such as age, sex, occupation, marital status, educational level, sample collection time, BMI (body mass index) and substance use were gathered. Additionally, we included information about their suicide behavior using the C-SSRS; to evaluate symptoms of depression we used the Hamilton Depression Scale (HAM-D). In the suicide attempt group, we also enquired about the family history of suicide attempts, number of suicide attempts, method of suicide attempt, as well as age of first and last suicide attempts.

Individuals With Suicide Attempt

The clinical diagnosis was made by at least one psychiatrist according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5) criteria for determining suicide attempt, and they used the C-SSRS (which is validated in Spanish and increases the ability to predict suicidal risk) full version including 16 questions with binary responses. The C-SSRS is used as an initial screening to guide clinicians in assessing suicide risk and to help stratify patients into categories of low, moderate or high lifetime patient risk. The C-SSRS is formed by four sub-scales: severity and intensity of suicidal ideation and severity and lethality of suicide behavior (17); and 20 categories: wish to be dead, with no-specific active suicidal thoughts; active suicidal ideation, with any methods, without intent to act; active suicidal ideation, with some intent to act, without specific plans; active suicidal ideation, with specific plan and intent; preparatory suicide acts or suicide behavior; aborted suicide attempt; interrupted suicide attempt; actual suicide attempt (non-fatal); and completed suicide. If one question is answered "yes", in categories 1–5 is suicidal ideation, in categories 6–10 is suicide behavior. In the same way, information about the number of suicide attempts was collected, age when the first suicide attempt occurred, age of last suicide attempt, family history of suicide attempts and whether they suffer from any psychiatric illnesses.

Psychiatric Individuals Without Suicide Attempt

The group of individuals with psychiatric diseases but without suicide attempt were diagnosed by psychiatrics according to the DSM-5. Who reported in the interviews that they did not have any previous suicide attempts and we corroborated that information in their medical records.

Control Group

The control group was formed by 56 individuals (64.3% males and 35.7% females) with an age range of 18–55 years and a mean of 34.30 years of age (±10.37), who were volunteer donors from the blood bank of The High Specialization Regional Hospital Dr. Gustavo A. Rovirosa Pérez. This group received a general check-up by physicians and they reported no psychiatric illness or history of suicide attempts.

Assessment of Depression

Depression symptoms were evaluated in individuals with suicide attempt using the HAM-D, consisting of 17 questions validated in Spanish and evaluates the depressive symptomatology of the patients (18). It was important to evaluate depression, since it is an important factor related to suicide attempts (19). The scale is widely available and has two common versions with either 17 or 21 items that score between 0 and 4 points. The first 17 items measure the severity of depressive symptoms and as examples the interviewer rates the level of agitation clinically noted during the interview or how the mood is impacting on an individual's work or leisure pursuits. The extra four items on the extended 21-point scale measure factors that might be related to depression, but are not thought to be measurements of severity, such as paranoia or obsessional and compulsive symptoms. The scoring is based on the 17-item scale and scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression; the maximum possible score is 52 on the 17-point scale.

Cortisol Samples

Peripheral blood samples were taken from three groups and the blood was placed in EDTA (Ethylenediamine tetraacetic acid) containing tubes [BD Vacutainer, K2 EDTA (K2E)] Plus Blood Collection Tubes, placed on ice. Samples from the group of individuals with suicide attempt were taken the day after their admission to the emergency room. After the peripheral blood samples were collected, they were immediately centrifuged and plasma aliquots were made and stored at −80°C. Cortisol concentrations in plasma were determined by means of the competitive Enzyme-Linked Immunoabsorption Assay (ELISA). The samples were analyzed using a commercially available Cortisol Competitive Human ELISA kit by Invitrogen. The mean of sample collection was at 11:00 am.

Data Analyses

Data were analyzed using the SPSS version 27.0 (IBM Corporation, Armonk, NY). Descriptive variables were expressed as means and Standard Deviation (SD) for continues variables, and frequencies and percentages for categorical variables. The initial comparison between patients with suicide attempt and the comparison groups were analyzed with X^2-test also for categorical variables and with independent samples *t*-test for continuous variables. In continues variables, an analysis of variance followed by Bonferroni correction were performed. Cortisol levels and confounding variables were analyzed by linear regression analysis. We performed linear regression with confounding variables (age, sex, education, marital status, socioeconomic level, time of collection and body mass index) which did not present statistical differences that influenced the cortisol levels of our study group. To determine the association between cortisol levels and suicide attempt, we performed an age-adjusted linear regression analysis. Significance was established at $p \leq 0.05$ for all analyses.

RESULTS

Sociodemographic Characteristics

In the **Table 1** are shown the characteristics of the study population. The majority in the overall population were men $n = 79$ (55.6%) and unemployed $n = 75$; the majority were not-married $n = 74$ (51.7%) and had studied more than 6 years $n = 116$ (81.1%). As for substances use, most of them did not consume alcohol $n = 75$ (52.4%), neither cannabis $n = 133$ (93%) nor smoke cigarettes $n = 123$ (88.35%).

The suicide attempt group included more women $n = 31$ (56.4), unemployed $n = 34$ (60.7%), mostly single $n = 39$ (69.6%), and with an education of more than 6 years $n = 49$ (87.5). The majority consumed alcohol $n = 30$ (44.1), but not cannabis $n = 45$ (85.7%) and no cigarette smoking $n = 44$ (80%), and the mean cortisol level was 14.68 μg/dL (SD 15.36).

The psychiatric diseases group included more men $n = 19$ (61.3%), single $n = 27$ (87.1%), and who had more than 6 years of schooling $n = 21$ (67.7%). Most of them, did not consume alcohol $n = 28$ (90.3%), neither cannabis $n = 29$ (93.5%) and no cigarette smoking $n = 24$ (82.8%).

In the healthy control group there were more men $n = 36$ (64.3%), unemployed $n = 16$ (64%), and married $n = 41$ (73.2%). The majority had studied more than 6 years $n = 46$ (82.1%). As for the substances abuse, most of them used alcohol $n = 35$ (62.5%) but not cannabis $n = 56$ (100%) and no cigarette smoking $n = 56$ (100%).

Comparison of groups using the cortisol levels are show in the **Table 2**. We observed difference between groups. In accordance with *post-hoc* comparisons, healthy controls and suicide attempt groups reported statistically significant. Since, the suicide attempt groups showed a higher cortisol levels that healthy controls groups. However, the *post-hoc* analysis of healthy controls and psychiatric controls not differences were observed.

Characteristics of the Individuals With Suicide Attempt

Table 3 shows the characteristics of the suicide attempts in the cases group, most of them had one suicide attempt $n = 37$ (66.1%), did not have familiar history of suicide attempts $n = 24$ (75%), the mean age of the first suicide attempt was at 29.28 years old ±12.90 and the last suicide attempt was at 31.64 years old ±13.82. Where the characteristics were compared between men and women, there were no statistical differences, in our study group sex was not related to suicide phenotypes.

Levels of Plasma Cortisol (μg/dL) in Subgroups of Suicide Attempters and Comparison Groups

In **Table 4**, we show the levels of cortisol in plasma μg/dL) in subgroups of suicide attempters and the comparison

TABLE 1 | Sociodemographic characteristics of suicide attempters, patients with psychiatric diseases and healthy individuals in a Mexican population.

Characteristics	All $n = 143$	Healthy controls $n = 56$	Psychiatric patients $n = 31$	Suicide attempt $n = 56$	Statistics
Sex					
Males	80 (55.6)	36 (64.3)	19 (61.3)	25 (43.6)	$X^2 = 5.30$, $\mathbf{p = 0.07}$
Females	63 (44.4)	20 (35.7)	12 (38.7)	31 (56.4)	
Occupation					
Unemployed	23 (16.1)	3 (5.4)	9 (29.0)	11 (19.6)	$X^2 = 42.62$, $\mathbf{p < 0.001}$
Home	36 (25.2)	8 (14.3)	15 (48.4)	13 (23.2)	
Student	16 (11.2)	5 (8.9)	1 (3.2)	10 (17.9)	
Part-time employment	25 (17.5)	9 (16.1)	4 (12.9)	12 (21.4)	
Full-time employment	43 (30.1)	31 (55.4)	2 (6.5)	10 (17.9)	
Marital status					s
Married	61 (42.7)	41 (73.2)	3 (9.7)	17 (30.4)	
Single	74 (51.7)	12 (16.2)	27 (87.1)	35 (62.5)	
Widowed	1 (0.7)	1 (1.8)	0	0	$X^2 = 43.34$, $\mathbf{p < 0.001}$
Separated/divorced	7 (4.9)	2 (3.6)	1 (3.2)	4 (7.1)	
Education					
<6 year of schooling	27 (18.9)	10 (17.9)	10 (32.3)	7 (12.5)	$X^2 = 5.14$, $p = 0.76$
>6 years of schooling	116 (81.1)	46 (82.1)	21 (67.7)	49 (87.5)	
Alcohol consumption					
Yes	68 (47.6)	35 (62.5)	3 (9.7)	30 (44.1)	$X^2 = 23.66$, $\mathbf{p < 0.001}$
No	75 (52.4)	21 (37.5)	28 (37.3)	26 (34.7)	
Cannabis use					
Yes	10 (7)	0	2 (6.5)	8 (14.3)	$X^2 = 8.8$, $\mathbf{p = 0.01}$
No	133 (93)	56 (100.0)	29 (93.5)	48 (85.7)	
Cigarette smoking					
Yes	16 (11.2)	0	5 (16.1)	11 (19.6)	$X^2 = 11.84$, $\mathbf{p = 0.003}$
No	127 (88.8)	56 (100)	26 (83.9)	45 (80.4)	

Numbers in bold show significant statistical difference.

TABLE 2 | Comparison of cortisol levels and age among groups.

	All $n = 143$	Healthy controls $n = 56$	Psychiatric patients $n = 31$	Suicide attempt $n = 56$	Statistics		*Post-hoc* comparison *p*-value (mean difference)		
		Mean (SD)	Mean (SD)	Mean (SD)	*F*	*p*-value	HC vs. SA	HC vs. PP	PP vs. SA
Cortisol level	11.97 ± 11.29	8.79 ± 6.74	12.79 ± 7.36	14.68 ± 15.36	**4.08**	**0.01**	**0.01 (5.89)**	0.32 (4.00)	1 (1.89)
Age	32.88 ± 11.04	34.30 ± 10.37	40.25 ± 9.50	32.50 ± 11.65	5.35	**0.006**	1 (−1.80)	0.13 (−5.95)	**0.05 (7.75)**

HC, Healthy controls; PP, Psychiatric patients; SA, Suicide attempts.
Numbers in bold show significant statistical difference.

groups (healthy individuals or with psychiatric diseases) in a Mexican population.

The results of the linear regression analysis were statistically significant when we compared cortisol levels between healthy controls and individuals with suicide attempt ($F = 7.26$, P-value $= 0.008$) (**Table 3**). But no statistically significant differences were observed when comparing with the psychiatric diseases group ($F = 1.49$, $p = 0.22$). Subsequently, we evaluated differences in the presence of symptoms of depression. We found that individuals with ($F = 8.99$, $P = 0.004$) and without depression showed increased cortisol levels in comparison with healthy controls *and/or* individuals with psychiatric diseases.

DISCUSSION

In this study, we evaluated plasma cortisol levels in individuals with suicide attempt in comparison with two groups, healthy individuals and individuals with psychiatric diseases (excluding depression). Up to date, research has not delivered conclusive outcomes that determine if cortisol levels are decreased or increased in individuals who attempt suicide (15, 20, 21). We also analyzed cortisol levels according to clinical and sociodemographic variables; to our knowledge, this is the first study that evaluates cortisol levels in Mexican individuals who have attempted suicide.

TABLE 3 | Characteristics of suicide attempt among males and females in Mexican population.

	All	Males	Females	Statistics
Number of SA				
1	37 (66.1)	14 (58.3)	23 (71.9)	$X^2 = 1.12$, $p = 0.29$
2 or +	19 (33.9)	10 (41.7)	9 (28.1)	
Familiar history of SA				
Yes	8 (25.0)	4 (33.3)	4 (20.0)	$X^2 = 0.71$, $p = 0.39$
No	24 (75.0)	8 (66.7)	16 (80.0)	
Age of the first SA	29.28 ± 12.90	31.04 ± 14.33	27.96 ± 11.77	$F = 0.43$, $p = 0.39$
Age of the last SA	31.64 ± 13.82	33.08 ± 14.08	30.56 ± 13.74	$F = 0.17$, $p = 0.50$
Depression				
Yes	14 (25)	5 (20)	9 (29.0)	$X^2 = 0.60$, $p = 0.43$
No	42 (75)	20 (80)	22 (70.9)	

SA, suicide attempts.

TABLE 4 | Level of plasma cortisol (μg/dL) in subgroups of suicide attempters and comparison groups (health and psychiatric group) in a Mexican population.

Groups	*n*	Age Mean ± SD	Cortisol Mean ± SD	Statistics *F*	*P*-value
Controls	56	32.55 ± 11.75	8.79 ± 6.74	Reference	
Psychiatric controls	31	43.71 ± 13.40	12.79 ± 7.36	5.53	**0.02**
Suicide attempted	56	34.30 ± 10.37	14.68 ± 15.36	7.26	**0.008**
PC vs. SA	56	43.71 ± 13.40	14.68 ± 15.36	1.49	0.22
SA-depression					
No	42	33.14 ± 12.15	8.79 ± 6.74	5.17	**0.02**
Yes	14	30.78 ± 10.67	18.32 ± 20.54	8.99	**0.004**
SA-number of attempt					
One	37	31.21 ± 12.44	13.42 ± 16.50	4.10	**0.04**
2 or +	19	35.15 ± 10.09	17.15 ± 12.76	13.56	**<0.001**

PC, psychiatric controls; SA, suicide attempted; SD, standard deviation.
Depression by Hamilton Scale Depression. Statistically significant are present in bold.

We found significantly elevated cortisol levels in the suicide attempt group in comparison with the healthy control group. Our results agree with other studies that have observed high cortisol levels in suicide attempt groups when compared with individuals without suicide behavior (22–29). Sociodemographic characteristics of cases and comparison groups in our population studied were very similar; however, their circulating cortisol levels differed significantly. Hence, we could assume that cortisol levels are related with an alteration of the stress regulation system in patients with suicide attempt (30). In the case of the individuals with psychiatric diseases (excluding depression), cortisol levels were not significantly different when compared with the suicide attempt group. Nevertheless, both groups had higher cortisol levels then the healthy individuals group. Some studies have concluded that individuals with psychiatric diseases (excluding suicide behavior and depression) show different cortisol levels than patients with suicide behavior (15). Other reports found that subjects with psychiatric disorders have shown HPA axis hyperactivity and alterations in cortisol levels (31, 32); furthermore, individuals with suicide attempt could have a more active HPA axis than individuals with other psychiatric disorders (11, 12).

On the other hand, we observed statistical differences when we analyzed the characteristics of the suicide attempt group associated with cortisol levels such as the presence or absence of depression. Significantly elevated cortisol levels were observed in the group of individuals who had attempted suicide, in comparison with the baseline cortisol levels of the healthy group, as some previous studies have recorded (23, 27, 33). Our results suggest that cortisol levels could be a phenotype of suicide attempters because of an alteration in the HPA axis, and this could be increased in the presence of depression or the number of suicide attempts.

A conclusive description of the increased levels of cortisol in patient with suicide attempt has not been reached yet. However, some explanations have been proposed: some studies correlate 5-HT1A receptors of serotonin (5-HT) with cortisol levels, stress and suicide attempt (34, 35). In this sense, the altered serotonin is associated with suicide behavior, making people more aggressive and more susceptible to mood disorders (36, 37). Also, the hippocampus plays an important role in feedback mechanisms of the HPA axis (38, 39), as well as in the levels of 5HT1A receptors. The hyperactivity of the HPA axis produced by chronic exposure to stress generates an elevation of plasma

corticosteroids, including cortisol (40). Having high levels of cortisol reduces the mRNA of 5HT1A receptors, decreasing their levels, resulting in low rates of serotonin metabolism, but when serotonin dysfunction occurs there is a risk of suicidal behavior (41–43). Another way in which high cortisol levels have been related to a decrease in 5-HT, is due to the increased tryptophan 2,3-dioxugenase (TDO) (20, 21); this enzyme is involved in the degradation of tryptophan (TRP) *via* the kynurenine pathway, which synthesizes 5-HT (44). With lower levels of TRP, there is not enough TRP available in brain to synthesize 5-HT, as there are more enzymes that metabolize TRP (45), and decreased amounts of the 5-HT neurotransmitter are associated with attempted suicide (46, 47).

The HPA hyperactivity in our group with psychiatric diseases is presumed to be different from our suicide attempt group, because one of the factors that contribute in the development of suicide ideation and suicide attempt is the presence of psychiatric illness (48–50) such as schizophrenia disorder (51, 52). In our results, suicide attempt group and psychiatric control group showed high cortisol levels, which indicates that there was hyperactivity of the HPA axis in both groups. But even if there were no significant differences between these groups, the suicide attempt group showed the highest cortisol levels. We assumed that this is a duality, where apart from suicidal behavior, a psychiatric illness is present, and both situations increased cortisol levels in patients who attempted suicide. Considering that cortisol levels in suicide attempt subjects were much higher when in presence of psychiatric illness and suicide ideation, it was important for us to include a control group with psychiatric illness to see any difference in cortisol levels. Our results support that we can use cortisol as a particular biomarker of suicidal attempt.

Some limitations in this study should be noted. First, we did not determine menstrual cycle, contraceptive use or hormone replacement in women who participated in the study. Second, the sample size could be considered small. However, it is the first study that explores cortisol levels in a Mexican population with suicide attempt. Third, this is a cross sectional study, then longitudinal studies that measure cortisol levels are needed. Also, we did not include the use of medications and if they received psychotherapy or some medication. Further, we did not aboard if the study population had been received psychological treatment in their childhood, neither, the evaluation of resilience capacity, or if they had some stressful life events, among other evaluations that could have been of great value for our study to include.

In conclusion, we found increased levels of plasma cortisol in individuals with suicide attempt. The level of cortisol is higher in presence of depression and in individuals with more than two attempts suicide. Then, levels of cortisol in individuals who attempt to die by suicide could be considered when searching for a biomarker of suicide attempts and become part of the preventing measures of this global problem.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by HRAESM/DG/UWI/351/2020. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

Conceptualization, writing-original draft preparation, and supervision: DD-G, TG-C, CT-Z, AG-M, IJ-R, ML-N, and RC-A. Methodology: DD-G, TG-C, CT-Z, and IJ-R. Formal analysis and investigation: DD-G, TG-C, and CT-Z. Editing: DD-G, TG-C, CT-Z, and RC-A. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.912021/full#supplementary-material

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Impaired Oxygenation of the Prefrontal Cortex During Verbal Fluency Task in Young Adults With Major Depressive Disorder and Suicidality: A Functional Near-Infrared Spectroscopy Study

*Hyewon Kim[1], JongKwan Choi[2], Bumseok Jeong[3], Maurizio Fava[4], David Mischoulon[4], Mi Jin Park[5], Hyun Soo Kim[6] and Hong Jin Jeon[7,8,9,10]**

[1] Department of Psychiatry, Hanyang University Hospital, Seoul, South Korea, [2] OBELAB Inc., Seoul, South Korea, [3] Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea, [4] Depression Clinical and Research Program, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [5] Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [6] Department of Psychiatry, Dong-A University Hospital, Busan, South Korea, [7] Department of Psychiatry, Depression Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [8] Department of Health Sciences and Technology, Department of Medical Device Management and Research, and Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea, [9] Department of Medical Device Management and Research, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, South Korea, [10] Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, South Korea

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***Correspondence:**
Hong Jin Jeon
jeonhj@skku.edu

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Background: Few previous studies have focused on prefrontal activation in young adults diagnosed with major depressive disorder (MDD) and suicidality *via* functional near-infrared spectroscopy (fNIRS).

Materials and Methods: A total of 59 healthy controls (HCs), 35 patients with MDD but without suicidality, and 25 patients with MDD and suicidality, between the ages of 18–34 years, were enrolled. Changes in oxygenated hemoglobin (oxy-Hb) levels of the prefrontal cortex at baseline, 4 weeks, and 8 weeks, were evaluated using a protocol consisting of three consecutively repeated trials of rest, speech, and verbal fluency test (VFT) *via* fNIRS. MDD was diagnosed and suicidality was evaluated based on Mini International Neuropsychiatric Interview (MINI).

Results: Oxy-Hb levels were impaired in patients with MDD compared with HCs (p = 0.018 for left prefrontal cortex; p = 0.021 for right ventromedial prefrontal cortex; p = 0.002 for left frontopolar cortex). Among the three groups including HCs, MDD without suicidality, and MDD with suicidality, prefrontal oxygenation was most decreased in MDD patients with suicidality. A significantly impaired prefrontal oxygenation in the right ventrolateral prefrontal cortex (VLPFC) was detected after adjusting for covariates in MDD patients with suicidality, compared to those without suicidality.

Conclusion: Impaired prefrontal oxygenation during cognitive execution may serve as a diagnostic biomarker for suicidality in young adult patients with MDD.

Keywords: major depressive disorder, fNIRS, prefrontal cortex, oxygenated hemoglobin, suicide

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric illness associated with significant morbidity (1). Symptoms of MDD are often distinguished as two symptom clusters: cognitive/affective subtype (e.g., lack of interest, suicidal thoughts, and guilt) and somatic/affective subtype (e.g., fatigue, psychomotor agitation/retardation, sleep problems, and appetite/weight disturbance) (2, 3). Previous studies have suggested that etiology or prognosis may differ according to the symptom clusters (3, 4). Suicidality, one of the cognitive/affective symptoms of MDD, is often the most immediate clinical concern among people with MDD. It is estimated that about 50% of all suicide occur within a depressive episode and people with MDD are about 20-fold more likely to die by suicide compared to the general population (5, 6).

Although the symptoms of people with MDD are highly heterogenous, age at onset is one of the most critical factors that lead to a rather homogenous subgrouping among them. The onset of MDD occurs before age of 40 years in about 50 percent of patients (7). There have been suggested that etiology, manifestation, and course of depression differ according to the age of onset; compared to later onset, earlier age at onset of MDD is associated with higher genetic loading, atypical symptoms, more irritability and anxiety, personality disorder, alcohol abuse, higher possibility of conversion to bipolar disorder, and poorer long-term outcome (7–9). Moreover, previous studies have consistently reported an increased suicidal risk in those with early onset (10–12). These findings suggest that there may be underlying neurobiological differences according to subgroup according to age.

Functional near-infrared spectroscopy (fNIRS) is an optic neuroimaging technology that uses near-infrared light to measure the local concentration of cortical oxygenated and deoxygenated hemoglobin. The fNIRS can be used to detect blood oxygen saturation by irradiating the cerebrum with near-infrared rays between a spectral window of 650 and 1000 nm and measuring the returned light with sensors according to the light absorption rate (13). Because fNIRS enables non-invasive monitoring of brain activity in real-time with similar spatial resolution and relatively higher temporal resolution compared with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), several studies have used fNIRS in the fields of psychiatry and neuroscience that utilize changes in brain activity as biomarkers (14).

Previous fNIRS studies conducted among patients with MDD have shown a reduced increase in the oxygenated hemoglobin (oxy-Hb) levels during verbal fluency test (VFT) in the prefrontal regions (15, 16) or frontotemporal regions (17, 18). In addition, the oxy-Hb concentration was negatively correlated with the degree of depression (19), and the correlation was stronger in the recurrent MDD group (20). Moreover, previous studies have shown the association of prefrontal hemodynamic changes *via* fNIRS and suicidality in patients with MDD, reporting a reduced prefrontal activation during cognitive tasks compared to those without suicidality (21, 22). Different brain regions were associated with such changes; an fNIRS study with the mean age of 37.6 years (SD, 10.0 years) and 38.8 years (SD, 9.7 years) for suicide attempters and non-attempters, respectively, showed that suicide attempters had reduced hemodynamic changes in the left precentral gyrus compared with non-attempters (22); another study with the mean age of 57.3 years (SD, 15.7 years) and 58.7 years (SD, 16.5 years) for MDD patients with suicide ideation and MDD patients without suicidal ideation, respectively, showed that the degree of suicidal ideation was negatively associated with the changes in oxy-Hb in the right orbitofrontal cortex (OFC), frontopolar cortex (FPC), and dorsolateral prefrontal cortex (DLPFC) (21); and, another fNIRS study with the mean age of 37.6 years (SD, 14.36 years) and 33.4 years (SD, 12.6 years) for patients with MDD and healthy controls (HCs), respectively, reported relatively greater left prefrontal activity during cognitive tasks in patients who diagnosed with MDD and suicidal ideation compared to those without suicidal ideation, and demonstrated that this prefrontal asymmetry (greater oxy-Hb in the left hemisphere) has a moderating effect between depression and suicidal ideation (23).

Although previous fNIRS studies have discovered features of hemodynamic changes during a cognitive task in people with MDD and suicidality, evidence in a targeted population of young adults is not yet available. In this study, we investigated hemodynamic changes in the prefrontal cortex *via* fNIRS monitoring of young adult patients with MDD. We hypothesized that (1) the increase in prefrontal cortical activity during a cognitive task is smaller in young adult patients with MDD than in HCs, and (2) differences in prefrontal hemodynamic changes occur during a cognitive task involving MDD patients with and without suicidality.

MATERIALS AND METHODS

Participants

The study enrolled 35 patients with MDD but no suicidality, 25 patients with MDD and suicidality, and 59 healthy controls (HCs), between the ages of 18 and 34 years. We did not stratify according to sex in the recruitment of subjects, and the number of males in each group was 27, 16, and 27, respectively. Patients with MDD were recruited through the outpatient clinic of Samsung Medical Center in Seoul, South Korea, and HCs were recruited from the community through advertisements released by the Clinical Trial Center of Samsung Medical Center between July 2018 and October 2020. The native language of all participants was Korean. Diagnosis of MDD and evaluation of suicidality were conducted based on the Korean version 5.0.0 of Mini International Neuropsychiatric Interview (MINI) (24). Patients diagnosed with MDD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV were included in the MDD group. We defined the suicidal group as those with moderate or high suicidality based on the MINI suicidality item. Exclusion criteria were: (1) MDD with psychotic features; (2) comorbid major psychiatric illnesses including bipolar disorder, schizophrenia, delusional disorder, delirium, neurocognitive disorder, intellectual disability, and other mental disorders due to another medical condition; (3) history of substance-related disorders except for tobacco-related disorders

within 12 months; (4) primary neurologic illness or history of brain damage; and (5) history of major physical illness. Patients' treatment was maintained according to standard treatment guidelines for depressive disorders including antidepressant medications and did not change during the study period. HCs did not have a history of major depressive episodes and scored seven or less on the Korean version of the Hamilton depression rating scale (HAM-D) (25), with the same exclusion criteria of the MDD group applied. The study design was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2018-04-137), and all participants provided written informed consent before study participation, in accordance with the Declaration of Helsinki.

Psychological Measures

At baseline, participants were evaluated using psychological scales including the MINI, HAM-D, the Korean version of the Hamilton anxiety rating scale (HAM-A) (26), the Korean version of the Barratt impulsiveness scale-11 (BIS-11) (27), and Clinical global impression scale - severity (CGI-S) (28).

Suicidality was evaluated based on the MINI suicidality item, which was scored according to responses to questions involving self-harm, suicidal ideation, suicidal plan, and suicide attempt. The range of suicidality scores was 0–33, and a score of 1–5 was rated as low risk, 6–9 as moderate risk, and $\geq$10 as high risk.

Functional Near-Infrared Spectroscopy and Verbal Fluency Task

Participants visited the experimental site 3 times at 4-week intervals, and we repeated fNIRS monitoring at each visit. At the monitoring, we extracted the concentrations of oxy-Hb using three consecutively repeated trials of rest, speech, and VFT (**Figure 1**), and the measured values during each trial reflected the prefrontal activity during baseline, speaking, and cognitive executive status, respectively. Each trial lasted 30 s. In each speech trial, participants were asked to repeat the articulation of "giyeog-nieun-digeud-lieul" (pronunciation of the Korean alphabets) for 30 s. During the VFT trial, participants were asked to generate as many words beginning with a specific consonant as possible. We adopted VFT to efficiently induce cognitive execution within a set time in the protocol. VFT, one of the brief psychological tests for cognitive assessment, is known to be particularly sensitive to depression due to the overlap between cognitive demands of VFT and cognitive deficits occurring in patients with depression (e.g., initiation, maintaining attention, retrieval, and persistence) (29, 30), and a previous fNIRS study reported that hemodynamic changes induced during cognitive tasks were specific to VFT, while other cognitive tasks including Stroop and the two-back task did not lead to significant changes (23).

In each channel, we calculated the average changes in oxy-Hb concentration during each VFT trial from the last 5 s of the preceding speech trial to measure the prefrontal activation corresponding to cognitive execution after excluding the effect of the speech made while performing the VFT, and the prefrontal activation at each visit was measured by averaging three consecutively calculated values. To increase the accuracy of the measurement value, subjects visited a total of 3 times at 4-week intervals and the process of fNIRS monitoring was repeated at each visit. We tried to reduce the intraindividual variation with repeated measures while reducing inattention resulting from the repetition of the same task by spacing each visit.

We used a high-density fNIRS device (NIRSIT, OBELAB, Seoul, South Korea). The sensor array comprised 24 dual-wavelength laser diodes (780/850 nm) and 32 photodetectors (31). A 3 cm distance separated the laser and detector pairs at 48 sensing areas in the prefrontal cortex including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), frontopolar cortex (FPC), and ventromedial prefrontal cortex (VMPFC), and the optical signal variation of each channel was sampled at 8.138 Hz. The hemodynamic changes in each channel during each VFT trial were extracted using the Modified Beer-Lambert Law (MBLL). After filtering detected light signals with a band-pass filter (0.005–0.1 Hz), the signal-to-noise ratio threshold was set to 30 dB based on the resting state, removing the slow drift of physiological and environmental noise.

Statistical Analysis

We presented continuous variables as mean $\pm$ standard deviation (SD) and categorical variables as numbers and percentages. Student *t*-tests, analysis of variance (ANOVA), and chi-square tests were used to compare the differences in factors between groups. A repeated-measures ANOVA (RM-ANOVA) was used for the comparison of changes in oxy-Hb during VFT between the groups and repeated-measures analysis of covariance (RM-ANCOVA) after adjusting for sex, age, alcohol intake, smoking status, systolic blood pressure (SBP), heart rate, and years of education was also used. The ANOVA Tukey *post hoc* tests were also applied to examine whether significant differences existed between the three groups. These statistical analyses were performed using IBM SPSS Statistics Software (version 24; IBM, New York, NY, United States). We considered a *p*-value less than 0.05 as statistically significant.

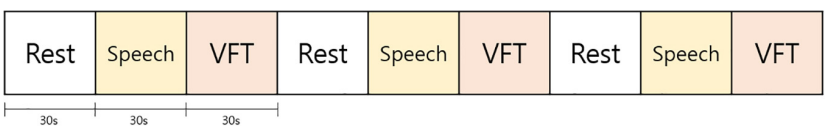

FIGURE 1 | Protocol of verbal fluency test (VFT). At each visit, subjects were exposed to three consecutively repeated trials of rest, speech, and VFT. Each trial lasted 30 s. In each speech trial, subjects were asked to repeat the articulation of "giyeog-nieun-digeud-lieul" for 30 s. In the VFT trial, subjects were asked to produce as many words beginning with a specific consonant as possible.

Additionally, we conducted permutation tests to compare the mean changes of oxy-Hb concentration during VFT extracted over the three visits between groups. The permutation test is a non-parametric statistical method and deals with the multiple comparisons issue when the assumptions of a parametric approach are untenable in functional neuroimaging (32). In this study, since the statistical analysis was performed on multiple brain regions, a statistical inference should be considered to reduce the risk of type I error by correcting for multiple comparisons. However, the brain regions of interest are located close to each other within the prefrontal cortex and hemodynamically highly correlated with each other (i.e., independent of each other), using classical parametric statistics with standard procedures for multiple comparison correction (e.g., Bonferroni correction) has the potential to inflate false negatives. This non-parametric resampling-based approach has been suggested as an effective and intuitive option for multiple comparison problems in fNIRS research (33–35). We ran 1000 permutations in each brain region of interest through R packages (R Foundation for Statistical Computing) and the "lmPerm" package was used for the analyses.

RESULTS

Demographic and Other Characteristics

Six of the enrolled subjects dropped out from the study (1 MDD without suicidality; 2 MDD with suicidality; 3 HCs). Four subjects were excluded from the analyses due to data error (3 MDD without suicidality; 1 HC). A total of 109 subjects were included in the analyses (31 subjects of MDD without suicidality; 23 subjects of MDD and suicidality; 55 HCs) (**Supplementary Figure 1**). Demographic and other baseline characteristics of participants are presented in **Table 1**. Male subjects included 87.1% of the MDD without suicidality group, 69.6% of the MDD and suicidality group, and 49.1% of the HCs. The mean ages of the MDD without suicidality group, the MDD with suicidality group, and the HCs were 24.26 (SD, 4.46), 24.43 (SD, 4.74), and 27.38 (SD, 3.48), respectively. 96.8% of MDD without suicidality group and 95.7% of MDD with suicidality group were taking antidepressants, and none of the HCs was under psychiatric medications. Alcohol intake was reported in about 74% of subjects in the MDD groups and 96.4% of the HCs. Heavy smokers included 41.9% of the MDD without suicidality group, 26.1% of the MDD with suicidality group, and 1.8% of the HCs. The mean score of HAM-D for the MDD without suicidality, the MDD with suicidality, and the HCs were 16.29 (SD, 5.31), 18.30 (SD, 5.60), and 1.84 (SD, 1.95), respectively. The mean scores of HAM-A for the MDD without suicidality, the MDD with suicidality, and the HCs were 17.19 (SD, 7.04), 17.57 (SD, 7.51), and 2.42 (SD, 2.34), respectively. The mean score of CGI-S for the MDD without suicidality, the MDD with suicidality, and the HCs were 3.45 (SD, 0.74), 4.15 (SD, 1.26), and 1.00 (SD, 0), respectively. BIS-11 was the highest at 71.43 (SD, 14.48) in the MDD and suicidality group and the lowest in the HCs at 57.49 (SD, 9.49).

Changes in oxy-Hb Concentration During Verbal Fluency Test

Table 2 and **Figure 2** show changes in oxy-Hb during VFT between groups. Using RM-ANOVA, significant differences were found between groups in the left FPC [$F_{(2,89)} = 3.596$, $p = 0.031$, partial $\eta^2 = 0.08$]. When the permutation test was performed on the difference in mean values in each group, significance was also maintained ($p = 0.013$). When the groups were compared after adjusting for age, sex, SBP, HR, alcohol intake, smoking status, and years of education, there was a significant difference in the left FPC [$F_{(2,81)} = 5.009$, $p = 0.009$, partial $\eta^2 = 0.11$]. The results of *post hoc* analyses are presented in **Supplementary Table 1**. The results of the comparison of changes in deoxygenated hemoglobin according to groups are presented in **Supplementary Table 2**.

Supplementary Table 3 shows the comparison between HCs and MDD (with or without suicidality). After adjusting for age, sex, SBP, HR, alcohol intake, smoking status and years of education, there were significant differences between groups in the left prefrontal cortex FPC [$F_{(1,82)} = 5.829$, $p = 0.018$, partial $\eta^2 = 0.07$], right VMPFC [$F_{(1,82)} = 5.548$, $p = 0.021$, partial $\eta^2 = 0.06$] and left FPC [$F_{(1,82)} = 9.997$, $p = 0.002$, partial $\eta^2 = 0.11$].

Table 3 presents the comparison between MDD patients with and without suicidality. In all prefrontal regions, changes in oxy-Hb were smaller among MDD patients with suicidality compared with those without suicidality. After adjusting for covariates, there was a significant difference in the right VLPFC [$F_{(1,35)} = 5.028$, $p = 0.031$, partial $\eta^2 = 0.13$].

The time series on average changes in oxy-Hb and deoxygenated Hb concentration during VFT are presented in **Supplementary Figure 2**.

DISCUSSION

In this study, we investigated the role of fNIRS as a biomarker to diagnose and evaluate depression and suicidality in a young adult population by measuring changes in oxy-Hb of the prefrontal area during cognitive tasks. The major findings were: (1) During the cognitive task, prefrontal activation was lower in patients with MDD than in HCs. (2) Impaired prefrontal activation was more prominent in MDD patients with suicidality than in those without suicidality. (3) The differences between the three groups were significant in the left frontopolar cortex after adjusting the covariates. These findings suggest that fNIRS may be a useful tool to diagnose and characterize patients with MDD.

We found that prefrontal activation was impaired during cognitive tasks in patients with MDD compared with HCs, which is consistent with the results of previous studies (15, 16). Left frontal inactivation in patients with MDD has also been consistently reported in studies using PET or electroencephalogram (36–39). In our study, a significant difference was detected in the left FPC. The FPC is known to play a role in higher and more complex cognitive functions such as planning, problem-solving, reasoning, and episodic memory

TABLE 1 | Baseline characteristics of participants.

	MDD without suicidality (*n* = 31)	MDD with suicidality (*n* = 23)	Healthy controls (*n* = 55)	*P*-value
	N (%)	N (%)	N (%)	
Sex				0.002
Male	27 (87.1)	16 (69.6)	27 (49.1)	
Female	4 (12.9)	7 (30.4)	28 (50.9)	
Education				<0.001
High school	21 (67.7)	16 (69.6)	9 (16.4)	
College	7 (22.6)	7 (30.4)	33 (60.0)	
Graduate school	2 (6.5)	0 (0)	13 (23.6)	
Marital status				0.114
Unmarried	29 (93.5)	21 (91.3)	45 (81.8)	
Married	1 (3.2)	2 (8.7)	10 (18.2)	
Occupation				0.121
Permanent employee	2 (6.9)	3 (13.0)	16 (29.1)	
Temporary employee	3 (10.3)	3 (13.0)	10 (18.2)	
Housewife	0 (0)		2 (3.6)	
Student	19 (65.5)	15 (65.2)	22 (40.0)	
Unemployed	5 (17.2)	2 (8.7)	5 (9.1)	
Alcohol intake	23 (74.2)	17 (73.9)	53 (96.4)	0.004
Smoking status				0.046
No	13 (41.9)	14 (60.9)	39 (70.9)	
Ever	5 (16.1)	3 (13.0)	15 (27.3)	
Heavy	13 (41.9)	6 (26.1)	1 (1.8)	
Use of psychiatric medications				
Antidepressants	30 (96.8)	22 (95.7)	0	<0.001
Benzodiazepines	12 (38.7)	7 (30.4)	0	<0.001
Psychiatric family history	7 (22.6)	6 (26.1)	2 (3.6)	0.008
Functional impairment				<0.001
No	4 (14.3)	2 (9.1)	32 (58.2)	
Mild	14 (50.0)	7 (31.8)	7 (12.7)	
Moderate	6 (21.4)	7 (31.8)	2 (3.6)	
Severe	4 (14.3)	6 (27.3)	0 (0)	
Childhood trauma	14 (48.3)	19 (82.6)	10 (18.2)	<0.001
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	***P-value***
Age (years)	24.26 (4.46)	24.43 (4.74)	27.38 (3.48)	0.001
Height (cm)	173.25 (7.61)	171.58 (8.31)	168.19 (7.70)	0.013
Weight (kg)	68.63 (12.21)	74.24 (18.03)	64.40 (14.31)	0.026
Systolic blood pressure (mmHg)	125.29 (14.34)	127.30 (14.83)	118.76 (15.14)	0.034
Diastolic blood pressure (mmHg)	74.48 (8.33)	75.74 (10.20)	70.62 (9.33)	0.045
Heart rate (bpm)	82.00 (10.89)	84.26 (13.00)	75.22 (8.27)	<0.001
Body temperature (°C)	36.75 (0.13)	36.71 (0.11)	36.74 (0.20)	0.636
Score of suicidality	2.71 (4.46)	10.60 (7.26)	0.07 (0.52)	<0.001
HAM-D	16.29 (5.31)	18.30 (5.60)	1.84 (1.95)	<0.001
HAM-A	17.19 (7.04)	17.57 (7.51)	2.42 (2.34)	<0.001
CGI-S	3.45 (0.74)	4.15 (1.26)	1.00 (0)	<0.001
BIS-11	69.55 (12.70)	71.43 (14.48)	57.49 (9.49)	<0.001

MDD, major depressive disorder; HAM-D, Hamilton depression rating scale; HAM-A, Hamilton anxiety rating scale; CGI-S, Clinical global impression scale-severity; BIS-11, Barratt impulsiveness scale-11.

retrieval (40, 41). Combined with the findings of previous studies, our results suggest that fNIRS can be used in the young adult population to diagnose or characterize MDD.

Additionally, impaired prefrontal activation was more prominent in patients with MDD and suicidality than in those without suicidality, and this result was consistent with those of previous studies (21, 22). In our study, although statistical significance was found only in the right VLPFC, the changes in oxy-Hb involving all prefrontal regions were smaller in those with suicidality. Previous studies

TABLE 2 | Comparison of changes in oxygenated hemoglobin during verbal fluency test according to groups.

(Unit: μ mol)	MDD without suicidality (*n* = 31)		MDD with suicidality (*n* = 23)		Healthy controls (*n* = 55)		RM-ANOVA			RM-ANCOVA[a]			Permutation test
	Mean	SD	Mean	SD	Mean	SD	F	*p*	*p* for interaction[b]	F	*p*	*p* for interaction[b]	*p*
Total prefrontal cortex	0.491	1.071	0.167	0.847	0.726	0.894	1.780	0.175	0.233	2.152	0.123	0.250	0.012
Right prefrontal cortex	0.687	1.317	0.150	1.010	0.793	1.019	1.471	0.235	0.511	1.775	0.176	0.335	0.015
Left prefrontal cortex	0.295	0.895	0.185	0.803	0.658	0.825	2.466	0.091	0.136	2.891	0.061	0.473	0.015
Right DLPFC	0.703	1.641	0.303	1.265	0.669	1.051	0.528	0.592	0.486	0.742	0.479	0.586	0.843
Right VLPFC	1.392	1.905	0.333	1.728	1.304	1.506	1.948	0.149	0.597	2.542	0.085	0.071	0.075
Right FPC	0.412	1.133	−0.019	0.809	0.586	0.900	2.180	0.119	0.373	2.385	0.099	0.255	0.005
Right VMPFC	0.366	1.177	−0.043	1.087	0.716	1.061	2.069	0.132	0.661	2.786	0.068	0.791	0.015
Left DLPFC	0.369	1.094	0.325	1.094	0.538	0.734	0.828	0.440	0.184	1.501	0.229	0.646	0.222
Left VLPFC	0.751	1.111	0.253	0.940	0.938	1.121	2.687	0.074	0.405	2.086	0.131	0.825	0.009
Left FPC	0.324	1.200	−0.007	0.768	0.662	0.963	3.596	0.031	0.532	5.009	0.009	0.650	0.013
Left VMPFC	−0.125	1.138	0.266	0.824	0.459	1.040	1.995	0.142	0.402	1.954	0.148	0.431	0.111

MDD, major depressive disorder; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; FPC, frontopolar cortex; VMPFC, ventromedial prefrontal cortex.

[a]*Adjusted by age, sex, systolic blood pressure, heart rate, alcohol intake, smoking status, and years of education.*

[b]*p-values for interactions between time (visit) and group.*

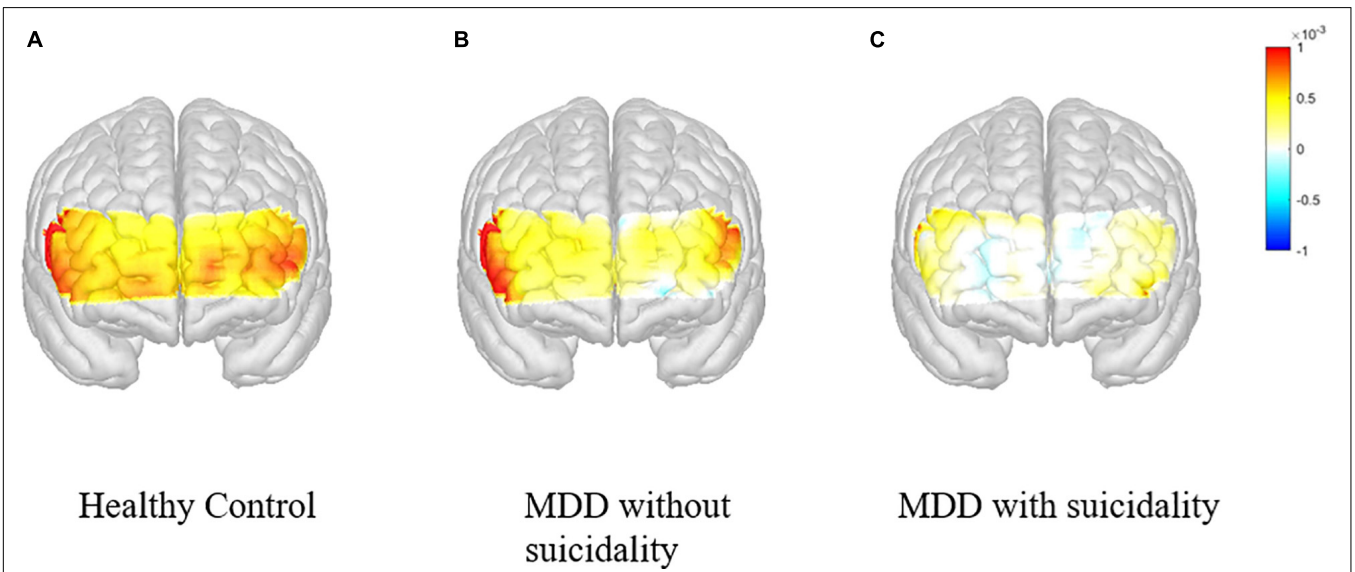

FIGURE 2 | Changes in the concentration of oxygenated hemoglobin in the prefrontal cortex during VFT according to participant groups. VFT, verbal fluency test. **(A)** Healthy control. **(B)** MDD without suicidality. **(C)** MDD with suicidality.

investigating MDD have reported the association between prefrontal function and executive impairment in patients with suicidality (42, 43). Combining these findings, our results show that executive impairment, which is a characteristic of suicidality in patients with MDD, can be correlated with the hemodynamic changes during cognitive execution and suggest that the measurement through fNIRS can be a biomarker characterizing or predicting suicidality in the young adult patients with MDD.

To our knowledge, this is the first study to identify the clinical and prognostic value of fNIRS by comparing the changes in oxy-Hb between HCs, patients with MDD without, and with suicidality among the young adult population. This study has strength in that the fNIRS data were repeatedly measured three times at intervals of 4 weeks to determine differences between groups. As a result, we tried to increase the accuracy by minimizing individual variation or error.

The study also has a few limitations. First, because we used only VFT to induce cognitive execution, the results should be interpreted within the limits of this methodology. Second, although the main outcomes were presented using RM-ANOVA and RM-ANCOVA based on the fNIRS results of three visits,

TABLE 3 | Comparison of changes in oxygenated hemoglobin during verbal fluency test between patients with MDD and suicidality and those without suicidality.

(Unit: μ mol)	MDD without suicidality (*n* = 31)		MDD with suicidality (*n* = 23)		RM-ANOVA			RM-ANCOVA[a]			Permutation test
	Mean	SD	Mean	SD	F	*p*	*p* for interaction[b]	F	*p*	*p* for interaction[b]	*p*
Total prefrontal cortex	0.491	1.071	0.167	0.847	0.966	0.331	0.342	0.823	0.371	0.408	0.172
Right prefrontal cortex	0.687	1.317	0.150	1.010	1.544	0.221	0.669	1.623	0.211	0.523	0.090
Left prefrontal cortex	0.295	0.895	0.185	0.803	0.237	0.629	0.092	0.055	0.816	0.333	0.615
Right DLPFC	0.703	1.641	0.303	1.265	0.714	0.403	0.508	0.864	0.359	0.526	0.196
Right VLPFC	1.392	1.905	0.333	1.728	2.901	0.096	0.922	5.028	0.031	0.808	0.054
Right FPC	0.412	1.133	−0.019	0.809	1.687	0.201	0.473	1.221	0.277	0.233	0.140
Right VMPFC	0.366	1.177	−0.043	1.087	0.257	0.615	0.425	0.035	0.854	0.546	0.290
Left DLPFC	0.369	1.094	0.325	1.094	0.425	0.518	0.151	0.075	0.786	0.543	0.882
Left VLPFC	0.751	1.111	0.253	0.940	2.266	0.140	0.454	1.345	0.254	0.930	0.084
Left FPC	0.324	1.200	−0.007	0.768	0.937	0.338	0.328	0.521	0.475	0.352	0.154
Left VMPFC	−0.125	1.138	0.266	0.824	1.935	0.171	0.359	2.448	0.127	0.293	0.293

MDD, major depressive disorder; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; FPC, frontopolar cortex; VMPFC, ventromedial prefrontal cortex.

[a]*Adjusted by age, sex, systolic blood pressure, heart rate, alcohol intake, smoking status, and years of education.*

[b]*p-values for interactions between time (visit) and group.*

the information regarding temporal variation is limited. In this study, subjects with MDD did not undergo any additional intervention during the study period and only maintained their treatment according to standard clinical guidelines, and the time by group interactions were not significant for the change of oxy-Hb concentration in the brain regions of interest. The time by group interactions was not significant. However, further studies are needed to elucidate the temporal changes in brain activity according to repetitive cognitive tasks. Third, subjects' handedness, one of the widely investigated forms of hemispheric asymmetries (44), was not considered in the enrollment and analyses in this study. Fourth, matching for major variables such as age and sex was not conducted in subjects' enrollment, which resulted in differences between groups, needing consideration in interpreting the results.

In conclusion, in this fNIRS study involving a young adult population, we found that, compared with HCs, patients with MDD showed decreased activation in the prefrontal cortex during cognitive tasks. In addition, patients with MDD and suicidality showed lower activation of the prefrontal cortex than those without suicidality.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Samsung Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HK: conceptualization, formal analysis, and writing—original draft, review and editing. JC: data curation and writing—review and editing. BJ, MF, DM, MP, and HSK: writing—review and editing. HJ: conceptualization, project administration, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.915425/full#supplementary-material

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EDITED BY
Çiçek Hocaoglu,
Recep Tayyip Erdogan University, Turkey

REVIEWED BY
Wen Min,
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Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Turkey
Maria Skibińska,
Poznan University of Medical Sciences, Poland

*CORRESPONDENCE
Carlos Alfonso Tovilla-Zárate
alfonso_tovillaz@yahoo.com.mx
Humberto Nicolini
hnicolini@inmegen.gob.mx

†These authors have contributed equally to this work and share first authorship

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Association between *TPH1* polymorphisms and the risk of suicide behavior: An updated meta-analysis of 18,398 individuals

Alma Delia Genis-Mendoza[1†], Yazmín Hernández-Díaz[2†], Thelma Beatriz González-Castro[2], Carlos Alfonso Tovilla-Zárate[3*], Rosa Giannina Castillo-Avila[4], María Lilia López-Narváez[5], Miguel Ángel Ramos-Méndez[4] and Humberto Nicolini[1*]

[1]Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, Ciudad de México, Mexico, [2]División Académica Multidisciplinaria de Jalpa de Méndez, Universidad Juárez Autónoma de Tabasco, Jalpa de Méndez, Mexico, [3]División Académica Multidisciplinaria de Comalcalco, Universidad Juárez Autónoma de Tabasco, Comalcalco, Mexico, [4]División Académica de Ciencias de la Salud, Universidad Juárez Autónoma de Tabasco, Villahermosa, Mexico, [5]Hospital Chiapas Nos Une "Dr. Gilberto Gómez Maza", Secretaría de Salud, Tuxtla Gutiérrez, Mexico

Objectives: We aimed to examine the association of *TPH1* polymorphisms with the risk of suicide behavior (SB).

Design: Systematic review and meta-analysis.

Method: All relevant studies that evaluated the association between the A218C (rs1800532), A779C (rs1799913) and A6526G (rs4537731) polymorphisms and the susceptibility to SB published up to September 2021 were identified through a comprehensive systematic search in PubMed, Scopus, EBSCO and Science Direct electronic databases. The association between *TPH1* gene polymorphisms and SB was evaluated using inherence models by odds ratio (OR) and 95% confidence interval (CI). Subgroup analyses, heterogeneity analyses, and publication bias were also tested in this meta-analysis.

Results: The meta-analysis for *TPH1* A218C revealed an increased risk of SB in the dominant model (OR = 1.11, 95%CI 1.01–1.22). We also observed a positive association in the allelic (OR = 1.13, 95%CI 1.05–1.21), homozygous (OR = 1.22, 95%CI 1.06–1.40), heterozygous (OR = 1.21, 95%CI 1.08–1.37) and dominant (OR = 1.21, 95%CI 1.09–1.34) inherence models with the suicide attempt. Additionally, in the heterozygous (OR = 0.84, 95%CI 0.73–0.97) and dominant (OR = 0.79, 95%CI 0.68–0.91) inherence models we detected an association with completed suicide. Based on ethnicity, an association of SB in the European population also was observed (OR = 1.29, 95%CI 1.12–1.51). However, for both A779C and A6526G polymorphisms we did not find evidence of an association with SB.

Conclusion: This meta-analysis suggests that the A218C polymorphism of *TPH1* gene could be a possible risk factor of SB. Future large-scale studies

are required to analyze the molecular mechanisms by which affect the susceptibility of developing suicide behavior.

KEYWORDS

tryptophan hydroxylase, meta-analysis, suicide behavior, polymorphism, risk allele

Introduction

Human behavior is governed by a complex interplay of numerous biological, genetic, psychological, cultural, social and family determinants. In particular, suicide behavior (SB) ranges from suicide ideation to suicide attempts and completed suicide and constitutes a multifactorial public health issue. The understanding of the genetic system that causes vulnerability to develop SB is largely incomplete, as its etiology is complex and diverse; however, epidemiological studies show that suicide behavior is partly heritable and polygenic (1, 2).

Serotonin, also known as 5-hydroxytryptamine (5-HT), is produced by generating 5-hydroxytryptophan out of tryptophan and the downstream decarboxylation using aromatic amino acid decarboxylase (3). Tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin. Serotonin is synthesized in the central nervous system (CNS) as well as gastrointestinal system, and it is produced by TPH, which can be present in two isoforms, TPH1 and TPH2 (4, 5).

The serotonergic system is implicated in the etiology and pathogenesis of several psychiatric disorders. Serotonergic pathways associated with mood disorders and SB include the inflammatory processes related to serotonin processing (6). The neuroimmunological kynurenine pathway has been implicated in major depressive disorder and suicide in adults. Kynurenine is formed from its precursor, tryptophan, if kynurenine levels are associated with tryptophan concentrations, these pathways are argued to have the ability to influence levels of serotonin. It has been reported that the kynurenine production is higher among individuals with a history of suicide attempts (1, 7).

The *TPH1* gene has been extensively studied as a candidate for suicide behavior due to its role in serotonergic neurotransmission (1, 8). This gene is located on chromosome 11p15.3-p14 and has two common polymorphisms in intron 7 consisting of A for C substitution at nucleotides 779 (A779C; rs1799913) and at 218 (A218C; rs1800532), plus one polymorphism in the promoter region consisting of A for G substitution at nucleotides 6526 (A6526G; rs4537731). These polymorphisms have been associated with suicide for they may influence the level of serotonin metabolites and their functionality (9, 10).

Although one meta-analysis (10) has already addressed the issue of the association between the *TPH1* polymorphisms and (11) SB, the sample sizes used were relatively small. Also, in the las years, the *TPH1* polymorphisms have been attracting attention and more studies have explored the association of *TPH1* polymorphisms and suicide behavior. Therefore, it is important to summarize the results from more studies to further validate the association of *TPH1* polymorphisms with the risk of suicide behavior. In this study, a systematic review and updated meta-analysis was performed on all eligible case-control studies to estimate the overall SB risk associated with three polymorphisms of *TPH1* gene: A218C, A779C and A6526G. Additionally, we conducted subgroup analyses stratified by ethnicity and diagnostic. The results of this meta-analysis can provide an opportunity to unveil the role that the *TPH1* gene plays in the susceptibility to suicide.

Materials and methods

The search strategy follows the PRISMA (http://www.prisma-statement.org/) reporting guidelines.

Search strategy

The following terms were used for searching potential studies: ("suicide" OR "suicidal") AND ("TPH1" OR "tryptophan hydroxylase 1"). We searched for articles were searched in PubMed, Scopus, EBSCO and Science Direct databases, dated up to September 2021. To find other potential studies, we examined the references of the eligible studies. The process of the study selection in the preset work is detailed in a flow diagram; Figure 1.

Eligible inclusion/exclusion criteria

The criteria applied for eligible studies were: 1- studies that evaluated the association between *TPH1* A218C, A779C and A6526G polymorphisms and suicide risk, 2- cases-controls designs studies, 3- individuals with a suicidal behavior

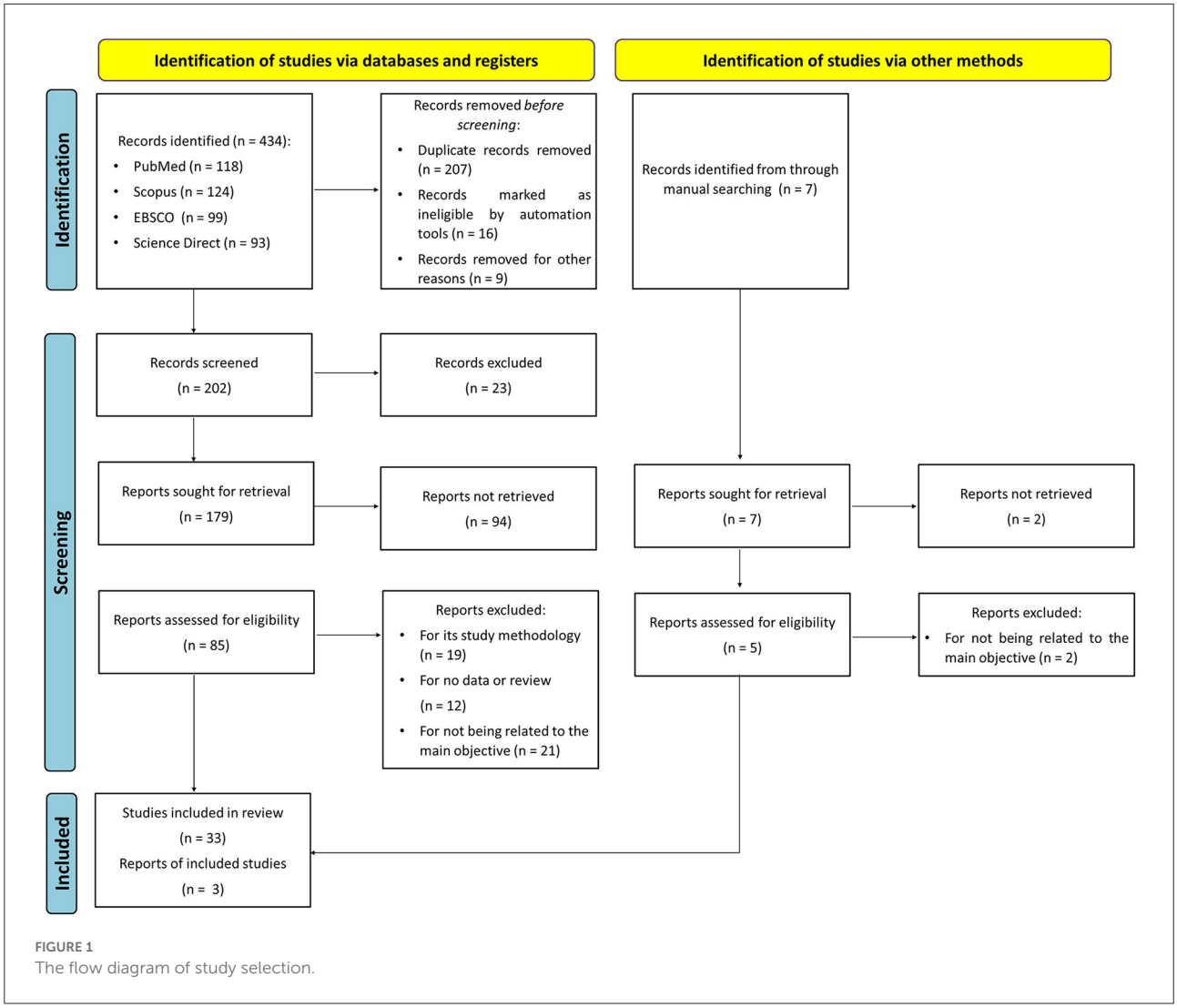

FIGURE 1
The flow diagram of study selection.

which identified by a specialist; we included all the suicidal behavior spectrum (attempt, ideation and completed suicide) addressed in the published studies, 4- sufficient data available to obtain genotypic frequencies to calculate odds ratio (OR) and 95% confidence interval (95%CI), 5- articles published in English. These data were not always available for all studies, but when needed, we contacted the authors to clarify the information not included in the papers. Reviews, meta-analysis, duplicates, case reports, book chapters, and animal studies were all excluded.

Data collection

The relevant data from each study were extracted by to reviewers (Hernandez-Díaz and Castillo-Avila) using standardized and structured forms. The following data were extracted: first author, year of publication, country, main outcome, criteria diagnostic, source of DNA, genotyping method, ethnicity, gender, sample size, genotype distribution for the cases and controls. Once encountering discrepancies, other authors re-checked the original articles until an agreement was achieved by all of them.

Assessment of methodological quality

The Newcastle-Ottawa Scale (NOS) was used to examine the quality of each study. Quality scores range from 0 to 9, and higher scores mean better quality of the study. Studies scoring six o higher were considered as high-quality studies. The qualities of the includes studies were evaluated by the same two investigators. Disagreements were resolved through discussion by a third investigator (Gonzalez-Castro).

TABLE 1 The characteristics of included studies in this meta-analysis for A218C polymorphism.

References	Country	Sample		Males		Mean age		SB	Genotypes						Alleles				P for HWE		NOS scale
		Case	Control	Case	Control	Case	Control		Case			Control			Case		Control		Case	Control	
									AA	AC	CC	AA	AC	CC	A	C	A	C			
A218C																					
Bellivier F (12)	France	52	94	-	57	-	43.7	SA	17	24	11	11	45	38	58	46	67	121	0.642	0.672	6
Kunugi H (14)	Japan	46	208		95	55	32.1	SA	10	29	7	55	105	48	49	43	215	201	0.07	0.876	7
Geijer T (19)	Sweden	165	98	57	64	41	38	SA	30	87	48	13	47	38	147	183	73	123	0.387	0.797	8
Paik I (21)	Korea	27	236		124	30	29.6	SA	4	12	11	66	116	54	20	34	248	224	0.806	0.824	7
Ono H (20)	Japan	132	132	90	90	48.3	47.2	CS	29	68	35	26	71	35	126	138	123	141	0.709	0.353	8
Souery D (25)	Belgium, Bulgaria, Croatia, Germany, Greece, Israel, Italy, Sweden, United Kingdom	167	167	-	-	-	-	SA	29	85	53	27	74	66	143	191	128	206	0.61	0.418	6
Abbar M (22)	France	231	281	105	170	36	43	SA	43	120	68	30	133	118	206	256	193	369	0.435	0.406	8
Zalsman G (27)	Israel	84	172	40	74	17.4	40.9	SA	16	34	34	41	85	46	66	102	167	178	0.164	0.887	8
Turecki G (26)	Canada	101	129	-	-	32.2	34	CS	18	48	35	18	71	40	84	118	107	151	0.826	0.128	6
Hong CJ (23)	Taiwan	140	251	-	123	35.3	33.8	SA	42	57	41	42	135	74	141	139	219	283	**0.028**	0.138	7
Rujescu D (28)	Germany	86	154	27	66	39	48	SA	10	48	28	19	78	57	68	104	116	192	0.12	0.328	8
Rujescu D (30)	Germany	147	326	52	-	40	-	SA	18	81	48	40	155	131	117	177	235	417	0.069	0.572	7
Jernej B (31)	Croatia	185	358	144	298	52	43	CS	84	85	16	202	141	15	253	117	545	171	0.395	0.115	8
Ohtani M (32)	Japan	132	214	94	114	55.4	63.5	CS	30	60	42	44	113	57	120	144	201	227	0.338	0.38	8
Stefulj J (34)	Croatia	160	284	160	284	48	44	CS	21	69	70	44	145	95	111	209	233	335	0.541	0.352	8
Stefulj J (36)	Croatia	247	320	247	320	65	65	CS	33	111	103	50	162	108	177	317	262	378	0.72	0.401	8
Viana MM (37)	Brazil	248	63	142	36	37.2	34.3	SA	45	125	78	7	31	25	215	281	45	81	0.679	0.569	9
Liu X (35)	China	297	174	171	98	46.1	42.8	SA	72	148	67	41	84	49	292	282	166	182	0.591	0.668	9
Yoon H K (38)	Korea	191	193	70	73	40.5	41.4	SA	49	97	45	60	85	48	195	187	205	181	0.823	0.107	8
Baud P (39)	Switzerland and France	544	1,027	166	-	39.1	-	SA	99	256	182	181	483	363	454	620	845	1,209	0.59	0.354	6
Wilson ST (40)	USA	71	101	-	39	34.2	40.5	SA	13	44	14	22	43	36	70	72	87	115	**0.043**	0.185	7

(Continued)

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TABLE 1 Continued

References	Country	Sample		Males		Mean age		SB	Genotypes						Alleles				P for HWE		NOS scale
		Case	Control	Case	Control	Case	Control		Case			Control			Case		Control		Case	Control	
									AA	AC	CC	AA	AC	CC	A	C	A	C			
Buttenschon HN (42)	Denmark	490	1,027	209	763	-	-	CS	80	228	182	181	483	363	388	592	845	1,209	0.546	0.354	6
Beden O (43)	Turkish	109	98	36	50	33.6	36.5	SA	24	53	32	14	42	42	101	117	70	126	0.816	0.509	8
Lee SM (46)	Korea	13	20	1	7	31.9	33.6	SA	1	8	4	7	10	3	10	16	24	16	0.279	0.852	8
Choi HY (45)	Korea	71	89	36	41	38.5	41.1	SI	14	46	11	20	46	22	74	68	86	90	**0.012**	0.666	8
Choi HY (45)	Korea	69	143	34	65	39.3	44.9	SA	13	42	13	32	74	37	68	68	138	148	0.052	0.664	8
Pan YF (47)	China	712	739	235	247	40.5	40.2	SA	156	362	194	156	387	196	674	750	699	779	0.598	0.17	9
Total		4,917	7,098																		

SA, suicide attempt; SI, suicide ideation; CS, completed suicide.

Statistical analysis

The relationship between *TPH1* gene polymorphism and SB risk was determined by calculating OR and 95%CI. To measure this association, we evaluated the effect by five genetic models: allelic (A vs. C), dominant (AA + AC vs. CC), recessive (AA vs. AC + CC), heterozygous (AC vs. CC) and homozygous (AA vs. CC).

Z-test was used to determine the significance of the OR ($P < 0.05$ was considered statistically significant). Cochrane *Q*-test and I^2 test was conducted to assess the between studies heterogeneity. Significant heterogeneity was defined with a *P*-value < 0.05 and $I^2 \geq 50\%$ and a random effect model (DerSimonian–Laird) was used in this case. Otherwise, a fixed effect model (Mantel–Haenszel) was applied. Subgroup analysis was used to further identify the factors influencing heterogeneity. Publication bias was assessed by funnel diagram that produces a diagram according to its OR and the standard error of each study, moreover, Egger's test was calculated ($P < 0.05$ was considered statistically significant). The data were analyzed using Comprehensive Meta-Analysis (CMA) software v.2.

Results

Literature search and study characteristics

A total of 441 potentially relevant studies emerged from the first search in PubMed, EBSCO, Science Direct, Scopus and manual searching. After excluding 351 unrelated publications, we screened 90 publications for eligibility of inclusion. Finally, thirty-six studies met the selection criteria and were finally enrolled for pooled analyses (11–47). The PRISMA flow diagram used for study selection process is summarized in Figure 1.

There were 6,214 cases and 12,184 controls in these 36 studies, 16 studies were conducted in European populations, 13 in Asian populations, 5 in American populations, 1 in Turkish and 1 in mixed populations (USA and Italy). In terms of the SB type, some studies evaluated suicide attempt ($n = 27$), suicide ideation ($n = 1$), and completed suicide ($n = 8$). The age of the individuals studied ranged from 17.4 to 65 years old. There were statistically significant deviations from the HWE in the control groups ($n = 3$); therefore, these studies were excluded from the meta-analysis.

According to the Newcastle–Ottawa scale, the quality score of each included study was >6, indicating good quality overall. Tables 1, 2 displays the main characteristics and quality assessment results of the eligible studies.

TABLE 2 The characteristics of included studies in this meta-analysis for A779C and A6528G polymorphisms.

References	Country	Sample		Males		Mean age		SB	Genotypes						Alleles				P for HWE		NOS scale
		Case	Control	Case	Control	Case	Control		Case			Control			Case		Control		Case	Control	
									AA	AC	CC	AA	AC	CC	A	C	A	C			
A779C																					
Nielsen DA (11)	USA	102	232	-	232	31	32	SA	17	57	28	49	106	77	91	113	204	260	0.186	0.268	7
Rotondo A (15)	Italy and USA	97	153	-	153	32	32	SA	12	50	35	33	68	52	74	120	215	201	0.363	0.229	7
Kunugi H (14)	Japan	46	208	7	95	55	32	SA	10	29	7	55	105	48	49	43	215	201	0.07	0.876	7
Roy A (24)	Sweden	24	158	15	77	-	-	SA	2	12	10	35	86	37	16	32	156	160	0.54	0.264	6
Rujescu D (28)	Germany	86	154	27	66	39	48	SA	10	47	29	20	76	58	67	105	116	192	0.166	0.526	8
Rujescu D (30)	Germany	147	326	52	148	40	46	SA	48	81	18	131	155	40	177	117	417	235	0.069	0.572	7
Pooley EC (29)	United Kingdom	129	329	52	138	38	38	SA	20	67	42	44	135	150	107	151	223	435	0.427	0.126	9
Ohtani M (32)	Japan	134	325	95	171	55.4	63.5	CS	30	59	42	45	138	82	119	143	228	302	0.294	0.311	9
Koller G (33)	Germany	80	241	-	79	27.3	42.6	SA	15	38	27	36	114	91	68	92	186	296	0.801	0.975	7
Liu X (35)	China	266	164	171	98	46.1	42.8	SA	77	126	63	43	85	36	280	252	171	157	0.414	0.622	9
Pompili M (44)	Roma	57	54	36	34	48.6	51.4	SA	8	25	21	13	27	17	41	67	53	61	0.899	0.717	8
Lee SM (46)	Korea	13	20	1	7	31.9	33.6	SA	1	8	4	8	9	3	10	16	25	15	0.279	0.858	8
Pan YF (47)	China	712	739	235	247	40.5	40.2	SA	158	361	193	163	386	190	677	747	712	766	0.659	0.21	9
Total		1,893	3,103																		
A6526G																					
Ono H (20)	Japan	132	132	90	90	48.3	47.2	CS	89	42	1	89	38	5	220	44	216	48	0.094	0.709	8
Turecki G (26)	Canada	101	129	-	-	32.2	34	CS	35	46	20	45	62	22	116	86	152	106	0.49	0.934	6
Liu X (35)	China	283	180	171	98	46.1	42.8	SA	163	96	24	87	77	16	422	144	251	109	0.074	0.859	9
Total		516	441																		
Systematic review																					
A218C																					
Tsai SJ (16)	China	41	200	-	91	-	-	SA	17	15	9	33	113	54	49	33	179	221	0.125	0.043	6
Du L (18)	Hungary	35	84	27	60	47.7	56.6	CS	6	24	5	13	52	19	36	34	78	90	0.027	0.025	8
Saetre P (41)	Denmark, Norway and Sweden	299	1,655	-	845	45	44	SA	99	150	50	570	391	694	348	250	1,531	1,779	0.591	0	7
Total		375	1,939																		
A779C																					
Saetre P (41)	Denmark, Norway and Sweden	299	1,655	-	845	45	44	SA	99	150	49	570	391	694	346	250	1,531	1,779	0.535	0	7
Total		674	3,594																		

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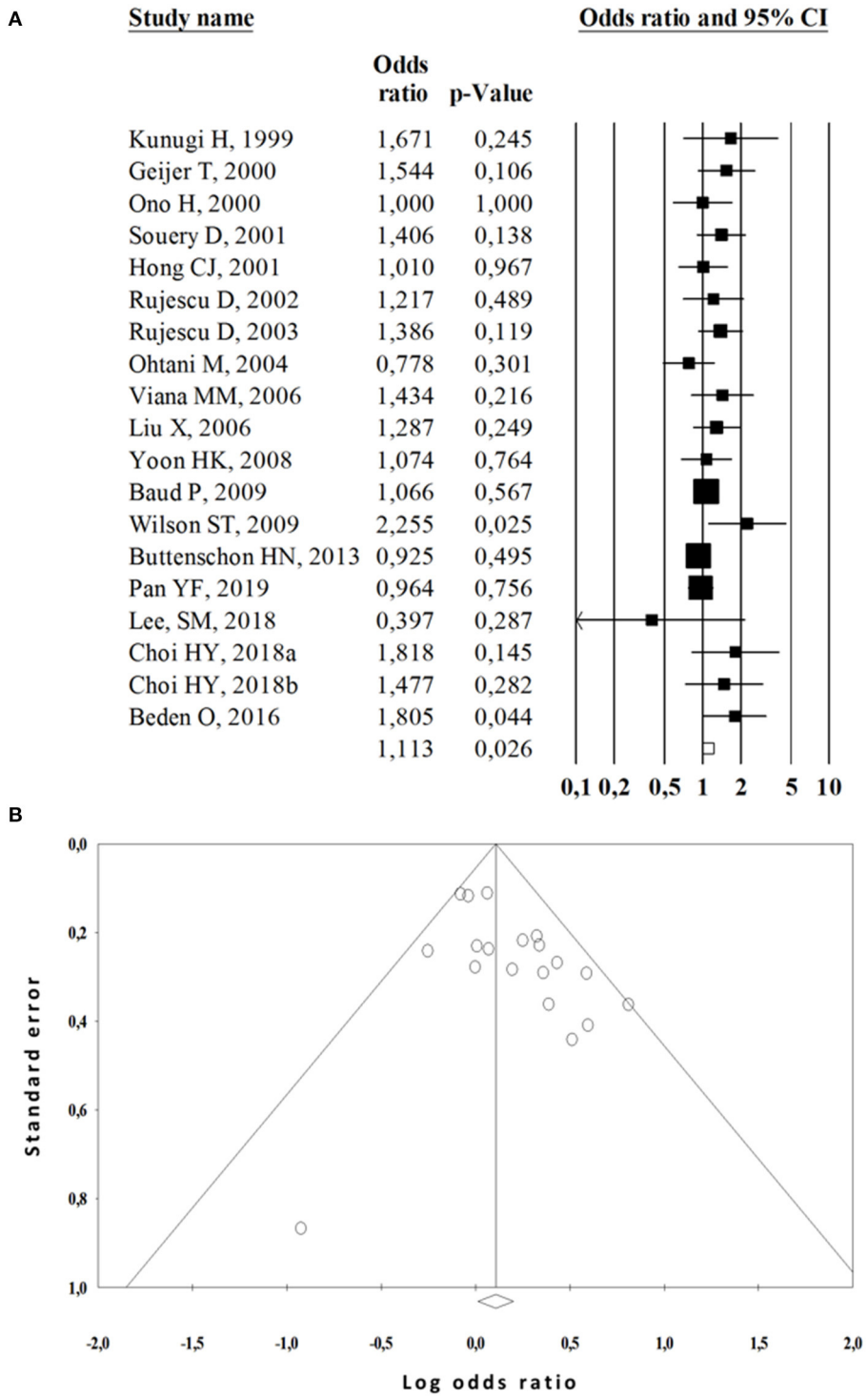

FIGURE 2
Meta-analysis of the association between A218C polymorphism and suicide behavior risk. **(A)** Forest plot of overall analysis in dominant comparison. **(B)** Funnel plot of overall analysis in dominant comparison.

TPH1 A218C polymorphism and the risk of SB

Twenty-seven studies (4,917cases and 7,098 controls) assessed the relationship between *TPH1* A218C polymorphism and the risk of suicide behavior (12, 14, 19–43, 45–47). The integrated analyses demonstrated that the AA/AC genotypes of A218C polymorphism was significantly associated with an increased risk of SB compared with the CC genotype (OR = 1.11, 95%CI 1.01–1.22; $P = 0.026$, Q test = 0.212, $I^2 = 19.90$) (Figure 2A).

Subgroup analyses were then performed based on ethnicity and diagnostic in order to investigate sources of heterogeneity (Table 3). We observed a positive association in the allelic (OR = 1.13, 95%CI 1.05–1.21; $P = 0.000$, Q test = 0.233, $I^2 = 19.72$), homozygous (OR = 1.22, 95%CI 1.06–1.40; $n = 0.004$, Q test = 0.117, $I^2 = 30.77$), heterozygous (OR = 1.21, 95%CI 1.08–1.37; $P = 0.001$, Q test = 0.186, $I^2 = 23.60$) and dominant (OR = 1.21, 95%CI 1.09–1.34; $P = 0.000$, Q test = 0.175, $I^2 = 24.71$) inherence models with the suicide attempt; while a decreased risk of completed suicide was observed in the heterozygous model (OR = 0.84, 95%CI 0.73–0.97; $P = 0.023$, Q test = 0.153, $I^2 = 33.09$) and dominant model (OR = 0.79, 95%CI 0.68–0.91; $P = 0.001$, Q test = 0.317, $I^2 = 14.38$) (Figure 3A). In the subgroup analysis based on ethnicity, A218C was associated with increased SB risk in European populations according to the dominant model (OR = 1.29, 95%CI 1.12–1.51; $P = 0.001$, Q test = 0.117, $I^2 = 43.22$). However, no significant associations were found in Asian populations.

TPH1 A779C polymorphism and the risk of SB

Thirteen studies (1,893 cases and 3,103 controls) assessed relationship between *TPH1* A779C polymorphism and the risk of suicide behavior (11, 14, 15, 24, 28–30, 32, 33, 35, 44, 46, 47). Overall, we did not observe an association between A779C polymorphisms of *TPH1* gene in the allele frequencies or any genotype model with an overall SB risk (Table 3). Either in a subgroup analysis by ethnicity or by diagnostic, no significant SB risk was identified.

TPH1 A6526G polymorphism and the risk of SB

Three case–control studies with 516 patients and 441 controls were included in the present meta-analysis (20, 26, 35). The major outcomes in this study are summarized in Table 3. The *TPH1* gene A6526G polymorphism was not significantly associated with suicide behavior under any genetic model.

Publication bias and sensitivity analysis

We estimated potential publication bias in this meta-analysis with funnel plots and Egger's test. Funnel plots were found to be overall symmetrical (Figures 2B, 3B) and the P values for Egger's test were >0.05 in all comparisons (Table 3). These results indicated that our quantitative pooled analysis results were not likely to be seriously influenced by publication biases. We carried out a sensitivity analysis to evaluate the influence of every study on the pooled OR by omitting an individual study at a time. The exclusion of any study did not alter the corresponding pooled OR; *P*-values demonstrated nonsignificant values ranging from 0.15 to 0.99.

Discussion

This meta-analysis, robustly estimated associations between gene polymorphisms in *TPH1* gene and the risk of suicide behavior. Considerable evidence has shown that the *TPH1* gene is a possible candidate involved in the etiology of suicide. Although one meta-analyses (10) has been conducted in the past 7 years evaluating the relationship between the *TPH1* gene polymorphisms and SB, its findings were inconclusive. Hence, to resolve inconsistencies and to decrease heterogeneity, we performed an updated meta-analysis. Regarding the essential role of genetic factors in the pathogenesis of suicide behavior, we categorized our results according to ethnicity and diagnostic.

First, the pooled analyses results showed that the A218C polymorphism was significantly associated with the risk of SB. The A218C polymorphism was found to be associated with SB in Koreans and Caucasian populations; moreover, A218C has been associated with anger related traits (16, 21, 48). Subgroup analysis based on ethnicity rejected any association between A218C polymorphisms and the SB risk in Asian populations; nonetheless, a significant association between A218C polymorphism and SB susceptibility was detected in European populations. Many reasons might contribute to the conflicting results. First of all, environmental factors that individuals are exposed and different genetic backgrounds, which may have effects on suicide risk. Considering the polygenic effect on psychiatric disorders, the genetic factors that have impacted on the original diseases could share their contributions to suicide as well. In future, large number of case–control studies could provide more evidence for the role of this polymorphism with respect to susceptibility to SB. These findings are consistent with the results of Ono et al. (20), Liu et al. (35) and Abbar et al. (22).

The A218C polymorphism has also been associated with an increased risk of suicide attempt; nonetheless, a protective role was observed in individuals who completed suicide. This polymorphism is localized at intron 7, a site that is a potential GATA transcription factor-binding site. The

TABLE 3 Integrated analyses for *TPH1* gene polymorphisms and suicide behavior.

Model	OR (CI 95%)	*Z P*-value	*Q*-test *P*-value	I^2	Egger's test *P*-value
A218C					
Overall					
A vs. C	1.02 (0.96–1.08)	0.456	0.175	22.29	0.343
AA vs. CC	1.01 (0.89–1.13)	0.875	0.109	27.65	0.989
AC vs. CC	1.03 (0.94–1.13)	0.482	0.122	27.29	0.191
AA vs. AC+CC	0.98 (0.88–1.08)	0.690	0.281	13.17	0.807
AA+AC vs. CC	1.11 (1.01–1.22)	**0.026**	0.212	19.90	0.212
Suicide attempt					
A vs. C	1.13 (1.05–1.21)	**0.000**	0.233	19.72	0.444
AA vs. CC	1.22 (1.06–1.40)	**0.004**	0.117	30.77	0.199
AC vs. CC	1.21 (1.08–1.37)	**0.001**	0.186	23.60	0.228
AA vs. AC+CC	1.11 (0.98–1.25)	0.091	0.128	29.49	0.765
AA+AC vs. CC	1.21 (1.09–1.34)	**0.000**	0.175	24.71	0.145
Competed suicide					
A vs. C	0.92 (0.81–1.04)	0.224	0.032	49.30	0.995
AA vs. CC	0.86 (0.72–1.03)	0.121	0.157	30.43	0.784
AC vs. CC	0.84 (0.73–0.97)	**0.023**	0.153	33.09	0.253
AA vs. AC+CC	0.88 (0.76–1.03)	0.114	0.594	0.000	0.664
AA+AC vs. CC	0.79 (0.68–0.91	**0.001**	0.317	14.38	0.179
European population					
A vs. C	0.96 (0.88–1.05)	0.392	0.146	38.99	0.702
AA vs. CC	1.00 (0.83–1.20)	0.975	0.345	11.04	0.620
AC vs. CC	1.12 (0.98–1.28)	0.084	0.102	41.52	0.372
AA vs. AC+CC	1.01 (0.86–1.18)	0.846	0.118	39.17	0.284
AA+AC vs. CC	1.29 (1.12–1.51)	**0.001**	0.117	43.22	0.107
Asian population					
A vs. C	1.01 (0.93–1.11)	0.674	0.256	19.71	0.272
AA vs. CC	1.06 (0.88–1.28)	0.494	0.260	19.23	0.326
AC vs. CC	1.00 (0.86–1.17)	0.957	0.189	26.75	0.595
AA vs. AC+CC	1.01 (0.81–1.26)	0.924	0.082	40.02	0.170
AA+AC vs. CC	1.00 (0.86–1.15)	0.998	0.344	10.53	0.856
A779C					
Overall					
A vs. C	0.98 (0.89–1.08)	0.738	0.552	0.000	0.337
AA vs. CC	0.97 (0.81–1.16)	0.778	0.224	21.71	0.115
AC vs. CC	1.05 (0.91–1.21)	0.484	0.256	18.58	0.842
AA vs. AC+CC	0.89 (0.77–1.04)	0.152	0.216	22.46	0.651
AA+AC vs. CC	1.02 (0.89–1.17)	0.686	0.202	23.90	0.637
Suicide attempt					
A vs. C	0.92 (0.79–1.07)	0.326	0.009	56.12	0.205
AA vs. CC	0.94 (0.78–1.14)	0.569	0.216	23.20	0.114
AC vs. CC	1.07 (0.92–1.24)	0.337	0.246	20.07	0.833
AA vs. AC+CC	0.90 (0.77–1.05)	0.210	0.250	19.71	0.134
AA+AC vs. CC	1.03 (0.90–1.19)	0.620	0.155	29.65	0.654
European population					
A vs. C	0.94 (0.79–1.13)	0.566	0.336	11.36	0.857
AA vs. CC	1.01 (0.73–1.41)	0.925	0.121	42.65	0.105

(Continued)

TABLE 3 Continued

Model	OR (CI 95%)	*Z P*-value	*Q*-test *P*-value	I^2	Egger's test *P*-value
AC vs. CC	1.20 (0.94–1.54)	0.140	0.195	32.11	0.109
AA vs. AC+CC	0.86 (0.66–1.12)	0.286	0.330	13.26	0.593
AA+AC vs. CC	1.23 (0.96–1.57)	0.088	0.259	24.31	0.107
Asian population					
A vs. C	0.99 (0.88–1.11)	0.917	0.382	4.411	0.475
AA vs. CC	1.00 (0.79–1.27)	0.951	0.366	7.189	0.552
AC vs. CC	0.92 (0.75–1.12)	0.412	0.575	0.000	0.699
AA vs. AC+CC	1.05 (0.86–1.27)	0.606	0.208	32.02	0.388
AA+AC vs. CC	0.94 (0.78–1.13)	0.549	0.608	0.000	0.998
A6526G					
Overall					
A vs. G	1.12 (0.91–1.38)	0.247	0.458	0.000	0.583
AA vs. GG	1.14 (0.69–1.86)	0.602	0.298	17.34	0.374
AG vs. GG	0.90 (0.55–1.47)	0.689	0.252	27.42	0.128
AA vs. AG+GG	1.20 (0.92–1.56)	0.175	0.378	0.000	0.108
AA+AG vs. GG	1.01 (0.63–1.60)	0.955	0.284	20.64	0.207

GATA transcription binding factors allow the initiation of transcription (49). The A218C polymorphism could affect the transcription level of *TPH1*. The TPH is an initial enzyme in the TRYCATs pathway, and its low expression may lead to stopping the pathway.

The tryptophan (TRY) metabolism has two large pathways: the methoxyindole pathway and the kynurenine pathway. Regarding the available TRYs in the body, approximately 1∼5% are synthesized as serotonin through the methoxyindole pathway and 95∼99% of TRYs are metabolized through the kynurenine pathway and form tryptophan catabolites (TRYCATs) (50, 51). These TRYCATs are important metabolites that may contribute to the pathophysiology of psychiatric disorders such as anxiety and depression (52). TRYCATs potentiate or antagonize relationships with various neurotransmission systems (53). TRYCATs could influence SB by directly contributing to neuroprotective-neurodegenerative changes in the brain. Activation of the TRYCAT pathway leads to the production of a range of neuroactive, neuroprotective and neurotoxic TRYCATs. For example, quinolinic acid act as potent neurotoxin which inhibit ATP production by mitochondria, provoke disrupt neuron glial communication, induce apoptosis of glial cells and directly damage neurons. Other TRYCATS also possess neurotoxic or neuroprotective properties via pro-oxidant and antioxidant effects (54, 55).

Moreover, this polymorphism could also influence individual differences in anger-related personality traits. Individuals carrying the AA genotype have a reduced capacity of controlling anger expression when they experience this emotion. Conversely, the alternative genotypes (AC and CC) can be considered as "protective" against the tendency to lose control when experiencing anger (39). Therefore, we suggest that suicide attempt and completed suicide could be under genetic control and regulated through capacity to control anger.

The observed differences in susceptibility, between suicide attempt and completed suicide, are likely due to the overall genetic background that modifies the SB prone risk factors. Moreover, this discrepancy in SB risk may be explained by daily lifestyle, geographic climate, dietary habits, ethnic diversity and so on. However, these results should be illustrated prudently and need further confirmation by more trials.

Second, A779C and A6526G polymorphisms were not associated with the risk of suicide behavior. Still, we cannot ignore the interaction between *TPH1* and other genes on SB susceptibility, such as *TPH2*. Therefore, it is necessary to systematically screen for functional variants within the *TPH1* gene and other related genes in the SB pathogenesis.

In González-Castro (10) meta-analysis in 2014, our results indicated that the A218C polymorphism was associated with SB, which is consistent with the present study. In comparison with the previous meta-analyses, some advantages of the current study should be addressed. Our study updated the data on *TPH1* polymorphism and the risk of SB and analyzed the role A6526G polymorphism on suicide behavior for the first time. Methodological issues were well explored (e.g., publication bias, sensitivity analysis, heterogeneity analysis) in the present work. Last but not least, the present work was carried out with five genetic models and sub-analyses by population and diagnostic subgroups were performed. Suicide attempt and completed suicide were not analyzed in previous meta-analyses.

The current meta-analysis also has some limitations. First, only articles published in English-language journals

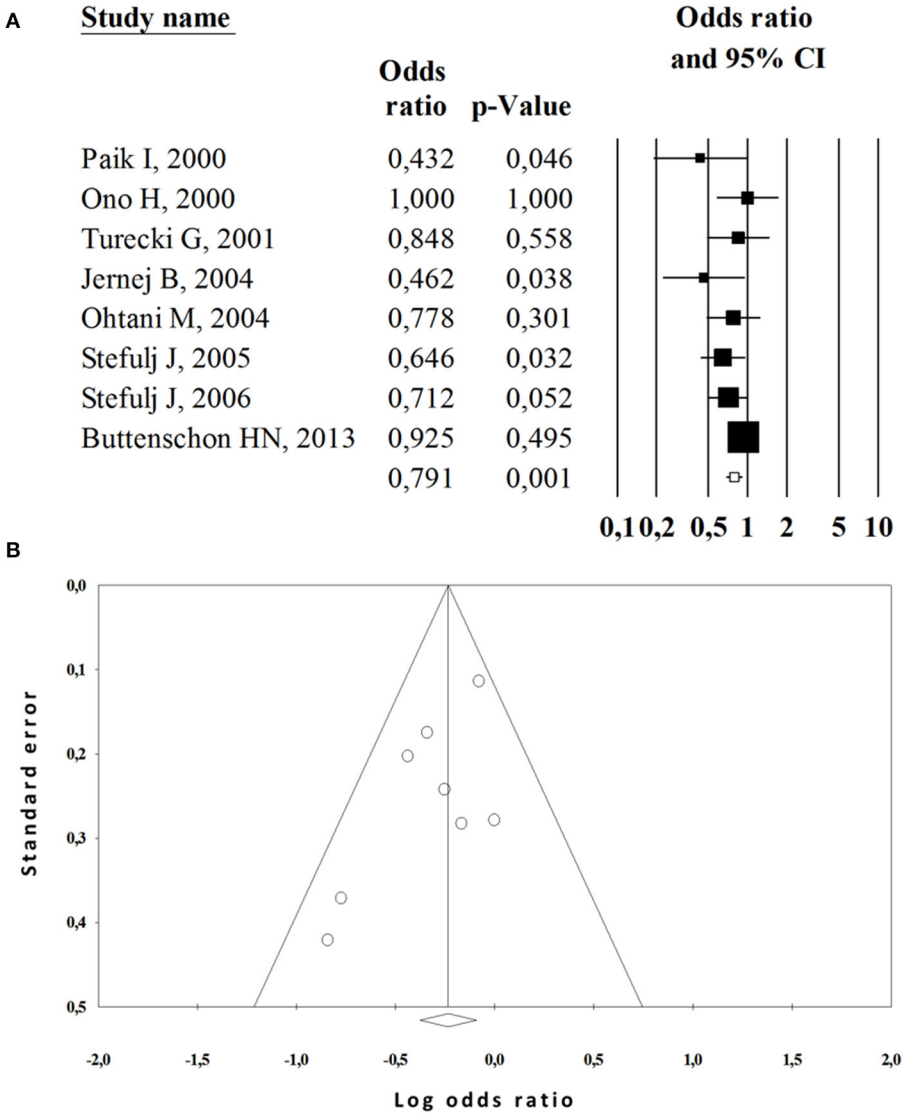

FIGURE 3
Meta-analysis of the association between A218C polymorphism and completed suicide risk. **(A)** Forest plot of subgroup analysis in dominant comparison. **(B)** Funnel plot of subgroup analysis in dominant comparison.

were included. Second, inter-gene and gene–environment interactions might also influence the accuracy of our outcomes. A lack of the original data restricted further evaluations of the potential inter-gene and gene–environment interactions. Related to, we recognized as a limitation that considerable percent of the studies were performed in some specific population (e.g. Croatian or German), this possible overlap of clinic center and sample population could introduce bias in the outcome. Therefore, the findings should be taken with caution. Finally, in the suicide ideation group, the number of relevant original documents was limited, there was not enough data to identify the relationship between *TPH1* and suicide ideation. Moreover, the inclusion of the studies that dealt with only ideation may have increased the heterogeneity of the analyzed data.

Conclusion

The current meta-analysis gives a comprehensive analysis of the available information for the association between the *TPH1* polymorphisms and suicide behavior. This meta-analysis revealed a significant association between the A218C polymorphism of *TPH1* gene and SB. However, neither in overall population nor in subgroup analysis was found a significant association between A779C and A6526G polymorphisms and

SB susceptibility. Therefore, the A218C polymorphism could be considered as one possible risk factor of SB. Further studies that investigate the relative contribution of *TPH1* polymorphisms and the mechanisms by which they affect the pathogenesis of SB are required to corroborate these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

Conceptualization, investigation, methodology, validation, visualization, roles/writing—original draft, and writing—review and editing: YH-D, TG-C, CT-Z, RC-A, ML-N, MR-M, and AG-M. Data curation: YH-D, TG-C, CT-Z, and RC-A. Formal analysis and resources: TG-C, CT-Z, ML-N, and AG-M. Funding acquisition: YH-D, TG-C, CT-Z, and ML-N. Project administration: YH-D, TG-C, and CT-Z. Software: YH-D, TG-C, and CT-Z. Supervision: CT-Z, RC-A, ML-N, MR-M, and AG-M. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Ali Saffet Gonul,
Ege University, Turkey

REVIEWED BY
Jie Yang,
Central South University, China
Gianluca Serafini,
San Martino Hospital (IRCCS), Italy

*CORRESPONDENCE
Li Kuang
kuangli0308@163.com

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Changes in gray matter volume following electroconvulsive therapy in adolescent depression with suicidal ideation: A longitudinal structural magnetic resonance imaging study

Xiao Li[1], Xiaolu Chen[2], Renqiang Yu[3], Linqi Dai[1], Ming Ai[1], Qian Huang[1], Yi Zhou[1], Wanjun Chen[1], Jiamei Guo[1], Anhai Zheng[1] and Li Kuang[1]*

[1]Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]The First Branch, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3]Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Objective: We aimed to investigate changes in whole-brain gray matter volumes (GMVs) before and after electroconvulsive therapy (ECT) in adolescents with major depressive disorder (MDD) and suicidal ideation (SI).

Methods: Thirty adolescents with MDD and SI were observed, and structural magnetic resonance imaging (sMRI) was performed at baseline and after ECT for each patient. But Twenty-five healthy controls (HCs) were scanned only at baseline. The voxel-based morphometry (VBM) techniques were used to examine GMVs.

Results: Compared with HCs, MDDs at baseline showed decreased GMVs in the left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, left precuneus, right precuneus, and left superior frontal gyrus. After ECT, MDDs showed increased GMVs in the right superior frontal gyrus and right superior temporal gyrus. Pearson's correlation found that Beck Scale for Suicide Ideation (BSSI) scores at baseline were negatively correlated with GMVs in the left superior frontal gyrus and HAMD and BSSI scores after ECT were negatively correlated with GMVs in the right superior temporal gyrus.

Conclusion: Frontal–temporal–precuneus structure changes may be a potential cause of depressive and suicidal symptoms in adolescents. ECT may improve depressive and suicidal symptoms in adolescents by regulating brain structures to compensate original defects.

KEYWORDS

MDD, ECT (electroconvulsive therapy), adolescent, Suicide Ideation, structural MRI (sMRI)

Introduction

Suicide is the third leading cause of death in adolescents (1) and is associated with major depressive disorder (MDD) (2). In addition to suicide deaths, suicidal ideation (SI) and suicide attempts also warrant attention, the development of SI to SA is a distinct phenomenon with different explanations, such as depressive symptoms, hopelessness, or even impulsivity that can predict ideation, but they struggle to distinguish those who have SA from those who only have SI (3). Klonsky et al. found the combination of pain and hopelessness, especially when pain exceeds connectedness, was the main factor causing SI and dispositional, acquired, and practical contributors to increased capacity for suicide were the main factors causing progression from ideation to attempts (4). Globally, lifetime prevalence rates were approximately 9.2% for SI and 2.7% for SA (5), and the prevalence rate of SA in adolescents was 4.1% in the United States and 4.2% in Europe (6). SI is defined as "thoughts of death, dying, plans for suicide, or desire for death" (7, 8), and it is thought to be the first step leading to suicide (3). Tan et al. found 32.09% of 12,733 adolescents in China reported SI (9), and Liu et al found the rate of SI was 20.6% in adolescents in Shandong province in China (10). Additionally, MDD adolescents with SI always have worse clinical outcomes (11). Therefore, measuring SI in MDD adolescents is necessary and may help determine the risk of suicide.

Previous structural magnetic resonance imaging (sMRI) studies showed that abnormalities gray matter volumes (GMVs) were associated with suicide in mood disorders. For example, reduced GMVs in the left and right dorsolateral prefrontal cortex (DLPFC) and right ventral lateral prefrontal cortex (VLPFC) were detected in patients with MDD and SI compared with MDD patients without SI and HCs (12). A longitudinal follow-up study on adolescents found a reduction in dorsal striatal GMVs in MDD adolescents with SI and may predict SI (13). Generally, understanding of alterations in GMVs in MDD adolescents with SI is still limited but of necessity and significance.

Electroconvulsive therapy (ECT) is a quick method to reduce depressive and suicidal symptoms, but for MDD adolescents with SI, the treatment effect of ECT was not so good compared with that adults (14), and due to the side effect, the caregivers always do not accept ECT as the first treatment option, a survey of 7,469 Australian psychiatric patients who received ECT showed only 0.2% of them were younger than 18 years (15), and another study containing 12,608 participants who received ECT from China showed only 3.2% (406) of them were adolescents (16). However, there were still some studies that demonstrated ECT was a good treatment option for MDD adolescents (17, 18). Previous studies demonstrated ECT could alternate GMVs in MDD patients. Qiu et al. (19) found GMVs were increased in bilateral amygdala and hippocampus in MDDs after ECT. Nordanskog et al. (20) found increased GMVs in bilateral hippocampus after 6–12 ECT sessions in MDD patients, and the increased GMVs in bilateral hippocampus correlate with clinical symptoms. However, how ECT changes GMVs in MDD adolescents is still unclear.

To our knowledge, few studies have explored the changes in GMVs in MDD adolescents with SI after ECT; therefore, we have hypothesized that (1) the adolescents with MDD and SI will show changed GMVs compared with HCs and (2) ECT would make GMVs changed in MDD adolescents with SI.

Materials and methods

Subjects

Thirty adolescents with MDD and SI aged 12–17 years were recruited, and the diagnosis was confirmed by senior psychiatrists using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). The severity of symptoms was accessed by both 17-item Hamilton Depression Rating Scale (21) and the Beck Scale for Suicide Ideation (22) at baseline and after ECT. The Chinese version of HAMD and BSSI has been found to be reliable and valid (23, 24). The inclusion criteria were as follows: (1) patients who fulfilled the MDD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; (2) patients with a total score of $\geq$ 17 points on the Hamilton Depression Rating Scale (HAMD-17); (3) first-onset MDD or diagnosed before but without antidepressants in recent 8 weeks, no history of ECT treatment; and (4) patients with suicidal ideation (SI) and Beck Scale for Suicide Ideation (BSSI) scores $>$ 11 points in recent one week. Patients were excluded if they had: (1) a neurological or serious physical condition, any history of alcohol or drug abuse, any other somatic diseases, or morphological anomalies of the brain; (2) any surgically placed electronic or metal materials that might interfere with MRI assessment; or (3) head motion exceeding 2.5 mm in translation or 2.5° in rotation.

Healthy controls were volunteers matched with the MDDs in sex, age, and educational level. The controls reported neither lifetime psychiatric disorder nor a family history of psychosis in their first-degree relatives. Otherwise, the exclusion criteria remained the same as MDDs.

The study protocol was approved by the Human Research and Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (no. 2017-157). All adolescents and their caregivers gave written informed consent after being informed about the details of the study.

Electroconvulsive therapy

The MDDs were treated by bi-temporal ECT using Thymatron DGx (Somatics, LLC, Lake Bluff, IL, USA) at

the First Affiliated Hospital of Chongqing Medical University. The first three sessions of ECT took place on continuous days; the remaining sessions of ECT were performed every 2 days, with a break on weekends, and each patient would take eight times of ECT. We used low 0.25 mode, and the initial energy for ECT was determined according to the patient's age: energy percent = age × 50%. The stimulation energy was adjusted based on the seizure time, and subsequent dosing was determined by seizure morphology adequacy. Anesthesia was induced with succinylcholine (0.5–1 mg/kg) and diprivan (1.5–2 mg/kg).

All MDDs received antidepressants during ECT sessions, with sertraline (n = 18, 60%), fluoxetine (n = 11, 36.7%), and escitalopram (n = 1, 0.03%). Twenty-six patients received antipsychotics, with quetiapine (n = 13, 43.3%), olanzapine (n = 8, 26.7%), aripiprazole (n = 4, 13.3%), and risperidone (n = 1, 0.03%). One patient received trihexyphenidyl (n = 1, 0.03%).

Magnetic resonance imaging acquisition

MR images were obtained using a 3T GE Signa HDxt scanner (General Electric Healthcare, Chicago, IL, USA) with an eight-channel head coil. During scanning, subjects were told to keep their eyes closed and awake, not to focus their thoughts on anything in particular. Foam pads and earplugs were used to fix their heads to minimize head motion and reduce machine noise, respectively. The settings used to obtain the 3D T1-weighted anatomical images were as follows: a repetition time of 8.4 ms, a flip angle of 12°, an echo time of 3.3 ms, a field of view of 24 cm × 24 cm, a matrix of 256, a field of view of 24-cm slices, 158 axial slices, and a slice thickness of 1 mm.

Voxel-based morphometry image preprocessing

The T1-weighted images were processed with Statistical Parametric Mapping 12 (SPM12) software package using voxel-based morphometry (VBM) toolbox. All T1 images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the "new segment" tool implemented in SPM12. During spatial normalization, inter-subject registration was achieved using respective registration based on group assignment. A modulation step was used to ensure that the overall amount of tissue in a class was unaltered. The segmented images were normalized to the Montreal Neurological Institute (MNI) template and were smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian filter. The voxel size of data acquisition was 1 mm^3, and the voxel size of normalized data was 1.5 mm^3.

Statistical analysis

Demographic data and symptom scores were analyzed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA). A two-sample t-test was performed in SPM12 to compare GMVs between MDDs at baseline and HCs, and paired t-tests were performed between MDDs pre- and post-ECT treatment. The GMV voxel was $p < 0.001$, the significance level was $p < 0.05$ with Gaussian random field (GRF) correction, and the cluster size was > 170.

At baseline, Pearson's correlation analyses were performed to examine the correlations between GMVs in the brain regions with significant differences and clinical symptoms (HAMD/BSSI). After ECT, Pearson's correlation analyses were performed to examine whether the changes in these measures were correlated with the changes in clinical symptoms.

Results

Clinical outcomes

The psychological measurements and demographic data are listed in Table 1. There were no significant differences between MDDs and HCs in age, sex, and educational level ($p > 0.05$). After ECT sessions, the total scores on the HAMD and BSSI were significantly decreased ($p < 0.05$) (Table 2).

TABLE 1 Demographics and clinical characteristics between HCs and MDDs.

Characteristics	HC (n = 25)	MDD (n = 30)	P-value
Age, mean (SD), y	15.48 (1.87)	14.60 (1.45)	0.197*
Sex (male/female)	6/19	8/22	0.657#
Duration time of symptoms, mean (SD), y	–	1.1 (1.0)	–
Education years, mean (SD), y	9.68 (2.21)	8.50 (1.70)	0.143*
HAMD, mean (SD)	1.60 (2.06)	29.03 (6.02)	<0.001*
BSSI, mean (SD)	0	22.10 (5.73)	<0.001*

MDD, major depressive disorder; HC, healthy control; HAMD, Hamilton Depression Scale; BSSI, Beck Scale for Suicide Ideation; SD, standard deviation.
*Two-sample t-test.
#Chi-square test.

TABLE 2 Comparison of the severity of clinical symptoms between pre- and post-ECT.

Characteristic	Pre-ECT	Post-ECT	*P*
HAMD, mean (SD)	29.03 (6.02)	13.77 (8.89)	<0.001*
BSSI, mean (SD)	22.10 (5.73)	8.10 (6.94)	<0.001*

ECT, electroconvulsive therapy; HAMD, Hamilton Depression Scale; BSSI, Beck Scale for Suicide Ideation; SD, standard deviation.
*Paired *t*-test.

Neuroimaging comparisons between major depressive disorders at baseline and healthy controls

Compared with HCs, MDDs showed decreased GMVs in the left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, left precuneus, right precuneus, and left superior frontal gyrus ($p < 0.05$ with GRF correction) (Figure 1 and Table 3) and the bar graph showed decreased GMVs in the left superior frontal gyrus in MDDs ($p < 0.01$) (Figure 2).

Neuroimaging comparisons between pre- and post-electroconvulsive therapy

Compared with pre-ECT, patients showed increased GMVs in the right superior frontal gyrus and right superior temporal gyrus ($p < 0.05$ with GRF correction) (Figure 3 and Table 4) and the bar graph showed increased GMVs in the right superior temporal gyrus in MDDs after ECT ($p < 0.05$) (Figure 4).

Pearson's correlation analysis

Pearson's correlation found that the BSSI scores at baseline were negatively correlated with GMVs in the left superior frontal gyrus ($r = -0.5234$, $p = 0.003$) (Figure 5), the HAMD scores after ECT were negatively correlated with GMVs in the right superior temporal gyrus ($r = -0.4076$, $p = 0.0254$) (Figure 6), and the BSSI scores after ECT were negatively correlated with GMVs in the right superior temporal gyrus ($r = -0.4326$, $p = 0.0170$) (Figure 7). There was no correlation between changed HAMD/BSSI scores and GMVs.

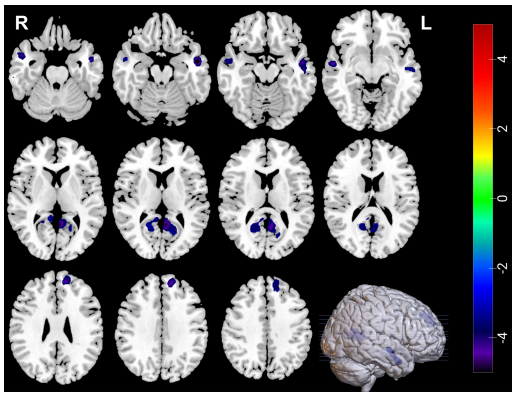

FIGURE 1
Blue regions mean decreased GMVs in the left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, left precuneus, right precuneus, and left superior frontal gyrus of MDDs compared with HCs (GMV voxel was $p < 0.001$; the significance level was $p < 0.05$ with GRF correction).

Discussion

This study found the HAMD score and BSSI score of MDD adolescents with SI significantly reduced after ECT, indicating that ECT could quickly decrease the depressive and suicidal symptoms of adolescent patients. In our study, we used VBM techniques and found decreased GMVs in the left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, left precuneus, right precuneus, and left superior frontal gyrus compared with HCs and increased GMVs in the right superior frontal gyrus and right superior temporal gyrus after ECT.

The frontal lobe locates in the front of the brain and is one of the most important areas, which is closely related to the individual's emotional regulation, thinking process, attention function, problem-solving, demand motivation, behavior planning, and other advanced cognitive activities. In this study, GMVs in the superior frontal gyrus changed

TABLE 3 Significant differences in GMVs between MDDs and HCs.

Brain regions	L/R	Voxel size	Peak *T*-value	MNI coordinates		
Middle Temporal gyrus	R	231	−4.7436	48	4.5	−27
Superior Temporal gyrus	R	177	−4.6108	56	−6	−11
Middle Temporal gyrus	L	608	−5.3776	−51	−3	−19.5
Precuneus	L	941	−4.8458	−6	−52.5	9
Precuneus	R	579	−4.2185	9	−43.5	10.5
Superior frontal gyrus	L	699	−4.7427	−12	48	28.5

GMV, gray matter volume; MNI, Montreal Neurological Institute.

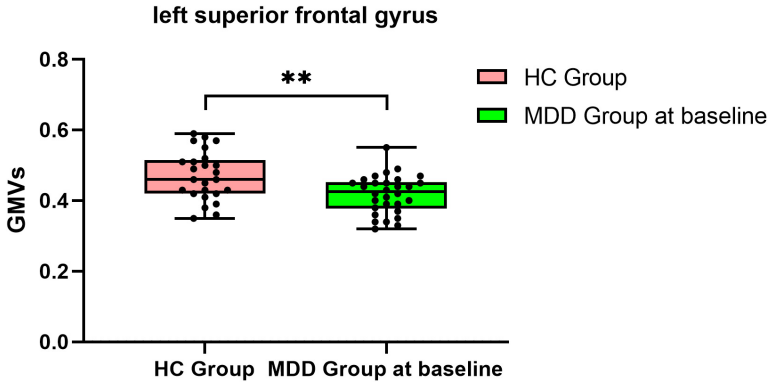

FIGURE 2
Bar graph showing decreased GMVs in the left superior frontal gyrus in MDDs compared with HCs, $^{**}p < 0.01$.

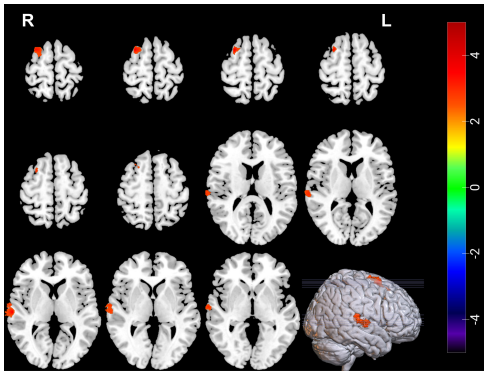

FIGURE 3
Red regions mean increased GMVs in the right superior temporal gyrus and right superior frontal gyrus of MDDs after ECT (GMV voxel was $p < 0.001$; the significance level was $p < 0.05$ with GRF correction).

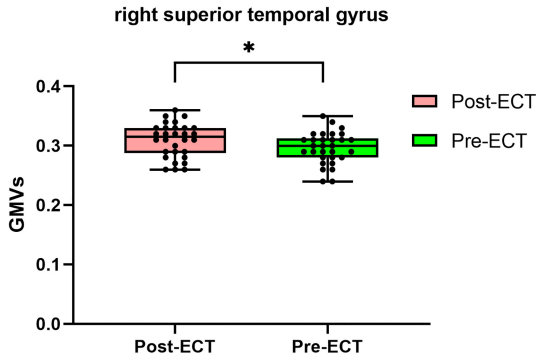

FIGURE 4
Bar graph showing increased GMVs in the right superior temporal gyrus in MDDs after ECT, $^{*}p < 0.05$.

in patients at baseline compared with HCs and also showed in MDDs before and after ECT, indicating that the superior frontal gyrus was an important area for the onset of depression and might be the area for the ECT response. Ma et al. found decreased GMV in the medial part of the left superior frontal gyrus in patients with depressive symptoms (25), which was consistent with our results. Seok et al. found decreased GMV in the right superior frontal gyrus in adolescents with irritability compared with healthy youths (26). Interestingly, we found ECT increased GMV in the right superior frontal gyrus, but not in the left superior frontal gyrus, and this inconsistency of two comparison results may be related to that ECT could trigger both efficacy and side effect. The precuneus is involved in many high-level cognitive functions of the brain, including episodic memory, self-attention, and information-related processing. Therefore, changes in brain structure in the region reflect abnormalities in emotional control, thought processes, and negative behaviors in patients with depression and suicide. In the current study, GMVs in precuneus in the MDDs at baseline significantly reduced, suggesting the abnormality of precuneus might be related to symptom onset of MDD adolescents with SI.

The middle temporal gyrus is involved in cue-directed attention and working memory (27, 28). Previous studies showed MDD patients had reduced GMVs in the temporal

TABLE 4 Significant differences in GMVs in MDDs between pre- and post-ECT.

Brain regions	L/R	Voxel size	Peak *T*-value	MNI coordinates		
Superior Temporal gyrus	R	608	3.7196	61.5	−18	4.5
Superior Frontal gyrus	R	425	3.8632	27	9	63

GMV, gray matter volume; MNI, Montreal Neurological Institute.

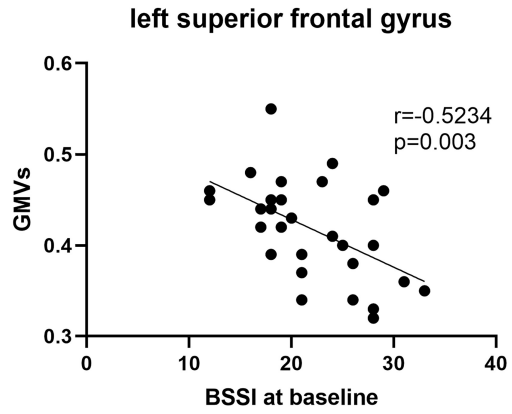

FIGURE 5
Negative correlations between the BSSI at baseline and GMVs in the left superior frontal gyrus (r = −0.5234, p = 0.003).

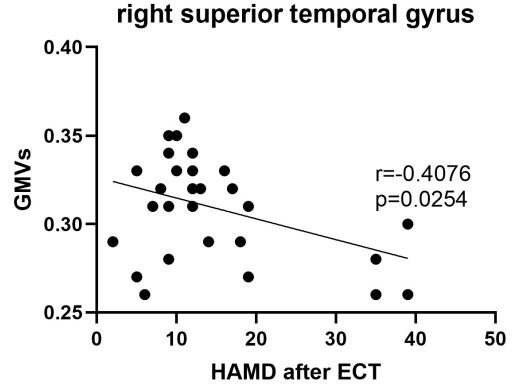

FIGURE 6
Negative correlations between the HAMD after ECT and GMVs in the right superior temporal gyrus (r = −0.4076, p = 0.0254).

cortex (29, 30). In this study, GMVs in bilateral middle temporal gyrus of the patient group at baseline reduced compared with HCs, which might reflect depressive symptoms. Previous studies found that ECT increased GMVs in the temporal cortex in patients with depression (31, 32). In addition to the middle temporal gyrus, the right superior temporal gyrus is also an important brain region for emotion processing. Previous studies showed that the superior temporal gyrus and middle temporal gyrus were related not only to recall of personal experiences, but also to perception of intentional behavior and memory (33, 34). In addition, these two brain regions were also involved in the regulation of emotional information and cognition (35–37). Therefore, aberrations of GMV in these two regions may lead to abnormal spontaneous brain activity and might contribute to emotional dysregulation, which would increase the risk of suicide in depression. Soloff et al. (38) found that the superior/middle temporal gyrus was negatively correlated with the impulsivity of the low-fatality suicide attempters, but positively correlated with the aggressiveness of the high-fatality suicide attempters. Therefore, suicide attempts might be related to impulsivity personality traits mediated by the superior/middle temporal gyrus.

In addition to sMRI, fMRI also focused on the relationship between the superior temporal gyrus and suicide. A previous study (39) showed the ALFF activity in the right superior temporal gyrus enhanced significantly in depressed patients with SA, but no similar results were found in the comparison between depressed patients without SA and HCs. Van Heeringen et al. (40) also found increased blood perfusion in the temporal lobe of MDD patients. As the superior temporal gyrus is involved in the regulation of emotion and cognition, researchers believe that the abnormal ALFF activity in depressed patients with suicide may lead to suicidal behavior through weakened decision making and increased impulsivity. In addition, studies showed that the right superior temporal gyrus was activated in healthy people when performing mind tasks. Suicide attempters were considered to have impaired cognitive control and decision-making ability, and cognitive rigidity and impaired decision-making ability were particularly pronounced in high-fatality suicide attempters.

We found ECT changed GMVs in the right superior temporal gyrus, and previous studies paid more attention to alteration in the brain function in this area after ECT. Wang et al. found the changes in local FCD of the right superior temporal gyrus were significantly correlated with the changes in Hamilton Rating Scale for Depression (HRSD) scores in MDD patients before and after ECT (41). Previous studies also focused on the superior temporal gyrus changed in MDD adolescents with suicidal behaviors. Pan et al. (42) found GMVs in the right superior temporal gyrus reduced in MDD adolescents with a history of suicidal symptoms, and abnormal temporal–parietal GMVs were associated with an increased risk of suicide in youth with depression (43). So, we considered ECT could decrease

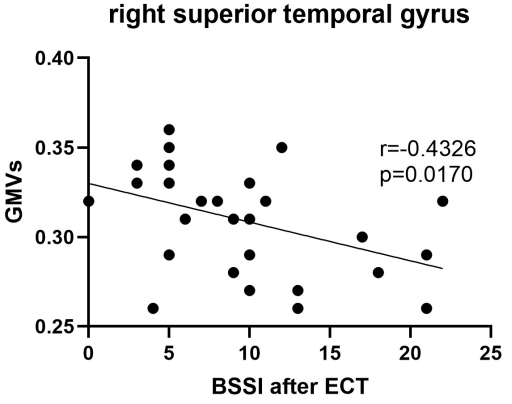

FIGURE 7
Negative correlations between the BSSI after ECT and GMVs in the right superior temporal gyrus (r = −0.4326, p = 0.0170).

the depressive and suicide symptoms by regulating the right superior temporal gyrus of brain.

Several limitations of our current study should be noted. First, our sample size was small, and further studies with larger samples are needed to verity our findings. Second, we did not assess childhood trauma or maltreatment in the MDDs and HCs, which could influence the brain structure. Third, we did not evaluate the side effect caused by ECT. Fourth, patients received antidepressants during ECT sessions, and though the duration of medications is only 2 weeks and antidepressants were always thought not to work (44, 45), we still could not exclude the impact on the brain structure.

Conclusion

Frontal–temporal–precuneus structural changes may be a potential cause of depressive and suicidal symptoms in adolescents. ECT may improve depressive and suicidal symptoms in adolescents by regulating brain structures to compensate original defects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Human Research and Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XL conceived the structure of the manuscript and wrote the manuscript. RY, YZ, QH, and LD prepared the samples and performed the fMRI. XC analyzed the data. JG, AZ, and WC performed the ECT in patients. MA and LK critically reviewed the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
E. Erdal Erşan,
Niğde Ömer Halisdemir University, Turkey

REVIEWED BY
Alessandra Costanza,
Université de Genève, Switzerland
Fengchun Wu,
The Affiliated Brain Hospital of Guangzhou Medical University, China

*CORRESPONDENCE
Yanmei Shen
ymshen@csu.edu.cn
Xiang Yang Zhang
zhangxy@psych.ac.cn

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Associations between anxiety, depression, and risk of suicidal behaviors in Chinese medical college students

Jia Li[1], Yaru Zhang[2], Bella Siu Man Chan[3], Sun Nee Tan[4], Jianping Lu[5], Xuerong Luo[2], Yanmei Shen[2]* and Xiang Yang Zhang[6]*

[1]Department of Applied Psychology, College of Preschool Education, Changsha Normal University, Changsha, Hunan, China, [2]Department of Psychiatry, and National Clinical Research Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China, [3]Department of Educational and Counselling Psychology, and Special Education, The University of British Columbia, Vancouver, BC, Canada, [4]Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine (Neuroscience), The University of British Columbia, Vancouver, BC, Canada, [5]Department of Child Psychiatry of Shenzhen Kangning Hospital, Mental Health School, Shenzhen Mental Health Center, Shenzhen University, Shenzhen, China, [6]CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

Background: Previous studies have established a strong association between depression and suicidal behaviors, yet the relationship between anxiety and suicidal behaviors remains unclear. This study examines whether anxiety and depression are independent risk factors for suicidal behaviors in medical college students, and further, whether anxiety may increase the greater risk of suicidal behaviors (SB) in participants with depression.

Methods: This cross-sectional study was conducted among 4,882 medical students. Demographic information, anxiety, and depression data were collected using online questionnaires or through a widely used social media app named WeChat.

Results: Anxiety and depression were independent risk factors for suicidal behaviors, and levels of risk correlated positively with the severity of both anxiety and depressive symptoms. A dose–response relationship was identified between the severity of anxiety and the risk of SB, as well as the severity of depression and SB. Furthermore, anxiety increased the risk of suicidal behaviors in participants with depression, with a dose–response relationship between the severity of anxiety symptoms and the risk of SB.

Conclusion: The findings highlight the importance of screening for anxiety and depressive symptoms in medical college students, as well as reducing anxiety in addition to depressive symptoms in treatment. This study provides valuable data as a reference for clinicians for suicide risk assessments.

KEYWORDS

suicidal behavior, depression, anxiety, medical college students, risk factors, suicide ideation

Background

Suicide is one of the leading causes of death throughout the world (1). Over 800,000 people globally die by suicide every year, which accounts for 1.4% of all global deaths (2). Suicide is also regarded as one of the most severe public health problems in China (1). Suicidal behaviors (SB) have a devastating influence on individuals, families, and communities (3, 4), and the prevention of suicide has been recognized as a significant public health challenge. It is therefore important to study SB in order to predict subsequent acts of suicide (3, 4).

Previous studies have suggested that nearly nine out of every ten suicides were associated with mental illnesses (5, 6). Depressive disorder is regarded as the primary mental illness associated with the greatest risk for SB (4, 7). This is affirmed by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), which identifies suicidal ideation as one of the symptoms of major depressive disorder (8). Despite having evidence of a strong association between depression and SB, determining suicide risks among people with depression remains challenging. As SB is considered to be a warning sign of fatal suicide (3), it is crucial to identify risk factors for suicidality among patients with major depression. Furthermore, although previous studies did show a consistent association between the severity of depressive symptoms and suicidality (9, 10), there is a lack of large-scale studies conducted among medical college students examining the association.

Although depression is strongly associated with SB, the role of anxiety symptoms in SB is less clear. Several studies have explored the impact of comorbid anxiety on SB in participants with depression; however, their findings remain inconsistent (7, 11). Recently, several studies showed that comorbid anxiety increased the risk of SB in patients with depression (11, 12). For example, Batterham et al. (11) reported that anxiety symptoms posed an even greater risk overall for SB than symptoms of depression. However, other studies reported different findings. For example, Eikelenboom et al. (7) found that anxiety might be protective against suicidality after adjusting for the severity of depressive symptoms. In their view, anxiety symptoms in depressed patients may stem from psychological fear of their illness, which is the opposite of a wish for death.

Several studies on anxiety, depression, and SB were mostly epidemiologic and clinical studies that examined the relationships between anxiety disorders and suicidality or depressive disorder and suicidality separately (11, 13). The question of whether anxiety is an independent risk factor for suicidality after controlling for comorbid depression has not been adequately addressed (7, 14, 15). Moreover, studies examining the magnitude of anxiety on SB in depression among Chinese populations in general and among Chinese college students in particular are scarce.

To the best of our knowledge, this is the first study to examine the relationship between anxiety and SB in Chinese medical college students with depression. The aims of this study are: first, to explore the associations between the severity of anxiety or depressive symptoms with SB; second, to examine whether anxiety and depression are both independent risk factors for SB after controlling for socio-demographics, severity of anxiety and depressive symptoms and comorbidity, and; third, to investigate the magnitude of anxiety symptoms on SB in a large cohort of participants with depression.

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; SDS, Zung's Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale; OR, odds ratio; BMI, Body Mass Index.

Materials and methods

Participants

Students from three medical educational institutions in Hunan, China, were selected as the target population. A cross-sectional design was employed with the convenience sampling method. A total of 80 students from two classes of the Hunan University of Chinese Medicine, 165 students from four classes at Changsha Health Vocational College, and 4,759 students from 50 classes at Yiyang Medical College were chosen to participate. The targeted two medical colleges (Changsha Health Vocational College and Yiyang Medical College) offer 3-year undergraduate programs; students accepted to these kinds of colleges generally have lower academic grades. The Hunan University of Chinese Medicine is a comprehensive medical university with an undergraduate medical program that spans 4 years. Students admitted to this university tend to have competitive academic scores.

A total of 5,004 students were screened between January and March of 2018. All students provided consent and were informed that they could refuse to participate or withdraw at any time. A total of 110 participants declined to participate. Participants who proceeded signed the consent forms, which were approved by the Ethics Committee of the Second Xiangya Hospital at Central South University in Changsha, China; 12 were excluded for incomplete questionnaires or missing data. Therefore, a total of 4,882 participants were enrolled in this study. Of them, 537 were males (11.0%) and 4,345 were females (89.0%). Their ages ranged from 17 to 22 years (mean age: 18.77 $\pm$ 1.09 years). College counselors and instructors were given trainings on how to instruct participants to fill out the scales before providing guidance to the respondents. Participants could fill the questionnaires either on a widely used social media app called WeChat (installed on mobile devices) or via computer.

Measures

Socio-economic demographics

The questionnaire included questions about gender, age, nationality, social economic status, whether they smoked or drank, community (urban or rural), parents' educational levels, and relationships with parents.

Suicidal behaviors

Suicidal behavior refers to the thoughts and behaviors related to the intention of committing suicide (16). Suicidal behaviors include suicidal ideation (SI), suicide plans, and suicide attempts (SA) (17). SI refers to passive thoughts about killing oneself or wishing for death. Suicidal plans entail planning and preparation for a suicide attempt. SA referred to any potentially self-harm actions the individual took against themselves, with at least some extent of intention to die (17, 18). Research shows "scales are used in clinical settings to measure the severity of suicidal behavior, and previous research has shown that current suicidal ideation is more easily disclosed via self-report measures than clinical interviews" (19). The latest research shows that "these scales could not discriminate between suicide ideators and suicide attempters" (20). We chose the questions probing suicidal ideations, suicide plans, and SA included: Have you ever had thoughts of committing suicide? Have you ever made a suicide plan? Have you ever tried committing suicide? If any of these questions were answered in the affirmative, additional detailed questions were asked (i.e., frequency of attempts and approaches of SA).

Based on the responses to SB, participants were categorized into two main groups: control and SB groups. Participants exhibiting the specific type of SB were further divided into three subgroups with suicidal ideations, plans, and attempts. Since overlapping occurred among three subtypes of suicidal behavior, those subjects with two or three subtypes of suicidal behavior were included in two or three subgroups.

Depression and anxiety

Zung's Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) (21, 22) were employed to evaluate symptoms of depression and anxiety over the past 7 days. The SDS and SAS have been broadly employed in studies on depression and anxiety among Chinese populations and are reported to have good psychometric properties (23, 24). The cut-off scores for SDS and SAS are 53 and 50, respectively. Participants with scores higher than 53 on SDS or above 50 on SAS are regarded as having depression and anxiety, respectively (25). The higher scores indicate the greater severity of depression or anxiety. Both the SAS and SDS scales have a 20-item self-report (1 for none or a little of the time, 2 for some of the time, 3 for good part of the time, and 4 for most or all of the time). The scores for items 5, 9, 13, 17, or 19 in SAS and the scores for items 2, 5, 6, 11, 12, 14, 16, 17, 18, or 20 in SDS are reversed (four for none or a little of the time, three for some of the time, two for a good part of the time, and one for most or all of the time). Multiplying the total score by 1.25 provides the standard scores for these two measurements (21, 22).

Data analysis

The chi-squared test for categorical variables and the analysis of variance (ANOVA) for continuous variables were used to compare the differences in clinical and demographic variables between the groups with different kinds of suicidal behaviors. The binary logistic regression method was applied to calculate the crude odds ratio (OR) and the adjusted OR together with 95% CI for suicidal behaviors (suicide ideations, plans, and attempts) after controlling for the related variables. We used two-tailed *t*-tests to calculate statistical significance with a threshold for *p*-value set at below 0.05 using the SPSS22.

Results

A total of 4,882 participants in this study were divided into controls (n = 3522) and those with SB (n = 1360). Further, among those with suicidal behaviors, 1,289 were included in the suicidal ideation subgroup, 371 in the suicide plans subgroup, and 682 in the SA subgroup. **Table 1** shows the demographic and clinical data of all the participants. Compared with the control group, individuals with all three subtypes of SB were more likely to have a history of physical disorders, live in urban areas, have a family history of mental disorders, have poor relationships with parents, develop smoking, and drinking habits or have anxiety or depression (all $p < 0.001$).

When compared to participants without anxiety, individuals with anxiety had higher risks of suicidal behaviors ($p < 0.01$). The severity of anxiety symptoms correlated positively with the risk of SB ($p < 0.01$). In the case of suicide plans and suicide attempts, the crude odds ratios (ORs) reached as high as 26.913 and 19.365, respectively (both $p < 0.001$). Anxiety remained an independent risk factor ($p < 0.001$) even after adjustments were made for demographics, smoking, drinking, and severity of depression symptoms. The risk of SB increased with the severity of anxiety symptoms after adjustments (with adjusted ORs of 3.670 for suicide ideation, 7.032 for suicide plans, and 6.164 for suicide attempts). Participants with depression also showed higher risks of SB; the risk of SB increased with the severity of depression symptoms; the crude ORs for suicidal ideation, suicide plans, and SA reached 47.811 (95% CI, 11.243−203.315), 128.571 (95% CI, 29.141−567.256), and 75.302 (95% CI, 17.313−327.522), respectively (all $p < 0.001$). The adjusted ORs remained independent and high even after adjustments were made for demographics, smoking, drinking, and severity of anxiety symptoms (all $p < 0.001$; see **Table 2**).

TABLE 1 Demographic characteristics of participants with suicidal behaviors and without suicidal behaviors (controls).

Variables	Controls (n = 3522)	Suicidal behaviors (n = 1360)	p	Suicide ideation (n = 1289)	P^a	Suicide plans (n = 371)	P^b	Suicide attempts (n = 682)	P^c
Age (years), mean (SD)	18.88 ± 1.087	18.57 ± 1.11	0.000***	18.59 ± 1.113	0.000***	18.47 ± 1.123	0.000***	18.48 ± 1.117	0.000***
BMI (kg/m^2), mean (SD)	20.093 ± 2.4181	20.26 ± 2.53	0.035*	20.278 ± 2.5705	0.021*	19.963 ± 2.4054	0.322	20.117 ± 2.5263	0.816
Males/females	418/3104	119/1241	0.002**	105/1184	0.000***	34/337	0.122	65/617	0.080
District: Rural/Urban	2586/936	934/426	0.001**	885/404	0.001**	228/143	0.000***	457/225	0.001**
Nationality: Others/Han	466/3056	156/1204	0.098	147/1142	0.092	32/339	0.012*	69/613	0.026*
Good relationship with mother	3447 (97.9%)	1276 (93.8%)	0.000***	1210 (93.9%)	0.000***	333 (89.8%)	0.000***	630 (92.4%)	0.000***
Good relationship with father	3402 (96.6%)	1232 (90.6%)	0.000***	1164 (90.3%)	0.000***	315 (84.9%)	0.000***	602 (88.3%)	0.000***
Physical disorder history	177 (5.0%)	149 (11.0%)	0.000***	144 (11.2%)	0.000***	45 (12.1%)	0.000***	85 (12.5%)	0.000***
Mental disorder history	22 (0.6%)	16 (1.2%)	0.049*	15 (1.2%)	0.058	11 (3.0%)	0.000***	15 (2.2%)	0.000***
Family history of mental disorders	50 (1.4%)	44 (3.2%)	0.000***	42 (3.3%)	0.000***	21 (5.7%)	0.000***	28 (4.1%)	0.000***
Smoking	130 (3.7%)	82 (6.0%)	0.000***	78 (6.1%)	0.000***	36 (9.7%)	0.000***	60 (8.8%)	0.000***
Drinking	487 (13.8%)	310 (22.8%)	0.000***	296 (23.0%)	0.000***	101 (27.2%)	0.000***	193 (28.3%)	0.000***
Anxiety	492 (14.0%)	480 (35.3%)	0.000***	460 (35.7%)	0.000***	178 (48.0%)	0.000***	302 (44.3%)	0.000***
Depression	882 (25.0%)	680 (50.0%)	0.000***	654 (50.7%)	0.000***	217 (58.5%)	0.000***	384 (56.3%)	0.000***
Social economic status									
Lower than 30,000/year	1478 (42.0%)	577 (42.4%)	0.262	548 (42.5%)	0.384	136 (36.7%)	0.110	284 (41.6%)	0.042*
30,000∼50,000/year	1222 (34.7%)	442 (32.5%)		422 (32.7%)		135 (36.4%)		211 (30.9%)	
More than 50,000/year	822 (23.3%)	341 (25.1%)		319 (24.7%)		100 (27.0%)		187 (27.4%)	
Father's education level									
Junior middle school and below	2284 (64.8%)	874 (64.3%)	0.836	833 (64.6%)		218 (58.8%)	0.016*	436 (63.9%)	0.446
High School or Technical School	901 (25.6%)	359 (26.4%)		335 (26.0%)	0.951	102 (27.5%)		170 (24.9%)	
College or University and above	337 (9.6%)	127 (9.3%)		121 (9.4%)		51 (13.7%)		76 (11.1%)	
Mother's education level									
Junior middle school and below	2591 (73.6%)	965 (71.0%)	0.166	913 (70.8%)	0.166	246 (66.3%)	0.010*	480 (70.4%)	0.216
High School or Technical School	720 (20.4%)	310 (22.8%)		292 (22.7%)		94 (25.3%)		154 (22.6%)	
College or University and above	211 (6.0%)	85 (6.3%)		84 (6.5%)		31 (8.4%)		48 (7.0%)	
Family type									
Extended families	1221 (34.7%)	485 (35.7%)	0.000***	460 (35.7%)	0.000***	127 (34.2%)	0.000***	233 (34.2%)	0.001**
Nuclear families	1983 (56.3%)	705 (51.8%)		666 (51.7%)		184 (49.6%)		357 (52.3%)	
Single parent/recombinant family	318 (9.0%)	170 (12.5%)		163 (12.6%)		60 (16.2%)		92 (13.5%)	

BMI, body mass index; p^a was generated by comparison of control group and suicidal ideation subgroup; p^b was generated by comparison of control and suicide plans; p^c was generated by comparison of control and suicidal attempts. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

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TABLE 2 Associations between suicidal behaviors with severity of anxiety symptoms and depression symptoms.

Variable	Suicidal ideation		Suicide plans		Suicide attempts	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Anxiety						
Without anxiety (SAS ≤ 49)	–	–	–	–	–	–
Mild (50 ≤ SAS ≤ 59)	3.018 (2.571–3.542)***	1.934 (1.605–2.331)***	4.491 (3.506–5.753)***	2.593 (1.916–3.508)***	4.154 (3.423–5.041)***	2.508 (1.987–3.166)***
Moderate (60 ≤ SAS ≤ 69)	5.516 (3.889–7.822)***	2.524 (1.703–3.740)***	12.274 (8.027–18.768)***	3.899 (2.302–6.605)***	8.844 (6.049–12.928)***	3.567 (2.278–5.587)***
Severe (70 ≤ SAS)	11.487 (4.890–26.983)***	3.670 (1.418–9.496)***	26.913 (10.477–69.135)***	7.032 (2.099–23.556)***	19.365 (7.979–46.997)***	6.164 (2.225–17.080)***
Depression						
Without depression (SDS ≤ 52)	–	–	–	–	–	–
Mild (53 ≤ SDS ≤ 62)	2.743 (2.369–3.177)***	2.091 (1.774–2.466)***	3.164 (2.466–4.061)***	1.976 (1.474–2.649)***	3.296 (2.734–3.974)***	2.116 (1.701–2.631)***
Moderate (63 ≤ SDS ≤ 72)	3.833 (3.070–4.785)***	2.328 (1.790–3.029)***	6.696 (4.899–9.152)***	3.196 (2.159–4.733)***	5.122 (3.939–6.660)***	2.438 (1.764–3.370)***
Severe (73 ≤ SDS)	47.811 (11.243–203.315)***	18.526 (4.135–83.003)***	128.571 (29.141–567.256)***	26.636 (5.302–133.811)***	75.302 (17.313–327.522)***	17.194 (3.632–81.393)***

OR, odds ratio. ***$p < 0.001$.

Table 3 showed the associations between anxiety and SB among participants with depression, as compared with those without anxiety. Those with anxiety showed higher risks of SB in all 3 categories as indicated by increasing values for crude and adjusted ORs. The crude ORs reached 8.568 (95%CI, 3.208−22.880), 16.217 (95%CI, 5.473−48.051), and 13.706 (95%CI, 4.964−37.848) (all $p < 0.001$) for SI, suicide plans, and suicide attempts, respectively. Even after controlling for demographics, smoking, and drinking, participants with anxiety were at higher risk of suicidal behaviors in all 3 categories. The adjusted ORs decreased to some extent but remained significant at 7.538 (95%CI, 2.757−20.606), 12.190 (95%CI, 3.789−39.224), and 11.922 (95%CI, 4.154−34.217) for suicidal ideation, suicide plans, and suicide attempts, respectively (all $p > 0.01$).

Discussion

This study confirmed the association between SB (suicidal ideation, suicide plans, and suicide attempts) and the severity of anxiety and depressive symptoms. Both anxiety symptoms and depressive symptoms were independent risk factors for suicidal behaviors, after controlling for the severity of these symptoms, demographics, and lifestyles (smoking and drinking habits). The severity of anxiety symptoms positively correlated with risks for SB among participants with depression. These findings shed light on the importance of screening for anxiety and depressive symptoms among medical college students as well as highlighting the importance of reducing anxiety symptoms and depressive symptoms to prevent suicide.

Furthermore, this study showed that even after controlling for the severity of depression, smoking, drinking, and demographics, anxiety disorder remained an independent risk factor for SB, although the adjusted OR decreased to some extent. This implies that the risks for suicidal behaviors associated with anxiety symptoms might be increased partly due to anxiety symptoms and partly due to comorbidities such as depression, smoking, and drinking. In addition, we found a dose–response relationship between the severity of anxiety symptoms and the risks of SB: severity of anxiety symptoms correlated positively to risks of SB. The finding that anxiety symptoms were associated with SB is consistent with several previous studies (12, 26–33). Several studies found that after controlling for depression, anxiety symptoms remained an independent risk factor for SB (12, 30, 33). A recent study conducted with a large sample of South Korean adults similarly reported an independent association between anxiety disorders and suicidal ideation and/or suicide attempts after adjustments were made for demographic variables and psychiatric comorbidities (26). Some studies suggested that anxiety might increase the risk of SB by adding more mental burden to the person (34). Other studies recommended

TABLE 3 Associations between anxiety and suicidal behaviors in participants with depression, with and without adjustment for socio-demographic characteristics, and smoking and drinking habits.

Variable	Suicidal ideation		Suicide plans		Suicide attempts	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Anxiety						
Without anxiety (SAS ≤ 49)	–	–	–	–	–	–
Mild (50 ≤ SAS ≤ 59)	1.821 (1.463–2.265)***	1.776 (1.417–2.225)***	2.322 (1.655–3.256)***	2.225 (1.555–3.185)***	2.382 (1.825–3.110)***	2.296 (1.740–3.030)***
Moderate (60 ≤ SAS ≤ 69)	2.902 (1.988–4.237)***	2.470 (1.664–3.669)***	5.424 (3.346–8.792)***	4.319 (2.547–7.324)***	4.335 (2.845–6.606)***	3.734 (2.388–5.840)***
Severe (70 ≤ SAS)	8.568 (3.208–22.880)***	7.538 (2.757–20.606)***	16.217 (5.473–48.051)***	12.190 (3.789–39.224)***	13.706 (4.964–37.848)***	11.922 (4.154–34.217)***

OR, odds ratio. ***$p < 0.001$.

that comorbidities should be taken into consideration for psychiatric disorders that often occur concurrently (35). Beck et al. (36) corroborated that hopelessness is the key variable linking depression to suicidal behavior. This finding has direct implications for the therapy of suicidal individuals. Alessandra Costanza highlights that assessment of demoralization may contribute to a more comprehensive suicide risk detection by the findings of a systematic review (37). Rodriguez and Kendall (38) suggested that the increased risks of SB among anxiety-disordered individuals might be related to intolerance of distress and emotional dysregulation. Evidence has shown that participants with anxiety display poorer tolerance of distress (39) and more emotion dysregulation (40, 41). Such individuals find it very difficult to tolerate and modulate negative emotions and may be more inclined to think about suicide as a way to gain relief from their distress or as a method of escape (38).

However, other studies reached alternative conclusions regarding the correlation between anxiety and SB. Some studies suggested that the correlation could just be a by-product of comorbid depression (7). Moreover, a specific part of the anxiety, namely, the somatic anxiety, might be protective against suicidality (7). Several explanations might be responsible for the inconsistency in the conclusions. First, the inconsistency may be in part caused by sample differences; participants mentioned in previous studies range from community members (26) to college students (33) to clinical patients (42). Second, the conclusions may have been inconsistent because the relationships between anxiety and suicidal behaviors vary according to subtypes of anxiety disorders. For example, a number of studies that did not find an independent association between anxiety and SB (43, 44) only examined the severity and symptomatology of generalized anxiety. In contrast, many studies that affirmed the positive association examined a wide range of anxiety disorders or employed broader measures of anxiety symptoms (45–48). The potentiality that specific anxiety disorders have varying relationships to suicidal behaviors therefore warrants further investigation. Third, the discrepant conclusions may reflect the different relationships that anxiety disorders have with the wide spectrum of SB (e.g., suicidal ideations, suicide plans, or suicide attempts). It is important to note that not all previous research works on anxiety and suicidality have addressed these components separately. Perhaps anxiety disorders are specific predictors of the SI, but not of the capability or intention to engage in suicide attempts (38).

This study revealed a positive correlation between depression and suicidal behaviors, which is consistent with previous studies (28, 49, 50). Depression was shown to be an independent risk factor for SB after adjustments were made for demographic variables and comorbidities, which is also consistent with previous studies (7, 51). The strong association between depression and suicidal behaviors revealed

in this study highlights the importance of paying attention to depressive symptoms in medical college students. As only 0.6% of the participants reported a history of mental disorder, this seemingly low prevalence of self-identified depression may be a result of stigma. Studies have suggested that medical students refrain from disclosing their depression with school counselors as they worry that they would be less respected, seen to have less adequate coping skills, and considered to be less capable of handling their responsibilities (52). As a result, medical students with depression do not get diagnosed or treated, which could in turn exacerbate their symptoms and increase their risk for suicidality. Thus, there is a need to develop a positive mental health environment in medical schools in China to provide medical students with easy access to mental health resources and treatment options. In this study, participants scoring high on suicidal ideation were recommended to seek help from school counselors. The recommendation is specified on the webpage after finishing the questionnaire.

Several studies reported that anxiety increased the risk of SB when comorbid with depression (12, 31–33, 53, 54). The finding from this study contributes to the question of how anxiety impacts SB in patients with depression using data from a large sample size, cross-sectional study. Our findings are consistent with results from the studies mentioned above and revealed a dose–response relationship between the severity of anxiety symptoms and the risks of SB in depression. Some studies suggested that concurrent anxiety disorders exacerbate symptoms of depression, which manifests into even more psychological distress, poorer physical functioning, and poorer social functioning (55)– all of which may account for the increased the risk of SB. In addition, patients with comorbid anxiety had lower scores on scales that measure their quality of life (56) and were reported to have a longer duration of depression (57) and more emotional distress (57), posing a negative influence on the risk of suicidal behaviors. However, several other studies suggested inconsistent conclusions (7, 57, 58): some studies found that anxiety actually protected individuals from SB (7, 58). The conflicting findings have several explanations. First, the inconsistency regarding findings on the relation between anxiety and suicidality could result from heterogeneities in methodology. For example, Li et al. (59) suggested that gender ratios, sample sizes, response rates, and differences in screening tools explained almost half of the inter-study variations. Second, anxiety disorders include Panic Disorder, Agoraphobia, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Acute Stress Disorder, and Generalized Anxiety disorder, as well as specific and social phobias. The effect of anxiety on SB in depression varied greatly with different kinds of anxiety disorders (7). Third, as previous studies suggested a serial of mediation from anxiety to SB through degree of depressive symptoms (34), the effect of anxiety on risks of SB may also differ in response to different levels of severity of depressive symptoms. It is also possible that depressive symptoms have a moderating effect on the relationship between anxiety and SB. In addition, Beck's work questioned whether hopelessness was more predictive than depression with regard to suicide risk (36). And assessment of demoralization may contribute to a more comprehensive suicide risk detection by the findings of a systematic review (37). In other words, the relationship between anxiety and risks for SB may change depending on the severity of depressive symptoms. Future studies need to be conducted in order to investigate this possibility.

This study has several limitations. First, self-report assessment scales were utilized to measure symptoms of anxiety, depression, and SB. Participants' stigmas toward mental illness may have led them to under-report their symptoms (59). Second, the study used a cross-sectional study design, which means the data were collected from one time point and so were insufficient to establish any causal relationships between anxiety symptoms, depression symptoms, and suicidal behaviors. Future research should employ a longitudinal design in order to examine the direct causality of SB with other related variables. Third, most of the participants were females. Future studies should include an equal sample size of both genders to increase representativeness of population. Finally, the sample consists of data collected from three medical colleges, most of them were from Yiyang medical school, it may not be representative of Chinese college students in general and is possibly not representative of the adult population in China, future studies should enroll a larger range of samples to improve the representativeness. Therefore, more future studies are required so that repeated, reproducible results from varying populations can confidently inform us of the interactions and relations, whether causal or correlation, among SB, anxiety, and depression symptoms (60). It is noteworthy to emphasize that future studies that recruit large sample sizes from different sample populations would be most beneficial.

Conclusion

In summary, this study found that SB was very common among medical students, besides, anxiety, and depression were independent risk factors for SB. Participants with severe anxiety and depression symptoms were at much high risk of SB. This indicates the importance of screening for anxiety and depression among medical college students in order to promote mental health wellbeing and prevent SB. This study also found that anxiety was associated with an increased risk of SB among individuals with depression, and, the risk of SB was increased with the severity of anxiety symptoms. All findings lead to important clinical implications. First, SB was very common

among medical students; it is imperative to screen for SB as well as anxiety and depressive symptoms among medical college students and to better prevent suicide. Second, the study also provides valuable data for healthcare professionals to refer to when assessing the risks of suicide for patients with anxiety, depression, and comorbid depression and anxiety.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The research protocol was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, China. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author contributions

XL, XZ, JL, and YS were responsible for the study design. JL, YZ, and JPL were responsible for recruiting the participants. BS and ST were involved in statistical analysis. JL and JPL were involved in manuscript preparation and drafting the manuscript. XL, BS, and ST were involved in editing and revising the manuscript. YS and XZ were responsible for the critical revision of the manuscript. All authors have contributed to the manuscript and had given approval for the submission of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
E. Erdal Erşan,
Niğde Ömer Halisdemir University, Turkey

REVIEWED BY
Razia Khanam,
Gulf Medical University, United Arab Emirates
Tommaso Martino,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy

*CORRESPONDENCE
Takenao Koseki
✉ tkoseki@fujita-hu.ac.jp

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A pharmacovigilance approach for assessing the occurrence of suicide-related events induced by antiepileptic drugs using the Japanese adverse drug event report database

Takenao Koseki[1]*, Mikako Horie[1], Satomi Kumazawa[1], Tetsuo Nakabayashi[2] and Shigeki Yamada[1]

[1]Department of Clinical Pharmacy, Fujita Health University School of Medicine, Toyoake, Japan, [2]Center for Regulatory Science, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Increased suicidality after antiepileptic drug (AED) treatment remains controversial. This study aimed to investigate the occurrence of suicide-related events (SREs) in Japan. SREs signals with AEDs used orally were evaluated by calculating reporting odds ratios (RORs) and information components (ICs) using the Japanese Adverse Drug Event Report (JADER) database from April 2004 to December 2021. Additionally, factors affecting the occurrence of SREs and time-to-onset from the initial AED treatment were analyzed. Of 22 AEDs, 12 (perampanel hydrate, nitrazepam, levetiracetam, clonazepam, clobazam, sodium valproate, phenobarbital, lamotrigine, lacosamide, gabapentin, zonisamide, and carbamazepine) showed signals of SREs. Patients in their 20 and 30 s, female sex, and concomitant use of multiple AEDs affected the occurrence of SREs. In six AEDs, the median time-to-onset of SREs in patients taking all AEDs was <100 days. The pharmacovigilance approach revealed that several AEDs displayed suicidality signals. Female patients, those in their 20 and 30 s, undergoing combination therapy with ≥2 AEDs, and patients early (<100 days from the initial treatment) in the course of AED therapy should be cautioned about SREs.

KEYWORDS

antiepileptic drugs, suicidality, pharmacovigilance, Japanese adverse drug event report, perampanel hydrate

1. Introduction

Pharmacotherapy with antiepileptic drugs (AEDs) is the main treatment to control epileptic seizures. Approximately 70% of people with epilepsy will achieve long-term remission from seizures with AEDs (1, 2). However, the risk of suicide during AED treatment remains controversial (3).

In 2008, based on a meta-analysis of 199 placebo-controlled randomized clinical trials, the Food and Drug Administration (FDA) issued a safety class label warning on the risk of suicidality associated with the following 11 AEDs: carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide (4). Subsequently, Klein et al. reported that there was no evidence of increased suicidality with five other AEDs (eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate), which were approved by the FDA since 2008 (5). Other case-control and cohort studies have evaluated the relationship between AEDs use and suicidality in epilepsy. Increased risk for suicidality has been reported for several AEDs by some studies (6, 7), whereas no such increase was found by others (8–10). Therefore, results regarding the association between AEDs and suicidality risk are inconsistent, partly because of methodological limitations. Nearly all studies were case-controlled studies or meta-analyses; few used pharmacovigilance databases.

Recently, pharmacovigilance signal detection studies have been conducted using a large accumulated database of adverse events reported by a spontaneous reporting system (11–13). The Japanese Adverse Drug Event Report (JADER) is a nationwide database of spontaneous adverse reports published by the Pharmaceuticals and Medical Devices Agency (PMDA), a pharmaceutical regulatory authority in Japan. The JADER database contains data of approximately 760,000 patients and 1,250,000 adverse events reported after April 2004. It is useful for detecting signals of rare adverse events, such as suicide-related events (SREs) in patients receiving AEDs.

The present study investigated the signals of SREs, factors affecting the occurrence of SREs, and the time to onset of SREs in patients taking orally administered AEDs using the JADER database.

2. Materials and methods

2.1. Data source

Data from the JADER database (open-access database) between April 2004 and December 2021 were obtained from the PMDA website.[1] The JADER dataset used in this study consisted of three data tables: demographic information "demo" table, drug information "drug" table, and adverse events information "reac" table, which included 758,542 patients, 4,076,538 cases, and 1,247,830 cases, respectively. The "demo" table included patient demographic data, such as sex and age. Patients with blank/unknown sex or age data in the "demo" table and those with duplicated data in the "drug" and "reac" tables were excluded. The demo table was linked to the "drug" and "reac" tables using the patient identification number of each case. In the "drug" table, the contribution of the drugs to the adverse events was classified into three categories: suspected drug, concomitant drug, and interaction. The "suspected drug" category was extracted in the present study. To evaluate the signals for SREs in patients who received AEDs orally, assuming they were outpatients, the AEDs with "oral" route of administration were selected. Data from 673,845 patients were included in this study (**Figure 1**).

2.2. Targeted antiepileptic drugs

Twenty-two orally administered AEDs approved for use in Japan (acetazolamide, acetylpheneturide, carbamazepine, clonazepam, clobazam, ethosuximide, ethotoin, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, perampanel hydrate, phenytoin, phenytoin · phenobarbital, phenobarbital, primidone, sodium valproate, sultiame, topiramate, trimethadione, and zonisamide) were evaluated.

2.3. Definition of suicide-related events

Suicide-related events were extracted from the "reac" table according to the preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA 25.0 J). Fourteen PTs were determined from Suicide/self-injury (code 20000037) in the Standardized MedDRA Queries (SMQ), which are groups of PTs related to SREs (**Table 1**).

2.4. Signal detection

Because the pharmacovigilance database is based on reports of drug-induced adverse events and the population of patients taking AEDs is unknown, it is not possible to calculate the incidence of SREs occurred among patients taking AEDs. However, as the World Health Organization, PMDA, and other regulatory authorities have suggested, it is possible to estimate the potential risk of adverse events associated with a target drug by calculating parameters such as reporting odds ratios (RORs) and information components (ICs) based on two-by-two contingency tables (12). In this study, RORs and ICs were used for the signal detection of SREs as previously

1 https://www.pmda.go.jp/english/index.html

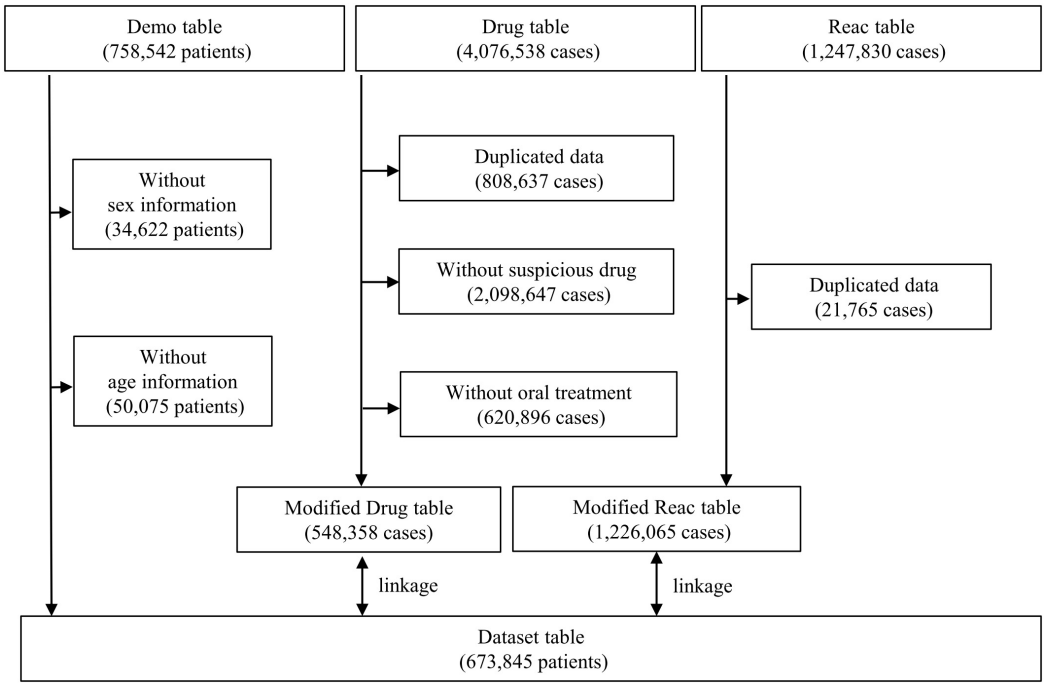

FIGURE 1
Flow diagram of the study.

TABLE 1 Definition of suicide-related events.

SMQ code	SMQ name
20000037	Suicide/self-injury
PT code	**PT name**
10079105	Assisted suicide
10075616	Columbia suicide severity rating scale abnormal
10010144	Completed suicide
10012397	Depression suicidal
10022523	Intentional overdose
10022524	Intentional self-injury
10036000	Poisoning deliberate
10051154	Self-injurious ideation
10065604	Suicidal behavior
10042458	Suicidal ideation
10042464	Suicide attempt
10077417	Suicide threat
10082458	Suspected suicide
10081704	Suspected suicide attempt

PT, preferred term; SMQ, standardized MedDRA queries.

reported (14, 15). RORs, ICs, and their 95% confidence intervals (CIs) were calculated using a two-by-two contingency table (Table 2) and equations as described below. The calculations

TABLE 2 Two-by-two contingency table.

	Target AEs	Other AEs	Total
Target drugs	N_{11}	N_{10}	N_{1+}
Other drugs	N_{01}	N_{00}	N_{0+}
Total	N_{+1}	N_{+0}	N_{++}

AEs, adverse events; N, number of patients.

were performed using Excel for Microsoft 365 (Microsoft Corporation). The signals for SREs were positive when the lower limit of the 95% CI of the ROR exceeded 1, and that of the IC exceeded 0.

ROR equations:

$$\mathrm{ROR} = \frac{N_{11}/N_{01}}{N_{10}/N_{00}} = \frac{N_{11}N_{00}}{N_{10}N_{01}}$$

$$\mathrm{ROR\ (95\%CI)} = e^{\ln(\mathrm{ROR}) = 1.96\sqrt{\frac{1}{N_{11}}+\frac{1}{N_{10}}+\frac{1}{N_{01}}+\frac{1}{N_{00}}}}$$

IC Equations:

$$E(\mathrm{IC}_{11}) = \log_2 \frac{(N_{11}+\gamma_{11})(N_{++}+\alpha)(N_{++}+\beta)}{(N_{++}+\gamma)(N_{+1}+\alpha_1)(N_{+1}+\beta_1)}$$

$$V(\mathrm{IC}_{11}) = \left(\frac{1}{\ln 2}\right)^2\left[\frac{N_{++}-N_{11}+\gamma-\gamma_{11}}{(N_{11}+\gamma_{11})(1+N_{++}+\gamma)}+\right.$$

$$\left.\frac{N_{++}-N_{+1}+\alpha-\alpha_1}{(N_{1+}+\alpha_1)(1+N_{++}+\alpha)}+\frac{N_{++}-N_{+1}+\beta-\beta_1}{(N_{+1}+\beta_1)(1+N_{++}+\beta)}\right]$$

$$\gamma = \gamma_{11} \frac{(N_{++} + \alpha)(N_{++} + \beta)}{(N_{+1} + \alpha_1)(N_{+1} + \beta_1)}$$

$$\gamma_{11} = 1,\ \alpha_1 = \beta_1 = 1,\ \alpha = \beta = 2$$

$$\mathrm{IC}\,(95\%\mathrm{CI}) = E\,(\mathrm{IC}_{11}) = 2\sqrt{V\,(\mathrm{IC}_{11})}$$

2.5. Factor analysis

To investigate the factors affecting the occurrence of SREs, univariable and/or multivariable logistic regression analyses were performed in patients with or without AEDs. Variables showing $p < 0.1$ in the univariable logistic regression analysis were entered in the multivariable logistic regression model. *P*-values < 0.05 were considered statistically significant. Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) as a graphical user interface for R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R Commander (version 1.54), designed to add statistical functions frequently used in biostatistics (16).

2.6. Time-to-onset analysis

Time-to-onset analysis was performed using the periods from the day of the initial administration of AEDs in "drug" table to the day of the first occurrence of the SREs recorded in the "reac" table. Patients with missing values or those without data were excluded. The median period and interquartile range (IQR) and Weibull shape parameters (WSPs) were determined (17–19). WSPs consist of parameters α and β, which determine the scale and shape of the distribution function, respectively. A larger and smaller α indicates a wider and shrinking data distribution, respectively. The shape parameter β indicates a hazard without a reference population. The hazard considerations are as follows: 95% CI of β includes 1 (hazard constant over time; random failure type), lower limit of the 95% CI of $\beta > 1$ (hazard increases over time; wear-out failure type), and upper limit of the 95% CI of $\beta < 1$ (hazard decreases over time; initial failure type). We evaluated AEDs with >10 patients reporting SREs between the day of the initial administration and the day of the first occurrence of SREs. Statistical analyses were performed using JMP 13.0 (SAS Institute Inc., Cary, NC, USA).

2.7. Ethical approval

Ethics approval and consent to participate were not required since this study was performed using an open access database.

3. Results

3.1. Patient characteristics

Table 3 summarizes the characteristics of 673,845 patients included in the study. For all adverse events, there were more male patients and those in their 70 s. For SREs, there were more female patients and those in their 30 s. Among those with SREs, 389 patients received 1 ≤ AEDs; nearly all patients with 1 ≤ AED were female and in their 20 and 30 s. Among the targeted AEDs, no SREs were reported for these seven: acetazolamide, acetylpheneturide, ethosuximide, ethotoin, primidone, sultiame, and trimethadione.

3.2. Suicide-related events signals

Table 4 shows RORs and CIs of AEDs for SREs. Signals were detected in patients who used 1 ≤ AEDs (all AEDs: ROR, 4.68 [95% CI 4.21–5.21] and IC, 2.06 [95% CI 1.91–2.22]). Among the AEDs with 1 ≤ SREs, signals for SREs were detected in 12: Perampanel hydrate, nitrazepam, levetiracetam, clonazepam, clobazam, sodium valproate, phenobarbital, lamotrigine, lacosamide, gabapentin, zonisamide, and carbamazepine. Of these, perampanel hydrate showed the highest signal index (ROR, 20.59 [95% CI 13.91–30.48] and IC, 3.52 [95% CI 2.96–4.09]); nitrazepam, levetiracetam, and clonazepam showed high signal indices (ROR, 12.47 [95% CI 8.55–18.20] and IC, 3.10 [95% CI 2.56–3.65]); (ROR, 8.95 [95% CI 7.23–11.97] and IC, 2.96 [95% CI 2.65–3.27]); (ROR, 8.73 [95% CI 6.11–12.46] and IC, 2.76 [95% CI 2.25–3.28], respectively). On the other hand, phenytoin · phenobarbital, topiramate, and phenytoin did not show SRE signals (ROR, 25.87 [95% CI 3.18–210.36] and IC, 0.93 [95% CI −1.33–3.19]); (ROR, 2.55 [95% CI 0.95–6.85] and IC, 0.95 [95% CI −0.35–2.25]); (ROR, 1.82 [95% CI 1.00–3.30] and IC, 0.76 [95% CI −0.08–1.60], respectively).

3.3. Factors associated with suicide-related events

To investigate the factors affecting the occurrence of SREs with AEDs, the effects of sex and age on the occurrence of SREs in all patients were first evaluated by multivariable analysis using logistic regression (Table 5). Since female outnumbered male patients among those with SREs and the 100 s was the center of the age groups in the percentage of SREs/all adverse events patients, male sex and 100 s age group were used as reference values. Multivariable analysis revealed that being female (odds ratio [OR] for females, 1.09 [95% CI 1.02–1.16], $p = 0.013$), and in ones' 20 s (OR for 20 s, 7.43 [95% CI 1.04–53.00], $p = 0.045$)

TABLE 3 Sex- and age-specific patient population with antiepileptic drugs for suicide-related events.

		Sex		Age											
		Male	Female	<10 years	10 s	20 s	30 s	40 s	50 s	60 s	70 s	80 s	90 s	100 s	Total
	Patients with all AEs	344,184	329,661	24,639	19,646	24,680	39,063	54,773	85,837	149,705	173,259	89,186	12,795	262	673,845
	Patients with SREs	1,619	2,082	19	282	677	760	657	465	357	332	129	22	1	3,701
Patients with SREs using antiepileptic drugs	All antiepileptic drugs	150	239	4	36	92	98	59	44	31	18	7	0	0	389
	Levetiracetam	43	48	4	12	17	20	11	6	12	6	3	0	0	91
	Lamotrigine	27	46	0	5	19	22	13	10	3	1	0	0	0	73
	Sodium valproate	25	48	0	4	30	21	7	6	5	0	0	0	0	73
	Carbamazepine	27	40	0	11	14	12	11	11	4	2	2	0	0	67
	Clonazepam	9	23	0	1	8	9	7	3	1	3	0	0	0	32
	Nitrazepam	8	21	0	2	5	7	7	3	4	1	0	0	0	29
	Perampanel hydrate	14	14	0	2	5	11	1	7	1	1	0	0	0	28
	Zonisamide	9	8	0	2	2	1	3	1	2	4	2	0	0	17
	Phenobarbital	7	9	0	2	3	5	0	5	1	0	0	0	0	16
	Phenytoin	6	5	0	2	1	2	0	3	3	0	0	0	0	11
	Lacosamide	7	4	0	1	1	1	2	2	2	1	1	0	0	11
	Gabapentin	3	4	0	0	0	4	2	1	0	0	0	0	0	7
	Clobazam	2	4	0	1	1	2	1	1	0	0	0	0	0	6
	Topiramate	2	2	0	0	0	2	1	1	0	0	0	0	0	4
	Phenytoin · phenobarbital	0	1	0	0	0	1	0	0	0	0	0	0	0	1

AEs, adverse events; SREs, suicide-related events.

10.3389/fpsyt.2022.1091386

TABLE 4 Reporting odds ratios and information components of antiepileptic drugs for suicide-related events.

Antiepileptic drug	All AE patients	SRE patients	ROR	[95% CI]	IC	[95% CI]
All antiepileptic drugs	16,169	389	4.68	[4.21–5.21]	2.06	[1.91–2.22]
Perampanel hydrate	276	28	20.59	[13.91–30.48]	3.52	[2.96–4.09]
Nitrazepam	453	29	12.47	[8.55–18.20]	3.10	[2.56–3.65]
Levetiracetam	1,973	91	8.95	[7.23–11.97]	2.96	[2.65–3.27]
Clonazepam	701	32	8.73	[6.11–12.46]	2.76	[2.25–3.28]
Clobazam	231	6	4.83	[2.15–10.88]	1.62	[0.51–2.73]
Sodium valproate	2,906	73	4.74	[3.75–5.99]	2.12	[1.78–2.47]
Phenobarbital	641	16	4.65	[2.83–7.65]	1.91	[1.20–2.62]
Lamotrigine	3,199	73	4.29	[3.40–5.43]	1.99	[1.65–2.34]
Lacosamide	458	11	4.19	[2.30–7.63]	1.77	[0.92–2.61]
Gabapentin	336	7	3.86	[1.82–8.16]	1.49	[0.46–2.52]
Zonisamide	1,139	17	2.75	[1.70–4.45]	1.31	[0.62–2.00]
Carbamazepine	5,188	67	2.39	[1.88–3.05]	1.20	[0.85–1.56]
Phenytoin · Phenobarbital	8	1	25.87	[3.18–210.36]	0.93	[−1.33–3.19]
Topiramate	288	4	2.55	[0.95–6.85]	0.95	[−0.35–2.25]
Phenytoin	1,108	11	1.82	[1.00–3.30]	0.76	[−0.08–1.60]

AE, adverse events; CI, confidence intervals; IC, information component; ROR, reporting odds ratio; SRE, suicide-related events.

TABLE 5 Odds ratios for suicide-related events.

	OR	95% CI	*P*-values
Sex (vs. male)			
Female	1.09	1.02–1.16	0.013
Age (vs. 100 s)			
<10 years	0.21	0.03–1.55	0.125
10 s	3.87	0.54–27.60	0.178
20 s	7.43	1.04–53.00	0.045
30 s	5.23	0.73–37.30	0.099
40 s	3.22	0.45–23.00	0.244
50 s	1.45	0.20–10.40	0.711
60 s	0.64	0.09–4.57	0.656
70 s	0.51	0.07–3.67	0.506
80 s	0.39	0.05–2.76	0.342
90 s	0.45	0.06–3.36	0.438

CI, confidence intervals; OR, odds ratio.

or 30 s (OR for 30 s, 5.23 [95% CI 0.73–37.30], $p = 0.099$) were associated with an increased occurrence of SREs.

Second, we assessed the effect of sex (female), age (20 and 30 s), and the number of concomitant AEDs used (1 other AED or 2 ≤ other AEDs vs. AED monotherapy) on the occurrence of SREs in patients who used AEDs for which signals were detected (Table 6). Univariable analysis revealed that female sex and 20 and 30 s age groups, but not concomitant use of AEDs, were associated with an increased occurrence of SREs in patients who used 1 ≤ AEDs (all AEDs; OR for female sex, 1.54 [95% CI 1.25–1.89], $p < 0.001$; OR for 20 and 30 s age groups, 3.42 [95% CI 2.79–4.18], $p < 0.001$). SREs occurred more frequently in female patients treated with these four AEDs: nitrazepam, clonazepam, sodium valproate, and carbamazepine. SREs were more frequent among patients in their 20 and 30 s, with nearly all AEDs, excluding lacosamide and zonisamide. The occurrence of SREs tended to increase with concomitant use of one other AED in patients taking phenobarbital and carbamazepine and concomitant use of 2 ≤ other AEDs in patients taking perampanel hydrate, lamotrigine, and carbamazepine. Multivariable analysis confirmed almost all the results of the univariable analysis.

3.4. Time-to-onset of suicide-related events

In the time-to-onset analysis, six AEDs (perampanel hydrate, nitrazepam, levetiracetam, sodium valproate, lamotrigine, and carbamazepine) with more than 10 reported SREs were evaluated. The histograms and WSPs of each AED are shown in Figure 2. The median period (IQR) to onset of SREs in patients with AEDs was as follows: perampanel hydrate (64 [32–256] days, $n = 19$), nitrazepam (61 [0–201] days, $n = 11$), levetiracetam (59 [9–235.5] days, $n = 45$), sodium valproate (92 [0–141] days, $n = 13$), lamotrigine (54 [8.5–215.5] days, $n = 44$), and carbamazepine (0 [0–542.5] days, $n = 16$). Levetiracetam,

10.3389/fpsyt.2022.1091386

TABLE 6 Univariable and multivariable analysis for associated factors of suicide-related events with antiepileptic drugs.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*-values	OR	95% CI	*P*-values
All antiepileptic drugs						
Female sex	1.54	1.25–1.89	<0.001	1.35	1.09–1.66	0.005
20 and 30 s age groups	3.42	2.79–4.18	<0.001	3.29	2.69–4.04	<0.001
Concomitant use of 1 other antiepileptic drug	0.96	0.68–1.34	0.793			
Concomitant use of 2 ≤ other antiepileptic drugs	1.38	0.83–2.30	0.217			
Perampanel hydrate						
Female sex	1.38	0.63–3.03	0.415			
20 and 30 s age groups	4.47	2.00–9.99	<0.001	4.64	2.05–10.50	<0.001
Concomitant use of 1 other antiepileptic drug	1.99	0.73–5.45	0.179			
Concomitant use of 2 ≤ other antiepileptic drugs	2.58	0.93–7.17	0.069	2.49	0.89–7.00	0.084
Nitrazepam						
Female sex	4.75	2.05–11.00	<0.001	4.44	1.91–10.30	<0.001
20 and 30 s age groups	2.26	1.04–4.89	0.039	1.91	0.87–4.21	0.108
Concomitant use of 1 other antiepileptic drug	0.51	0.17–1.49	0.215			
Concomitant use of 2 ≤ other antiepileptic drugs	NA					
Levetiracetam						
Female sex	1.31	0.86–2.00	0.210			
20 and 30 s age groups	2.72	1.76–4.19	<0.001			
Concomitant use of 1 other antiepileptic drug	0.67	0.37–1.23	0.195			
Concomitant use of 2 ≤ other antiepileptic drugs	1.02	0.48–2.16	0.961			
Clonazepam						
Female sex	1.67	1.02–2.73	0.040	2.01	0.90–4.49	0.087
20 and 30 s age groups	2.77	1.69–4.55	<0.001	3.99	1.92–8.28	<0.001
Concomitant use of 1 other antiepileptic drug	0.60	0.24–1.49	0.269			
Concomitant use of 2 ≤ other antiepileptic drugs	0.73	0.21–2.49	0.615			
Sodium valproate						
Female sex	1.91	1.17–3.11	0.010	1.93	1.17–3.18	0.010
20 and 30 s age groups	8.04	4.84–13.40	<0.001	8.61	5.16–14.40	<0.001
Concomitant use of 1 other antiepileptic drug	0.48	0.25–0.91	0.026	0.37	0.19–0.72	0.003
Concomitant use of 2 ≤ other antiepileptic drugs	0.67	0.29–1.58	0.361			
Phenobarbital						
Female sex	1.68	0.62–4.57	0.310			
20 and 30 s age groups	3.84	1.42–10.40	0.008	3.71	1.36–10.10	0.010
Concomitant use of 1 other antiepileptic drug	2.80	0.84–9.32	0.093	1.80	0.64–5.08	0.268
Concomitant use of 2 ≤ other antiepileptic drugs	2.54	0.72–8.92	0.145			
Lamotrigine						
Female sex	0.97	0.60–1.57	0.896			
20 and 30 s age groups	2.28	1.43–3.63	<0.001	2.28	1.43–3.64	<0.001
Concomitant use of 1 other antiepileptic drug	0.44	0.16–1.23	0.117			
Concomitant use of 2 ≤ other antiepileptic drugs	2.07	0.88–4.88	0.096	2.21	0.95–5.28	0.066

(Continued)

TABLE 6 (Continued)

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*-values	OR	95% CI	*P*-values
Lacosamide						
Female sex	0.67	0.19–2.32	0.528			
20 and 30 s age groups	0.77	0.16–3.63	0.742			
Concomitant use of 1 other antiepileptic drug	2.29	0.56–9.35	0.249			
Concomitant use of 2 ≤ other antiepileptic drugs	3.97	0.77–20.5	0.100			
Gabapentin						
Female sex	1.57	0.35–7.13	0.558			
20 and 30 s age groups	6.79	1.48–31.20	0.014			
Concomitant use of 1 other antiepileptic drug	NA					
Concomitant use of 2 ≤ other antiepileptic drugs	NA					
Zonisamide						
Female sex	0.89	0.34–2.33	0.816			
20 and 30 s age groups	0.92	0.26–3.23	0.896			
Concomitant use of 1 other antiepileptic drug	1.84	0.66–5.12	0.241			
Concomitant use of 2 ≤ other antiepileptic drugs	0.49	0.06–3.88	0.501			
Carbamazepine						
Female sex	1.67	1.02–2.73	0.040	1.57	0.95–2.57	0.076
20 and 30 s age groups	2.77	1.69–4.55	<0.001	2.48	1.50–4.11	<0.001
Concomitant use of 1 other antiepileptic drug	1.89	1.00–3.58	0.051	1.76	0.93–3.34	0.083
Concomitant use of 2 ≤ other antiepileptic drugs	2.35	1.00–5.54	0.051	1.97	0.83–4.71	0.126

CI, confidence intervals; OR, odds ratio; NA, not applicable.

sodium valproate, and lamotrigine showed a lower limit of 95% CI of WSP $\beta < 1$ (initial failure type). No AEDs were reported with an upper limit of 95% CI of WSP $\beta > 1$.

4. Discussion

Suicide-related event signals, the factors affecting the occurrence of SREs, and their time-to-onset were studied based on the JADER database in Japan. Among the 22 targeted AEDs, the occurrence of one or more SREs was reported in 15 and SREs signals were detected in 12. SREs were more frequent among patients in their 20 and 30 s among patients across nearly all AEDs, in females, and with concomitant use of other AEDs in patients using some AEDs. In addition, some AEDs were classified as the initial failure types. Our results obtained using the pharmacovigilance approach may provide new insights into suicidality risk associated with AEDs.

Among the AEDs associated with SREs, perampanel hydrate, nitrazepam, levetiracetam, and clonazepam showed high SREs signal indices. Perampanel hydrate is an orally active, non-competitive, selective glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (20). In a recent meta-analysis, perampanel hydrate did not show the risk of suicidal ideation and suicidal attempt in patients without a history of suicidality; and suicidal ideation (including suicide attempt) was reported in only 3 of 1119 (0.27%) patients treated with perampanel hydrate (5). Conversely, suicidal ideation, intentional drug overdose, and suicide attempt were reported in 10 of 482 (2.1%) patients treated with perampanel hydrate, who had no medical history of suicidal behavior in an observational 52-week cohort study (21); although a history of suicidal behavior could not be determined, our results suggest that patients with epilepsy should be monitored for signs of suicidal behavior during treatment with perampanel hydrate. The neurobiological mechanism of suicidality is still unknown. Upregulation of the binding of the AMPA receptors in the caudate nucleus of individuals who had completed suicide has been reported (22, 23). Antagonism of AMPA receptors by perampanel hydrate might be involved in suicidal behaviors, as indicated by the alteration of AMPA receptor function in patients who completed suicide. In addition, it has been reported that individuals taking perampanel hydrate have a high frequency of aggression, and that aggression is strongly correlated with suicidality risk (21, 24). Aggression is associated with

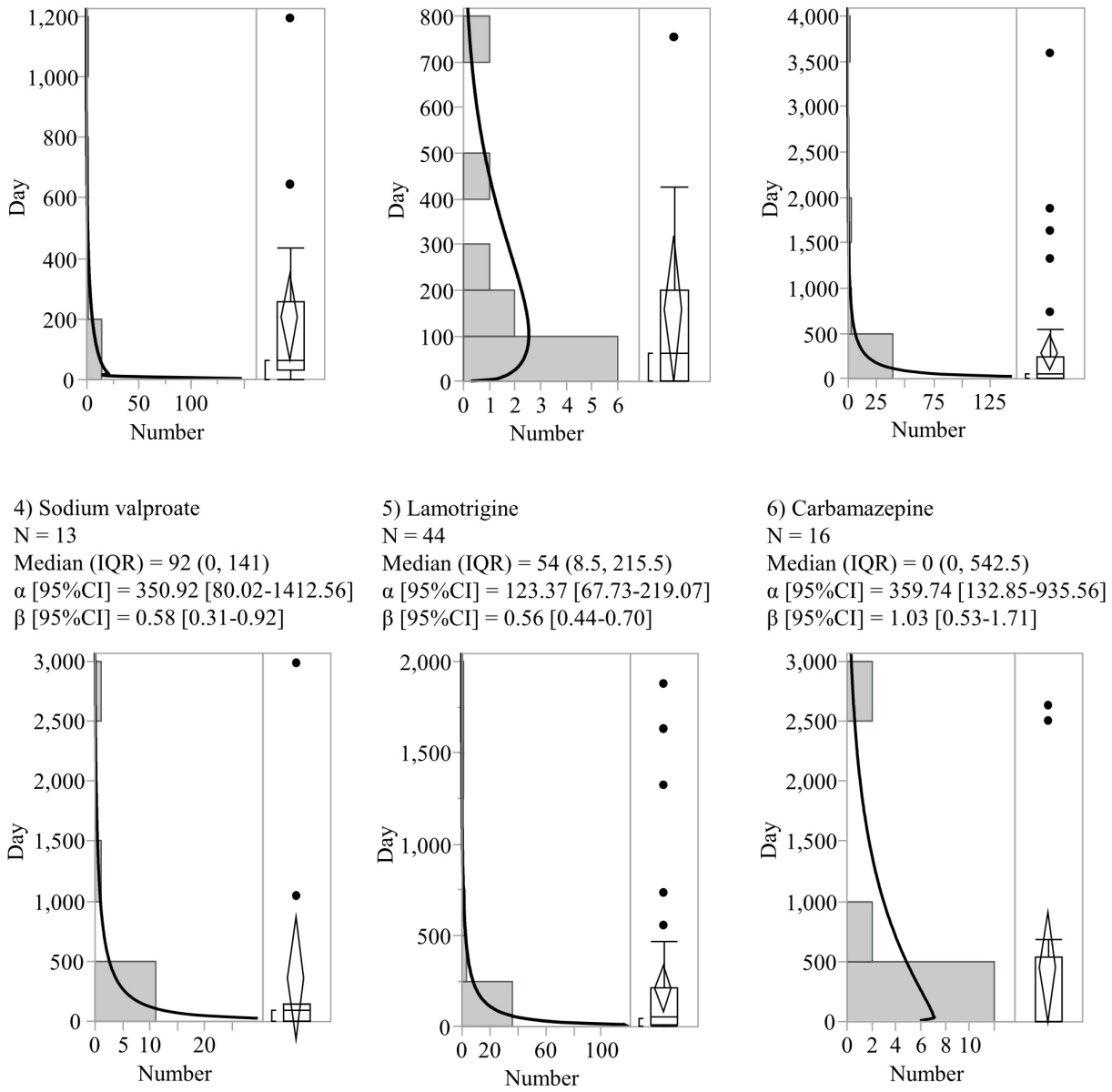

FIGURE 2
Histograms and Weibull shape parameters of suicide-related events. CI, confidence intervals; IQR, interquartile range; N, number of patients.

increased glutamate levels in the amygdala, hypothalamus, and periaqueductal gray matter, and with stimulation of glutamate receptors (25, 26). Blockade of AMPA receptors can either increase or decrease aggressive behavior (27, 28). The *N*-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine, is associated with increased aggression at low doses, and reduced aggression at higher doses (29). Perampanel hydrate may cause increased aggression through AMPA receptor antagonism and subsequent alteration of NMDA receptor function, and the increased aggression may be associated with increased suicidality risk. Further, the frequency of NMDA-dependent spontaneous excitatory postsynaptic currents (EPSCs) is higher in the hippocampus of patients with mesial temporal lobe epilepsy than in non-epileptic controls (30), so the potential

risk of SREs associated with perampanel hydrate use may be particularly high in patients with epilepsy. Benzodiazepines as antiepileptics, including nitrazepam and clonazepam were not included in the FDA's meta-analysis; however, several case reports and case cohort studies have reported that these benzodiazepines increased showed suicidality risk or contributed to the cause of suicidality in various populations (6, 31–34). Our results support these reports and confirm that patients treated with benzodiazepines are at risk for suicidality. In general, benzodiazepines may reduce anxiety in epilepsy and lower suicidality risk owing to their gamma-aminobutyric acid (GABA) agonist properties (35). However, it was reported that cerebrospinal fluid concentrations of GABA were higher in individuals with a history of suicidal behavior than in those without this history (36), indicating that the effects of benzodiazepines on suicidality may depend on differences in individual neural abnormalities, including GABAergic neurons in patients with epilepsy. Several case-crossover/control studies reported that levetiracetam also increased the risk of suicidality (6, 7, 37, 38). Levetiracetam is thought to suppress seizures in patients with epilepsy by acting on synaptic vesicle protein 2A and AMPA receptors to decrease the amplitude and frequency of miniature EPSCs in cortical neurons (39, 40). As observed with perampanel hydrate, the AMPA receptor may play an important role in the occurrence of SREs in levetiracetam-treated patients.

In addition, being female, in ones' 20 and 30 s, and concomitant use of AEDs increase the occurrence of SREs for some AEDs. Overall suicidality risk increases with age and is higher in men in the general population, whereas it decreases with age and is higher in female with epilepsy (41). Despite differences between patients with epilepsy and those receiving AEDs, we found that female patients, those in their 20 and 30 s, and who are on multiple AEDs are at higher risk for SREs, consistent with this report. Few studies have focused on the differential impact of monotherapy vs. combination therapy with one or more other concomitant AEDs on the suicidality risk in patients receiving AEDs. In our study, the risk of SREs was not affected by concomitant use of one or more other AEDs compared to AED monotherapy in patients receiving AEDs overall. Increased risk of SREs was seen in patients concomitantly using perampanel hydrate, lamotrigine, and carbamazepine with $1 \leq$ other AEDs. Carbamazepine and lamotrigine are considered AEDs with anti-suicidal properties because they improve mood in epileptic patients *via* serotonergic mechanisms of action (42). Additionally, carbamazepine decreases the antiepileptic effects and adverse events of concomitant AEDs by inducing cytochrome P450 isoenzymes (1). Contrary to expectations, carbamazepine and lamotrigine appear to increase suicidality risk in monotherapy as well as in combination therapy with other AEDs. The principle of epilepsy treatment should be started as AED monotherapy; if unsuccessful after titrating to an optimal dose, combination therapy with other AEDs should be considered (1, 43). In addition to changes in efficacy and safety due to drug interactions, it may be necessary to note an increased suicidality risk for some AEDs, such as perampanel hydrate, lamotrigine, and carbamazepine, when multiple AEDs are used in combination therapy. In time-to-onset analysis, all of the 6 AEDs evaluated in this study had a median time to SREs onset of <100 days, and 3 AEDs were classified as "initial failure type" and other three AEDs were classified as "random failure type." In FDA's report, a higher risk of suicidal behavior or ideation was observed as early as 1 week after the first dose and persisted over time for at least 24 weeks. In support of this report, our results suggest that suicide risk induced by AEDs is more likely to occur early in the course of epilepsy therapy and requires particular attention within the first 100 days of treatment.

Our study had several limitations. Because spontaneous reporting systems, such as JADER are passive reporting systems, many biases, such as under-reporting, over-reporting, and confounding by comorbidities, exist. There is a strong association between epilepsy and psychiatric diseases (41). Although epileptic patients with or without a history of psychiatric diseases have a high risk of suicidality (41), and suicidal risk induced by AEDs in patients with epilepsy was reported to have the largest estimated OR compared to that of psychiatric patients by subgroup analysis (4), the influence of comorbidity of psychiatric diseases cannot be ruled out. Furthermore, the number of SREs reported for several AEDs is small. To avoid false-positive detection, we defined SRE signals as those with a significant difference in both the RORs and ICs. Despite these limitations, we believe that our approach using a pharmacovigilance database will contribute to the discussion on suicidality induced by AEDs and the factors affecting it.

In conclusion, based on a pharmacovigilance database several AEDs, such as perampanel hydrate, nitrazepam, levetiracetam, and clonazepam showed SREs signals. Female patients, those in the 20 and 30 s, and using multiple AEDs concomitantly increased the risk for SREs. New insights from our results may help in understanding the association between AEDs and suicidality, and aid clinicians and other medical staff to predict and prevent suicidality induced by AEDs.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html.

Author contributions

TK designed this study and performed the statistical analyses. TK and MH conducted the survey using the JADER

database. TK, MH, SK, TN, and SY drafted the manuscript. All authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Çiçek Hocaoğlu,
Recep Tayyip Erdoğan University, Türkiye

REVIEWED BY
Mehmet Hamdi Örüm,
Elazığ Eğitim Ve Araştırma Hastanesi, Türkiye
Chutima Roomruangwong,
Chulalongkorn University, Thailand

*CORRESPONDENCE
Ricardo Tavares Pinheiro
ricardo.pinheiro@ucpel.edu.br

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Can glutathione be a biomarker for suicide risk in women 18 months postpartum?

Paula Michele da Silva Schmidt[1], Jéssica Puchalski Trettim[1], Aline Longoni[1], Mateus Grings[2], Mariana Bonati de Matos[1], Luciana de Avila Quevedo[1], Ana Paula Ardais[1], Fernanda Nedel[1], Gabriele Ghisleni[1], Guilhian Leipnitz[2,3], Ricardo Tavares Pinheiro[1]* and Adriano Martimbianco de Assis[1]

[1]Graduate Program in Health and Behavior, Center of Health Science, Universidade Católica de Pelotas - UCPel, Pelotas, Brazil, [2]Graduate Program in Biological Sciences: Biochemistry, ICBS, Universidade Federal do Rio Grande do Sul - UFRGS, Porto Alegre, Brazil, [3]Department of Biochemistry, Universidade Federal do Rio Grande do Sul - UFRGS, Porto Alegre, Brazil

Background: Suicide risk is prominent among the problems affecting populations, mainly due to the broad family, psychosocial and economic impact. Most individuals at suicidal risk have some mental disorder. There is considerable evidence that psychiatric disorders are accompanied by the activation of neuro-immune and neuro-oxidative pathways. The aim of the study is to evaluate the serum levels of oxidative stress biomarkers in women at risk of suicide after 18 months of postpartum.

Methods: This is a case-control study, nested within a cohort study. From this cohort, 45 women [15 without mood disorders and 30 with mood disorders (Major depression and Bipolar disorder)] were selected at 18 months postpartum, the depression and suicide risk were assessed using the Mini-International Neuropsychiatric Interview Plus (MINI-Plus) instrument, module A and C, respectively. Blood was collected and stored for later analysis of the reactive species (DCFH), superoxide dismutase (SOD), and glutathione reduced (GSH). For data analysis, the SPSS program was used. To compare the nominal covariates with the outcome GSH levels, the Student's *t*-test or analysis of variance (ANOVA) was used. Spearman's correlation was performed for analysis between the quantitative covariates and the outcome. To analyze the interaction between the factors, multiple linear regression was performed. Bonferroni analysis was used as an additional/secondary result to visualize differences in glutathione levels according to risk severity. After the adjusted analysis, p-values < 0.05 were considered statistically significant.

Results: The percentage of suicide risk observed in our sample of women at 18 months postpartum was 24.4% (n = 11). After adjusting for the independent variables, only the presence of suicide risk remained associated with the outcome ($\beta = 0.173$; $p = 0.007$), low levels of GSH at 18 months after postpartum. Likewise, we verified the difference in GSH levels according to the degree of suicide risk, observing a significant association between the differences in glutathione means in the group

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of women with moderate to high risk compared to the reference group (no suicide risk) (p = 0.009).

Conclusion: Our findings suggest that GSH may be a potential biomarker or etiologic factor in women at moderate to high risk of suicide.

KEYWORDS

glutathione, antioxidants, psychiatric disorders, suicide risk, mood disorders, oxidative stress

Introduction

Suicide takes a featured place among the problems that affect populations, mainly due to the broad family, psychosocial and economic impact. More than 800,000 people worldwide commit suicide annually and it is estimated that, for each completed case, there are more than 20 attempts. In Brazil, the suicide mortality rate is about 5.5 deaths per 100,000 inhabitants, with about 10,000 suicide deaths annually (1). While not every person who attempts suicide has a mental illness, the vast majority suffer from depression (2). It is estimated that the lifetime risk of suicide in people with depression is 6 to 15% (3), with a man's risk of suffering from the disease being 11%, while that of a woman can reach 18.6% (2).

Interventions have emerged to prevent suicide, but what makes prevention difficult is precisely not knowing the situations that influence suicidal ideation or behavior. In addition, several studies have sought more effective alternatives for the drug treatment of individuals with suicidal behavior. Glutaminergic dysregulation has already been identified as a potential pathological pathway in psychiatric disorders, including depression and schizophrenia (4, 5). As well, oxidative damage and redox dysregulation appear to play important roles in the pathogenesis of psychiatric disorders due to the brain's vulnerability to oxidative stress (6).

The central nervous system (CNS) is particularly sensitive due to the high rate of oxygen consumption, the high levels of polyunsaturated lipids (capable of undergoing lipid peroxidation) (7) and the auto-oxidation of some neurotransmitters, which can lead to the formation of reactive oxygen species (ROS) (8). In addition, the brain is quite vulnerable to oxidative damage, given its relatively low content of antioxidant defenses and the high content of metals (iron, zinc, magnesium and copper), which can catalyze the formation of reactive oxygen and nitrogen species (8).

Glutathione (GSH, L-γ-glutamyl-L-cysteinyl-glycine) is an endogenous antioxidant found in many tissues, however, in the brain, it plays a major role and is widely used by neurons to neutralize oxidative stress and maintain neural cell functionality and viability adequate (9). However, low concentrations of GSH have been reported in some of the major psychiatric disorders (10, 11), including major depressive disorder (MDD) (12), bipolar disorder (13), and schizophrenia (14–18).

Furthermore, the literature shows that stressful conditions (shock) increase brain energy demand, which results in an increase in ROS and consequently a decrease in GSH levels in the cerebral cortex of mice, an effect that was reversed by antidepressants (19). GSH may be an endogenous neuromodulator of mood (20, 21). Thus, our study hypothesis is that women with suicidal risk present cerebral redox imbalance resulting in a decrease in blood GSH levels. Therefore, the objective was to evaluate the serum levels of oxidative stress biomarkers in women at risk of suicide after 18 months of postpartum.

Materials and methods

Design

This is a case-control study nested within a population-based cohort study, conducted within a city in the south of Brazil. The cohort project to which this case is linked was approved by the committee of research ethics of the Catholic University of Pelotas, under-report number 1.729.653. For more details on sample capturing, read the publications of Pinheiro et al. (22, 23).

For this study, 45 women [15 without mood disorders (control) and 30 with mood disorders (case)] from the central project were selected, all of them participating in the 18-month postpartum phase and coming from an initial selection (case) that considered a diagnosis of mood disorders (Figure 1).

Instruments

The instrument used to assess depression and the risk of suicide in this research was the Mini-International Neuropsychiatric Interview Plus (MINI-Plus 5.0.0 Brazilian version), module A and module C,

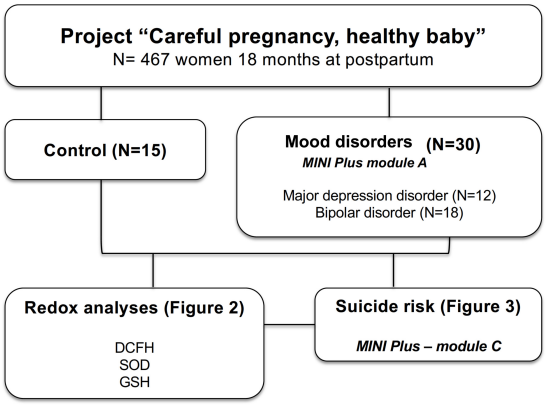

FIGURE 1
Study organization chart. Women (control and mood disorder) were selected from the cohort entitled "Careful pregnancy, healthy baby" for analysis of plasma biomarkers of oxidative stress and risk of suicide.

respectively (24). The MINI-Plus is a brief standardized diagnostic interview (15–30 min), compatible with the criteria of the diagnostic and statistical manual of mental disorders (DSM-IV) and the international classification of diseases (ICD-10), which is intended for use in clinical practice and research in primary care and psychiatry. The suicidality section inquires about several components of suicide risk with the following questions: over the last month: (1) Have you wished you were dead? (score: 1 point); (2) Have you wanted to harm yourself? (2 points); (3) Have you thought of committing suicide? (6 points); (4) Have you planned how to commit suicide? (10 points); (5) Have you attempted suicide? (10 points), and (6) Have you ever attempted suicide? (4 points). The risk for suicide range was "low" (score 1–5), "moderate" (score 6–9), and "high" (score eN10). For analysis, the scores were dichotomized as absent (low or absent risk) or presence (moderate or high risk), as recommended by the MINI-Plus author (25, 26). The suicidality module of MINI-Plus is largely used with adequate validity and reliability (27, 28). Women variables, like age and schooling (collected in completed years and later categorized in terciles), were collected *via* questions of the structured general questionnaire.

TABLE 1 Sample characteristics of women (control or mood disorder) at risk of suicide.

	Control *N* (%)	Mood disorder *N* (%)	*p*-value
Age (years)			1.000
Up to 23	3 (20.0)	6 (20.0)	
24–29	6 (40.0)	12 (40.0)	
30 or more	6 (40.0)	12 (40.0)	
Skin color*			0.304
White	10 (76.9)	15 (57.7)	
Non-white	3 (23.1)	11 (42.3)	
Schooling			0.236
8 years or less	14 (93.3)	23 (76.7)	
9 years or more	1 (6.7)	7 (23.3)	
Suicide risk score			0.026
Without	15 (100.0)	19 (63.3)	
Low	0 (0.0)	6 (20.0)	
Moderate/severe	0 (0.0)	5 (16.7)	
Total	15 (100.0)	30 (100.0)	

*Variable with missing.

Blood sample collection and processing

The collection of biological material to assess the redox assays was performed by venipuncture and stored at −80°C for further analysis of blood parameters (29).

Redox assays

Glutathione reduced

The GSH dosage was analyzed according to Browne and Armstrong (30). Samples (approximately 0.09 mg of protein) were treated with 2% metaphosphoric acid (1:1) and centrifuged at 7,000 *g* for 10 min. After deproteination, an aliquot of supernatant (30 μL) was then added to a medium containing 185 μL of 100 mM sodium phosphate buffer, pH 8.0, with 5 mM EDTA, and 15 μL o-phthaldialdehyde (1 mg/ml in methanol), and incubated for 15 min at room temperature in a dark room. The fluorescence was measured at 350 (excitation) and 420 (emission) nm. A calibration curve was prepared using a GSH standard solution (0.001–1 mM) and the results were expressed as nmol GSH/mg protein.

2′,7′-dichlorofluorescein assay

To assess reactive species levels, 2′,7′-dichlorofluorescein (DCFH-DA) was used as a probe (29). Sixty microliters of the diluted sample were incubated at 37°C in the dark for 30 min, with the addition of 240 μL of DCFH diacetate (DCFH-DA) in a 96-well plate. DCFH-DA was cleaved by cellular esterases and formed DCFH, a non-fluorescent compound that was oxidized by reactive species present in the sample, producing a fluorescent compound, DCF. Several one-electron-oxidizing species will oxidize DCFH to DCF including hydroxyl radicals ($^{\cdot}OH$), compounds I and II formed from peroxidase or heme interaction with H_2O_2, $^{\cdot}NO_2$ formed from the myeloperoxidase/H_2O_2/NO_2^- system, hypochlorous acid (HOCl), and reactive species formed from peroxynitrite ($ONOO^-$/ONOOH) decomposition (29). DCFH oxidation was fluorometrically measured using a 488 nm excitation and 525 nm emission wavelength. A standard curve, using standard DCF (0.25–10 mM), was performed in parallel with the samples, and the results were expressed as nmol/mg protein.

Superoxide dismutase activity

Superoxide dismutase (SOD) (EC 1.15.1.1) activity was assessed by quantifying the inhibition of the superoxide-dependent autoxidation of epinephrine and analyzing the absorbance of the samples at 480 nm. In microplate wells containing a sample (30 μL–60 μg of protein), 140 μL of glycine buffer (50 mM; pH 10.2) and 10 μL of catalase (EC 1.11.1.6) (10 μM) were added. In the standard wells, only 180 μL of glycine buffer (50 mM; pH 10.2) and 10 μL of catalase (10 μM) were added. The reaction was initiated by adding 10 μL of epinephrine (60 mM) in all wells. Zero time absorbance was taken at 480 nm, followed by recording the absorbance after 10 min at 32°C. SOD activity was defined as the amount of enzyme required to inhibit the oxidation of epinephrine by 50%. The data were calculated as units/mg protein (29).

Statistical analysis

After coding the instruments, double data entry was performed in the EpiData 3.1 program to test typing inconsistencies. The statistical package for the social sciences program was used for data analysis. To compare the nominal covariates (economic level and suicide risk) with the outcome glutathione levels, the Student's *t*-test or ANOVA was used. Spearman's correlation was performed for analysis between the quantitative covariates (age and education) and the outcome. To analyze the interaction between the factors, multiple linear regression was performed. Bonferroni analysis was used as an additional/secondary result to visualize differences in

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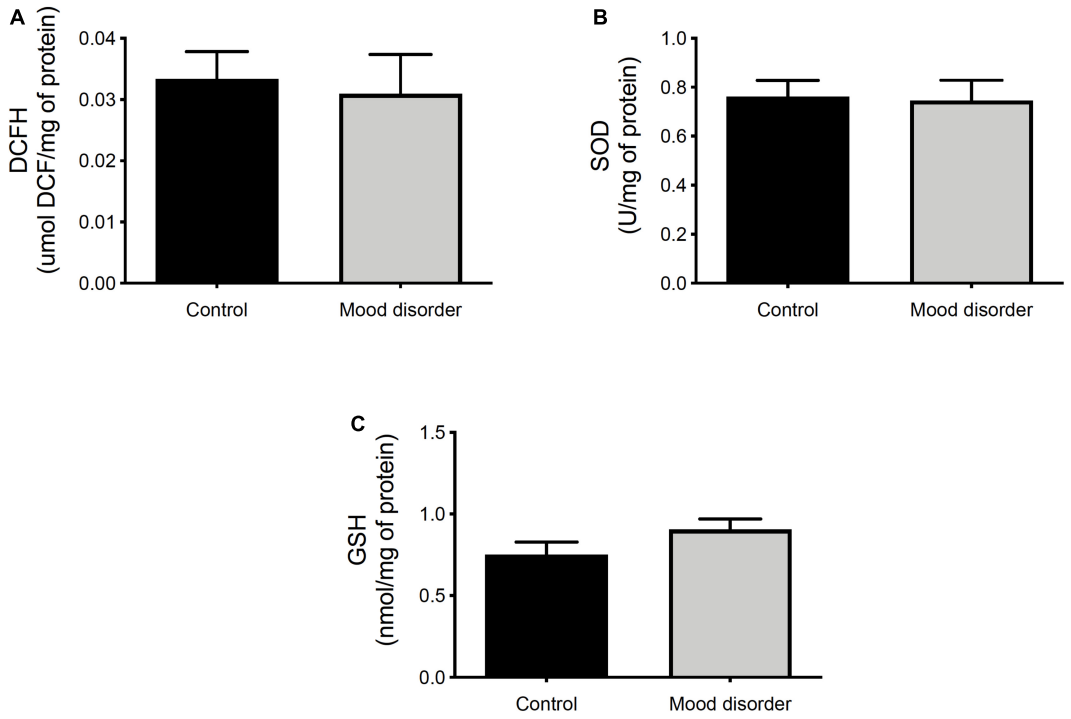

FIGURE 2
Oxidative stress analysis in plasma of women (control, N = 15 and mood disorder, N = 30) at 18 months postpartum. **(A)** DCFH is expressed as μmol/mg of protein; **(B)** superoxide dismutase (SOD) activity is expressed as U/mg of protein; and **(C)** GSH content is expressed as nmol/mg of protein. Statistical analysis was analyzed by t-test.

glutathione levels according to risk severity. After the adjusted analysis, p-values < 0.05 were considered statistically significant.

Results

The distribution of the sample is shown in Table 1. The prevalence of suicide risk in the mood disorder group is 36.7% (20% low risk and 16.7% moderate/severe risk). The suicide risk was associated with a mood disorder ($p < 0.05$). The raw analysis showed no significant difference in suicide risk according to age, skin color, and schooling ($p > 0.05$).

In Figure 2, we compare the redox status in the serum of women without (control) or with a mood disorder and did not observe any statistical difference in reactive species analyses (Figure 2A), SOD activity (Figure 2B), and glutathione reduced (Figure 2C).

Analyzing Table 1 of the total number of women participating in this study (n = 45), the mean age was 27.67 years (SD1 = 5.372; minimum = 17; maximum = 37), schooling had a mean of 11.58 complete years of schooling (SD = 3.876) and the predominant social class in our sample was C (71.1%; n = 32). The percentage of suicide risk observed in our sample of women at 18 months postpartum was 24.4% (n = 11) and of women without suicide risk was 75.6% (n = 34). Regarding the bivariate analysis, Table 2 also shows an association between GSH levels and the risk of suicide (p = 0.002).

Again, in Table 2, all independent variables were taken into multiple analyses by linear regression to adjust for the effect of suicide risk (primary exposure) on glutathione levels (outcome). After adjustment, only the presence of risk of suicide remained associated with the outcome (β = 0.173; p = 0.007).

According to the degree of suicide risk, 13.3% (n = 6) of the women had a low risk of suicide and 11.1% (n = 5) had a moderate to high risk. In Figure 3, as an additional analysis by Bonferroni, we verified the differences in glutathione levels according to the degree of suicide risk, observing a significant association between the differences in glutathione means in the group of women with moderate to high risk compared to the reference group (without risk of suicide).

Discussion

Unfortunately, the incidence of suicide is increasing and now represents the leading cause of mortality for people aged 15 to 44 years (3). Our sample was within this age group and this may explain the high prevalence of women at risk of suicide in this study. It is also worth mentioning that the selection of women for our study was carried out by convenience since the participants were part of another follow-up study, which affected the study's sample size, which may be these limitations for the interpretation of our results. However, the present work presents promising results from the translational point of view, where we confirm the hypothesis of the study demonstrating that women with suicide risk (moderate to high) present cerebral redox imbalance resulting in a decrease in blood GSH levels.

While the risk of death and suicide attempts is lower during and shortly after pregnancy than in the general female population, suicides account for up to 20% of all postpartum deaths and represent a leading cause of mortality in the peripartum period, which corroborates the high prevalence of suicide risk in our sample of

TABLE 2 Analysis of the serum level of glutathione according to age, education in years, social class (A/B, C, and D/E), and risk of suicide diagnosed by MINI-Plus (Yes/No) of women at 18 months postpartum.

Variables		Glutathione reduced					
		Bivariate analysis			Multivariate analysis		
	Average (± SD)	*R*		*p*-value	β	CI 95%	*p*-value
Age (years)	27.67 (5.37)	0.29	–	0.049	0.007	−0.003; 0.017	0.165
Education (in years of study)	11.58 (3.88)	−0.67	–	0.660	−0.003	−0.020; 0.014	0.747
	N (%)	Average	SD				
Social class				0.117	0.040	0.081; 0.161	0.510
A/B	08 (17.8)	−0.08	0.18	–	–	–	–
C	32 (71.1)	−0.14	0.19	–	–	–	–
D/E	05 (11.1)	0.04	0.08	–	–	–	–
Suicide risk				0.002*	0.173	0.050; 0.296	0.007*
No	34 (75.6)	−0.15	0.17	–	–	–	–
Yes	11 (24.4)	0.04	0.14	–	–	–	–

*Significance level 5%. SD, standard deviation; CI, confidence interval.

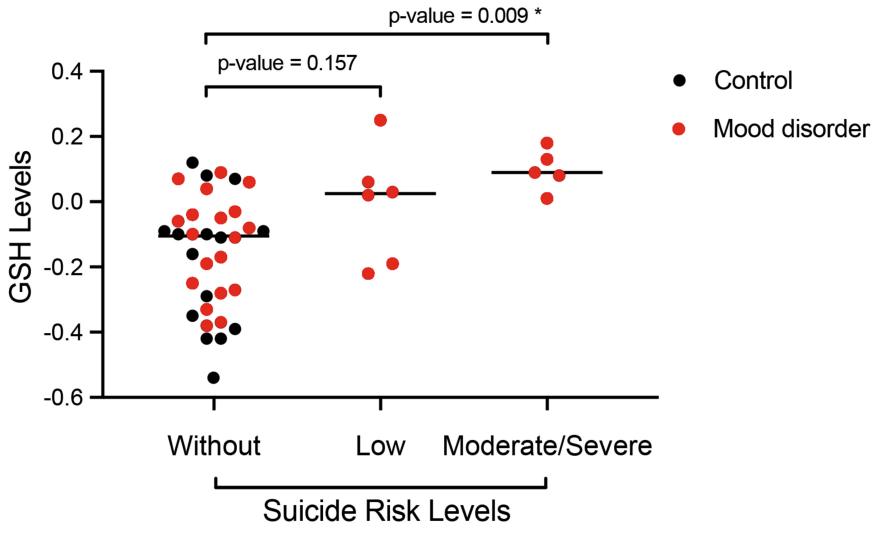

FIGURE 3
Post hoc analysis by Bonferroni of the serum glutathione reduced (GSH) level according to the degree of suicide risk classified by MINI-Plus module C (without, low, and moderate/severe risk) of women (control, *N* = 15 and mood disorder, *N* = 30) at 18 months postpartum. *$p < 0.05$ indicates a significant difference.

women (24). According to Hirst and Moutier (24), the transition to parenthood is a stressful event in life, and exposure to such events can trigger the first episodes of mania or potentially severe mixed states. Furthermore, the increased risk of suicide is related to stressors such as life events (25). The percentage of women in our sample at risk of suicide (24.4%) at 18 months postpartum was of concern from the point of view of women's health.

Under basal physiological conditions, there is a controlled balance between pro-oxidant molecules and antioxidant molecules, and an imbalance between these molecules is called oxidative stress (31). Glutathione is the brain's main antioxidant, and recent post-mortem and genetic data support its involvement in the pathophysiology of bipolar disorder (20, 32, 33). GSH is therefore a sensitive and reliable endogenous marker of oxidative stress. A post-mortem study showed lower levels of GSH in the prefrontal cortex of patients with MDD, bipolar disorder, and schizophrenia when compared to healthy controls (34). Our study found lower levels of GSH in women at risk of suicide. In line with our result, in 2017, Freed et al. (20) suggested that a lower GSH may be a potential marker of MDD early in the course of the disease. GSH levels in the occipital cortex were lower in adolescents with MDD compared to controls. It should also be noted that MDD in adolescents is associated with a high risk of suicide (32).

Other studies examining blood serum and plasma GSH concentrations have also identified significantly lower GSH in MDD patients compared with healthy patients (33, 35). In addition, lower brain levels of GSH were found in rodents with symptoms of depression (36, 37). More relevantly, using magnetic resonance imaging, Shungu et al. (38) measured and then compared occipital cortex (COC) GSH levels in unmedicated adults with MDD to healthy participants and found 21% lower GSH levels in MDD patients. Similarly, another recent 1H MRS study reported lower

in vivo levels of GSH in the COC of unmedicated adults with MDD versus healthy controls (39). When we evaluated the degree of suicide risk, we found that serum GSH levels were significantly lower for moderate to high suicide risk than for women without suicide risk, suggesting an association of glutathione with the degree of suicide risk. However, in contrast to our findings, for Freed et al. (20), glutathione levels did not correlate with MDD severity.

Oxidative damage and redox dysregulation appear to play important roles in the pathogenesis of psychiatric disorders due to the brain's vulnerability to the toxic effects of oxygen-free radicals (31). Regarding studies of potential treatments, N-acetylcysteine (NAC) is believed to exert therapeutic antioxidant effects as a substrate for glutathione synthesis. NAC readily crosses the blood-brain barrier providing a cysteine substrate for GSH synthesis in the brain, in addition to acting directly as a scavenger of ROS (40). Hans et al. (41) suggest that NAC may have potential use as an adjunct to fast-acting treatment in MDD. Although preliminary, our findings appear to imply reduced glutathione as a potential biomarker or etiologic factor among women at risk of suicide, with therapeutic implications. For example, NAC may be one such therapeutic strategy as it restores GSH and has been investigated as a therapeutic agent in adults with various neuropsychiatric disorders (40, 42). According to the results of a recent meta-analysis, NAC was moderately effective in relieving depression symptoms in adults with MDD, bipolar disorder, and other psychiatric conditions (43, 44). Furthermore, NAC directly evidenced antidepressant-like effects in rodent models of depression through its role as an antioxidant (45, 46).

Mechanisms of oxidative stress have been implicated in the pathogenesis of psychiatric disorders (31). This hypothesis has a theoretical appeal, as the brain is considered particularly vulnerable to oxidative damage for several reasons. These include its comparatively high utilization of oxygen and therefore generation of free radical byproducts, its modest antioxidant defenses, its lipid-rich constitution that provides substrates ready for oxidation, the reducing potential of certain neurotransmitters, and the presence of redox-catalytic metals, like iron and copper (47). This intrinsic oxidative vulnerability of the brain and growing evidence of neurodegenerative changes associated with many psychiatric syndromes suggests that oxidative damage may be a plausible pathogenic candidate. We can see that women with reduced GSH levels who demonstrate a risk of moderate/severe suicide were in the mood disorder group, despite knowing that psychiatric disorders alter the brain redox state (31), the effect observed in our study (GSH levels) is not only of these disorders but related to the risk of suicide (mainly outcome), since most women in the mood disorder group are at no risk for suicide and without changes in GSH levels.

Conclusion

Our work had some limitations, including the small sample size, the selection by the convenience of sample for the study, and the lack of follow-up of women's GSH levels at other time points (longitudinal study). However, the present study has contributed evidence in support of the role of oxidative stress in mood disorders and is the first study to our knowledge that examined GSH in women at risk for suicide. If replicated in a larger sample, the present finding of GSH deficit in women at risk of suicide may provide important information for the development of new paradigms of assessment, prevention, and treatment. As stated earlier, although preliminary, these findings seem to imply GSH as a potential biomarker or etiologic factor among women at moderate to high risk of suicide, and according to the literature, with therapeutic implications. For example, NAC, which restores GSH, has been investigated as a therapeutic agent in adults with various neuropsychiatric disorders. Since the mechanisms associated with the risk of suicide may differ in the episodes presented. Future studies evaluating glutathione with a larger sample size with statistical power to differentiate the association proposal by manic or depressive episodes, as well as the use of NAC as a suicide risk reducer, seem justified.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Comitê de Ética em Pesquisa da Universidade Católica de Pelotas. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Çiçek Hocaoğlu,
Recep Tayyip Erdoğan University, Türkiye

REVIEWED BY
Gözde Bacik Yaman,
Süleyman Demirel University, Türkiye
Xiangyang Xu,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
John A. Tsiouris
✉ john.tsiouris@opwdd.ny.gov

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Downregulation of cyclic adenosine monophosphate levels in leukocytes of hibernating captive black bears is similar to reported cyclic adenosine monophosphate findings in major depressive disorder

John A. Tsiouris[1,2]* and Michael Flory[3]

[1]George A. Jervis Clinic, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, United States, [2]Department of Psychiatry, State University of New York Downstate Medical Center, Brooklyn, NY, United States, [3]Research Design and Analysis Service, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, United States

Introduction: Cyclic adenosine monophosphate (cAMP) levels in the lymphoblasts and leukocytes of patients with major depressive disorder (MDD) have been reported to be downregulated compared to in controls. cAMP is a derivative of adenosine triphosphate (ATP), and low ATP turnover has been reported in the state of hypometabolism associated with human MDD and with mammalian hibernation due to suppression of mitochondrial metabolism. Similarities have been noted between many state-dependent neurobiological changes associated with MDD in humans and with mammalian hibernation.

Methods: To compare cAMP levels between human MDD and mammalian hibernation and to investigate whether cAMP downregulation is another state-dependent neurobiological finding, we measured cAMP concentrations in lysed leukocytes, plasma, and serum in serial blood specimens from nine female captive black bears (*Ursus americanus*; CBBs), and cortisol levels in serum from 10 CBBs.

Results: Cortisol levels were significantly higher during hibernation in CBBs, confirming previous findings in hibernating black bears and similar to findings in humans with MDD. cAMP levels were significantly lower during hibernation versus active states (pre-hibernation and exit from hibernation) and were similar to the cAMP downregulation reported in MDD patients versus euthymic patients or controls. cAMP level changes during the different states (hibernation, pre-hibernation, active) confirm their state-dependent status.

Discussion: These findings are similar to the neurobiological findings associated with the hypometabolism (metabolic depression) observed during mammalian hibernation and reported during MDD. A sudden increase in cAMP levels was observed before entrance into pre-hibernation and during exit from hibernation. Further investigation is suggested into the possible role of elevated cAMP levels in initiation of the chain reaction of changes in gene expression, proteins, and enzymes leading to the suppression

of mitochondrial metabolism and to low ATP turnover. This process leads to hypometabolism, the old adaptive mechanism that is used by organisms for energy preservation and is associated with both mammalian hibernation and human MDD.

KEYWORDS

cAMP downregulation, leukocytes, hypometabolism, mammalian hibernation, black bears, major depressive disorder

Introduction

The cyclic adenosine monophosphate (cAMP) signaling pathway is a second messenger, and because its regulation at the intracellular level is critical for the transduction of cellular response, the role of cAMP generation in bipolar disorder and especially major depressive disorder (MDD) has been studied extensively [see review, (1)]. Most of these studies, using different materials, specimens, and methods, reported a downregulation in the production of cAMP in patients with MDD versus normal controls and patients in a euthymic or a manic state (1).

Mean levels of cAMP in the plasma of patients with bipolar disorder were not different between the different phases of their illness or compared to controls (2). Beta adrenoreceptor–mediated cAMP formation, using histamine, prostaglandin E1, or isoproterenol, was not different in the lymphoblasts of depressed patients versus controls (3), and no difference was found either in the affinity or the density of beta receptors on lymphoblasts between patients with bipolar disorder and controls (3, 4). Studies of histamine-stimulated and beta adrenoreceptor–mediated cAMP formation in leukocytes from patients with MDD and controls reported lower cAMP levels (i.e., downregulation) in patients with MDD versus controls (5–7). When cAMP formation was measured in isoproterenol-stimulated lymphocytes and not in leukocytes, lower cAMP levels were found only in patients with MDD and psychomotor agitation, not in patients with psychomotor retardation (8, 9). Reduction in beta-adrenoreceptor–linked cAMP-dependent protein kinase (PKA) was reported in patients with MDD and melancholic features versus controls (10), suggesting low levels of cAMP.

The heterogeneity of the subjects and the differences in disease severity, in the specimens in which cAMP was measured (plasma, stimulated leukocytes/lymphocytes, and platelets), and in the methods used for determination of cAMP levels may have contributed to the different, and in certain studies, opposite, findings (1).

The theory of cAMP dysfunction as a cause of MDD and of depression in general was proposed (11) on the basis of findings of cAMP-signaling downregulation in MDD and its upregulation with chronic administration of antidepressants in one postmortem study in humans (12) and in studies in rodents (13). This theory was further supported by findings of decreased cAMP signaling in the brains of unmedicated depressed patients and increased cAMP signaling after treatment with a selective serotonin reuptake inhibitor using $_{11}$C-(R)-rolipram PET scan to image phosphodiesterase 4 (PDE4) (14). Neither of these studies nor any cAMP studies investigated whether the reported changes are state-dependent or not.

The mitochondrial dysfunction theory of MDD was proposed to explain the downregulation of cAMP and the hypometabolism observed during MDD (15, 16). However, recent studies have linked suppression of mitochondrial function, including low adenosine triphosphate (ATP) turnover, but not mitochondrial dysfunction, to MDD and have suggested the need for further investigation of mitochondrial changes during MDD (17–20).

A theory explaining the origin of the hypometabolism observed during MDD was proposed by the first author in 2005 (21), arguing that a *form* of metabolic depression, a primitive adaptive process for energy preservation that is homologous to the one responsible for mammalian hibernation—and not mitochondrial dysfunction—is the process underlying the observed hypometabolism, state-dependent neurobiological changes (22, 23), and vegetative symptoms of MDD in humans. Supporting evidence for this metabolic depression theory of MDD and for its link to the process of mammalian hibernation (21) is the finding that suppression of mitochondrial metabolism is the process responsible for mammalian hibernation (24, 25), including low ATP turnover (26, 27), as well as the similarities to the findings from mitochondrial studies in MDD (17–20).

The following state-dependent neurobiological changes that have been documented as being similar between MDD in humans and mammalian hibernation offer further support for the metabolic depression theory of MDD (21): reversible subclinical hypothyroidism (28, 29), increased serum cortisol concentration (30–32), acute phase protein response (33–38), low respiratory quotient (39–42), oxidative stress response (43–45), and decreased neurotransmitter levels (39, 46, 47). Black bears (*Ursus americanus*) were suggested and used as an animal model for MDD to study the process of hypometabolism during hibernation (21) because many of the similar neurobiological changes between MDD and mammalian hibernation had been observed in studies of bears, especially black bears, during hibernation (29, 32, 36, 37, 40, 45). The full rationale for using this model has been explained previously [(21); see pp. 830–831]. Black bears in the wild withdraw into dens in October, and by November 1st, most are in the state of hibernation proper without becoming hypothermic (32, 40, 41). Hypothermia, which is common in all other hibernating mammals, suppresses gene expression and the translation and transcriptional machinery of many proteins (48).

Mammalian hibernation is a state of metabolic stress, which leads to the dephosphorylation of ATP through the activation of adenylyl cyclase and the formation of cAMP, which is converted

to adenosine 5' nucleotidase (5' AMP) (1, 49). According to these findings (49), higher cAMP concentration would be expected in the lysed leukocytes of black bears before entrance into hibernation, the basic state of hypometabolism, when the process shifts from normal to the state of metabolic depression, and low cAMP levels are expected during hibernation proper. To compare our expected findings of cAMP level changes during mammalian hibernation with the reported findings during MDD in humans, to investigate the state-dependent status of cAMP levels, and to obtain additional supporting evidence for the metabolic depression theory of MDD (21), we measured the baseline changes of cAMP levels in serial blood samples obtained every 15 days during active, pre-hibernation, and hibernation states from nine female captive black bears (CBBs) kept in captivity from October to May 15. Serum cortisol levels also were measured from the serial samples obtained from these same CBBs plus one additional CBB. We report our findings here.

Materials and methods

Materials

The cyclic AMP (direct) colorimetric ELISA kit and the cortisol ELISA kit were obtained from Assay Designs Inc. (Ann Arbor, MI, United States). All other chemicals were of reagent grade.

Subjects

Serial blood samples were obtained every 15 days from 11 female CBBs 3 to 21 years of age (mean age 11, SD 6.67), six of which were pregnant. These CBBs were kept in captivity from October to April at the Center for Ursid Research at Virginia Polytechnic Institute and State University (VPI) in Blacksburg, VA, United States. One of these CBBs was captive from October 2002 to May 15, 2003; seven, from October 2003 to May 15, 2004; and three, from October 2004 to May 15, 2005. Ages of the CBBs from which specimens were obtained for analysis were 3–8 years (n = 3 for cAMP levels, and n = 4 for cortisol levels), 9–15 years (n = 4), and older than 15 years (n = 2). Although specimens were obtained from 11 CBBs from October 2002 to May 2005, only nine were included in the analyses for cAMP levels, and 10 for serum cortisol levels. One CBB, 2 years of age, was excluded from the cortisol and cAMP level analyses because it never fell into hibernation, and a second one was excluded from cAMP analyses because only one cAMP specimen was obtained. During the active state after captivity, in October, only a few cAMP specimens were received and thus were excluded from analysis. The serum cortisol specimens obtained in October also were excluded from analysis, because of the sudden increase in levels resulting from the stress of captivity.

Trapping and immobilization of animals

All of the CBBs were captured in the George Washington National Forest and Jefferson National Forest in western Virginia. They were trapped in either Aldrich leg-hold snares or culvert traps, and all were anesthetized with a 2:1 mixture of ketamine hydrochloride (Ketaset®, Fort Dodge Animal Health, Fort Dodge, IA, United States) and xylazine hydrochloride (Rompum®, Bayer Corporation, Shawnee Mission, KS, United States) (concentration 300 mg/mL) at a dose rate of 1 mL/45 kg body mass. Telazol® was not used. No CBBs were in a trap for more than 20 h, and most were in traps for less than 12 h. All CBBs were healthy when the blood samples were drawn. Protocols for handling wild black bears and CBBs were approved by the VPI Animal Care Committee and the Institutional Animal Care and Use Committee at the New York State Institute for Basic Research in Developmental Disabilities (IBR). For further details, see Tsiouris et al. (37) and Donahue et al. (50).

Captive black bears entered hibernation proper between late December and January 1—not by November 1, as in most black bears in the wild (32, 41)—because of food availability and the higher temperature of the quarters in which they were kept captive. Each CBB was fed a daily ration of 2,000 g of dry high-protein (23%) dog food until November 30. Rations were cut to 1,000 g on December 1, to 500 g on December 10, and to 250 g on December 20. Feeding was terminated on December 30 and not resumed until April 1. Pregnant CBBs gave birth to their cubs during the last week of January without exiting the hibernation state. CBBs exited the hibernation state and became active in late March through April 1st similarly to black bears in the wild.

States during captivity

Active State: After captivity; October 1–October 31.

Pre-hibernation State: November 1–December 18 (early December).

Proper Hibernation State: December 19 (late December)–March 18 (early March).

Exit from hibernation/Active State: March 19 (late March)–May 15.

Black bear blood and sera

The number of blood specimens obtained from the nine CBBs for cAMP levels was 58, and of serum specimens obtained from 10 CBBs for cortisol levels was 137. Sera were prepared on-site and stored frozen at VPI until shipped. Whole-blood samples were collected in heparinized tubes and immediately shipped overnight to IBR on ice packs. Because only one specimen was obtained from each of four CBBs at the end of April after exit from hibernation, they were not included in the analysis.

Harvesting of black bear leukocytes

Whole blood was centrifuged for 10 min @ 2,000 × g (4°C). The buffy coat was collected and washed once in tris-buffered saline (TBS). The cells were collected by centrifugation, and the pellets were suspended in TBS, aliquoted, and stored at −80°C until needed.

Assay of protein concentration

Protein concentrations were determined by the method of Lowry et al. (51) by using bovine serum albumin as standard.

cAMP levels in black bear leukocytes

Preparation of leukocytes

Blood was drawn from female CBBs in heparinized (green-top) tubes and shipped by overnight express from VPI to IBR. The tubes were centrifuged at 800 × g for 15 min at room temperature (RT). The plasma and buffy-coat were removed to clean tubes and were centrifuged at 2,000 × g for 15 min at RT. The plasma was removed, and the cells were washed with an isotonic tris-buffered saline (TBS; pH 8.0) and re-centrifuged. The washing was repeated once. The cells were re-suspended in TBS, quick-frozen on dry ice, and stored at −80°C.

Assay of adenosine 3′, 5′–cAMP

The concentration of cAMP in leukocytes was determined with direct cAMP colorimetric ELISA kit (Assay Designs, Inc., Ann Arbor, MI, United States), following the manufacturer's protocol. This kit is designed for use with cell culture and tissue and includes 0.1 M HCl, which is used to lyse the cells, stop endogenous PDE activity, and stabilize the released cAMP. The 0.1% Hcl-treated samples are then analyzed directly in a microtiter plate without extraction, drying, and reconstitution. Because the sample-to-sample yield of leukocytes was variable, aliquots of the cells were removed to measure the total protein concentration, after which the cAMP values were normalized to 100 μg of total protein.

Cortisol levels in black bear sera

The levels of cortisol in black bear sera were determined by using the cortisol ELISA kit (Assay Designs, Inc.) following the manufacturer's protocol.

Results

Assays of cAMP levels were performed on 137 serum samples, 58 plasma samples, and 58 samples of lysed leukocytes. Levels of cAMP from plasma samples and from lysed leukocytes were positively correlated (r = 0.49, $p = 0.0001$, $N = 57$), although samples from serum were negatively correlated with measurements of both plasma (r = −0.50, $p = 0.0002$, $N = 50$) and lysed leukocytes (r = −0.33, $p = 0.02$, $N = 51$). However, these correlations are in large part autocorrelations among repeated measures; correlations adjusted for autocorrelation are much lower (lysed leukocytes and plasma, rho = 0.07, $p = 0.62$; lysed leukocytes and serum, rho = −0.01, $p = 0.94$; plasma and serum, rho = −0.004, $p = 0.9815$) (52, 53). Measurements of cAMP levels in lysed leukocytes were used for analyses for both robustness of measurements and comparison with published research.

Before the analyses were performed, distributions of cAMP and cortisol measurements were tested for normality using

TABLE 1 Cortisol levels (ng/ml) by pregnancy status and age.

		State of hibernation											
		Active (Oct 1–Oct 31)			Pre-hibernation (Nov 1–Dec 18)			Hibernation (Dec 19–Mar 18)			Exit (Mar 19–May 15)			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Total		4	5.78	5.31	30	2.59	3.40	65	4.28	4.71	38	3.71	4.75	137	3.80	4.50
Pregnant?	No	1	8.82	–	8	0.90	0.65	19	1.75	1.96	7	0.55	0.43	35	1.51	2.01
	Yes	3	4.77	6.01	22	3.20	3.79	46	5.32	5.12	31	4.43	4.99	102	4.58	4.84
Age group (years)	3–8	2	6.46	7.42	14	1.97	3.07	25	4.02	5.78	18	2.95	4.38	59	3.29	4.85
	9–15	2	5.10	5.26	13	2.61	3.84	28	4.11	3.76	13	3.79	4.46	56	3.72	3.93
	>15	–	–	–	3	5.36	1.99	12	5.20	4.50	7	5.54	6.28	22	5.33	4.72

N, number of measurements; SD, standard deviation.

TABLE 2 Cyclic adenosine monophosphate (cAMP) levels (pmol/ml) by pregnancy status and age.

		State of hibernation											
		Active (Oct 1–Oct 31)			Pre-hibernation (Nov 1–Dec 18)			Hibernation (Dec 19–Mar 18)			Exit (Mar 19–May 15)			Total		
		N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Total		2	24.48	3.13	10	50.62	27.74	30	17.44	13.97	16	30.37	29.23	58	26.97	24.40
Pregnant?	No	1	26.70	–	6	37.29	13.49	11	20.17	8.27	6	43.94	33.61	24	30.66	20.63
	Yes	1	22.27	–	4	70.63	33.39	19	15.86	16.41	10	22.23	24.50	34	24.37	26.73
Age group (years)	3–8	–	–	–	2	28.38	13.13	11	15.60	11.85	7	21.74	15.34	20	19.03	13.26
	9–15	2	24.48	3.13	8	56.18	28.06	14	19.11	16.94	7	44.40	37.95	31	34.73	29.36
	>15	–	–	–	–	–	–	5	16.83	10.57	2	11.50	12.62	7	15.31	10.38

N, number of measurements; SD, standard deviation.

the Shapiro-Wilk W test. Measurements of both factors were found to be severely skewed to the right. A square-root transformation was applied to both variables, making them acceptably normal. Comparisons of groups were performed using generalized estimating equations (GEEs) (54, 55) to avoid the distortion of variance estimates arising from autocorrelation of each bear's multiple measurements. Robust estimates of variance were employed in all analyses. Analyses were performed using Stata version 16.1 (56).

Tables 1, 2 provide the number of measurements, their means, and the standard deviations for cortisol and cAMP levels by state of hibernation, overall, and divided by pregnancy status and age group.

Figures 1–3 show cortisol and cAMP levels throughout captivity, overall, and divided by pregnancy status and age group.

Cortisol levels were found to be very high in the sera of the CBBs after their captivity. The levels of cortisol decreased in the weeks after the start of captivity during the month of November, increased during hibernation, and decreased again after the exit from hibernation into the active state. The age and pregnancy status of the CBBs influenced the levels of cortisol, but not the direction of level changes, in the sera during the active and hibernation states. Cortisol levels were significantly higher during hibernation (mean 4.28, SD 4.71, $N = 65$) than during pre-hibernation and the exit state immediately following hibernation (mean 3.22, SD 4.22, $N = 68$, Wald chi2(1) = 9.88, $p = 0.0017$).

Cyclic adenosine monophosphate levels in the lysed leukocytes of CBBs were higher in the active state after captivity and before the entrance into pre-hibernation (November and early December) than during the hibernation state (late December–early March). Levels increased again moderately at the end of hibernation (late March) during exit from hibernation (active state). The age and pregnancy status of the CBBs influenced the levels of cAMP, but not the direction of level changes, in the lysed leukocytes during the different active and hibernation states. Levels of cAMP were significantly lower during hibernation (mean 17.44, SD 13.97, $N = 30$) than during pre-hibernation and the exit state immediately following hibernation (mean 38.16, SD 29.84, $N = 26$, Wald chi2(1) = 4.24, $p = 0.0395$).

Thus, the changes in the levels of cAMP in lysed leukocytes and of cortisol in serum were in opposite directions with entry into pre-hibernation: cAMP levels increased, and cortisol levels decreased. Both levels increased in late March during the exit from hibernation.

Discussion

Our findings of significantly increased cortisol levels in the serum of hibernating CBBs confirm similar previous findings (32, 57) and are similar to the increased cortisol levels reported in the severe type of MDD in humans (30, 31).

The high levels of cortisol measured in the serum of the CBBs immediately after their captivity are due to the glucocorticoid stress responses to the capture of wild, free-living mammals (58) and have similarities to the stress response in humans (59).

Our findings of significantly lower cAMP levels in CBBs during hibernation versus their active state are similar to the findings

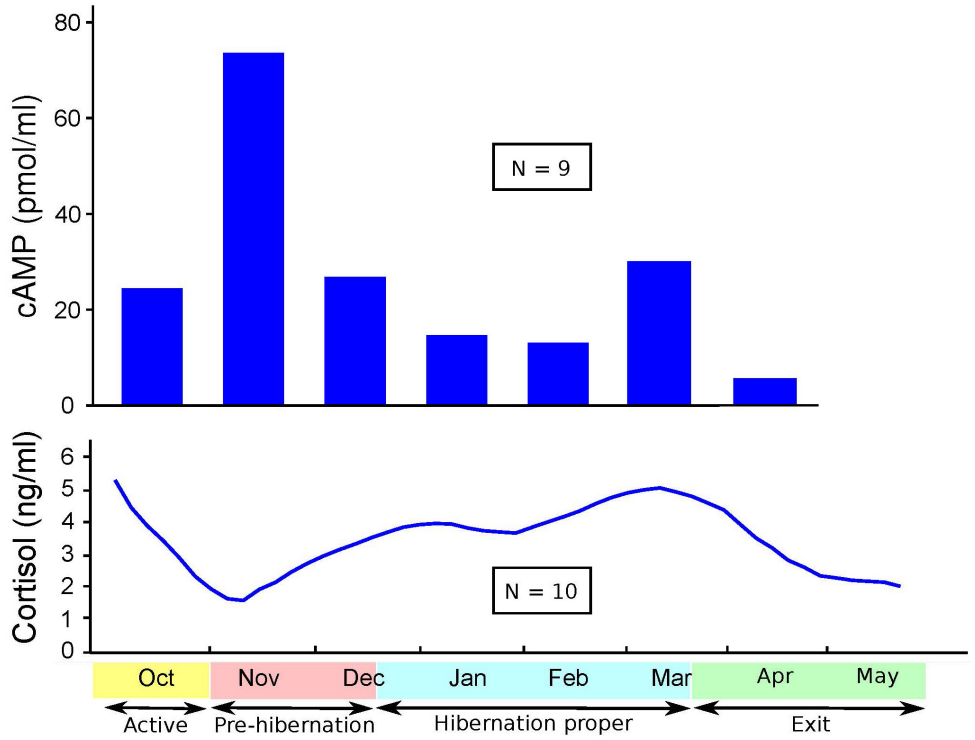

FIGURE 1
Levels of cyclic adenosine monophosphate (cAMP) and cortisol over time.

of lower cAMP levels in humans with MDD versus in controls (5–7, 10) and in humans with MDD with psychomotor agitation (8). The lack of differences reported in the cAMP levels in the plasma of patients in different states (depressed, manic, euthymic) and matched controls (2) could be explained by our findings of a very weak correlation between the cAMP levels in leukocytes and plasma in CBBs. These findings suggest that plasma is not a good medium for documenting changes in cAMP levels in different states. cAMP levels in the serum of CBBs were negatively correlated with both plasma and leukocyte cAMP levels. Also, our findings were opposite to the lack of differences observed in cAMP production between patients diagnosed with schizophrenia or MDD versus drug-free normal controls (60). The increase in cAMP levels during the entrance into pre-hibernation, especially in pregnant and 5–15 years-old CBBs, and the decrease in cAMP levels in the following weeks are a new finding, which must be replicated in male and female black bears in the wild and in captivity, and in humans when entering into severe MDD, especially with melancholic/catatonic features.

The age and pregnancy status of CBBs influenced the degree of changes in both cortisol and cAMP levels but not the direction of the changes. Similar variability in the findings has been reported in cAMP levels in human MDD (1).

Metabolic stress triggers the dephosphorylation of ATP and the formation of cAMP (49). Whether the increase in cAMP levels in CBBs in the month of November is associated with low levels of ATP due to dephosphorylation and formation of cAMP in mammalian hibernation (27, 58, 59) and possibly in MDD (17–20) must be investigated.

Low cAMP levels, which decrease activation of PKA, and lower ATP turnover are both associated with reduced energy production, which leads to hypometabolism (metabolic depression), the process underlying mammalian hibernation (24, 26, 27, 61, 62). There are no published studies measuring cAMP level changes during active or hibernation states in bears or other large mammals that hibernate without becoming hypothermic (40) against which our findings can be compared. Research will be required to confirm our findings and their similarities with the findings in MDD.

Research also will be required to determine whether the drop in cAMP level after its increase with the initiation of pre-hibernation in CBBs and with the possible initiation of hibernation in black bears in the wild is associated with the increased production of 5' AMP through the enzymatic hydrolysis of cAMP carried out by PDE4. PDE4 cleaves the 3;5' PDE bond in cAMP, thus inhibiting the phosphorylating activity of PKA (49).

5' AMP levels have been found to be elevated in mice during dark/dark periods, and injection of 5' AMP in light/dark periods in non-hibernating mice produced torpor-like changes (63). 5' AMP has been reported to be one of the triggers (circadian signals) for the initiation of the hypometabolic state and the molecular process involved in 5' AMP-induced hypometabolism, but this process occurs at the metabolic interconversion level rather than at the gene or protein expression level, as it has been observed that widespread suppression of energy-generating metabolic pathways occurs during this process (64).

Hypometabolism is the result of reduced energy production (19), which occurs secondary to decreased ATP turnover respiration in depressed patients versus controls (18), and to decreased brain levels of ATP and differentially expressed proteins

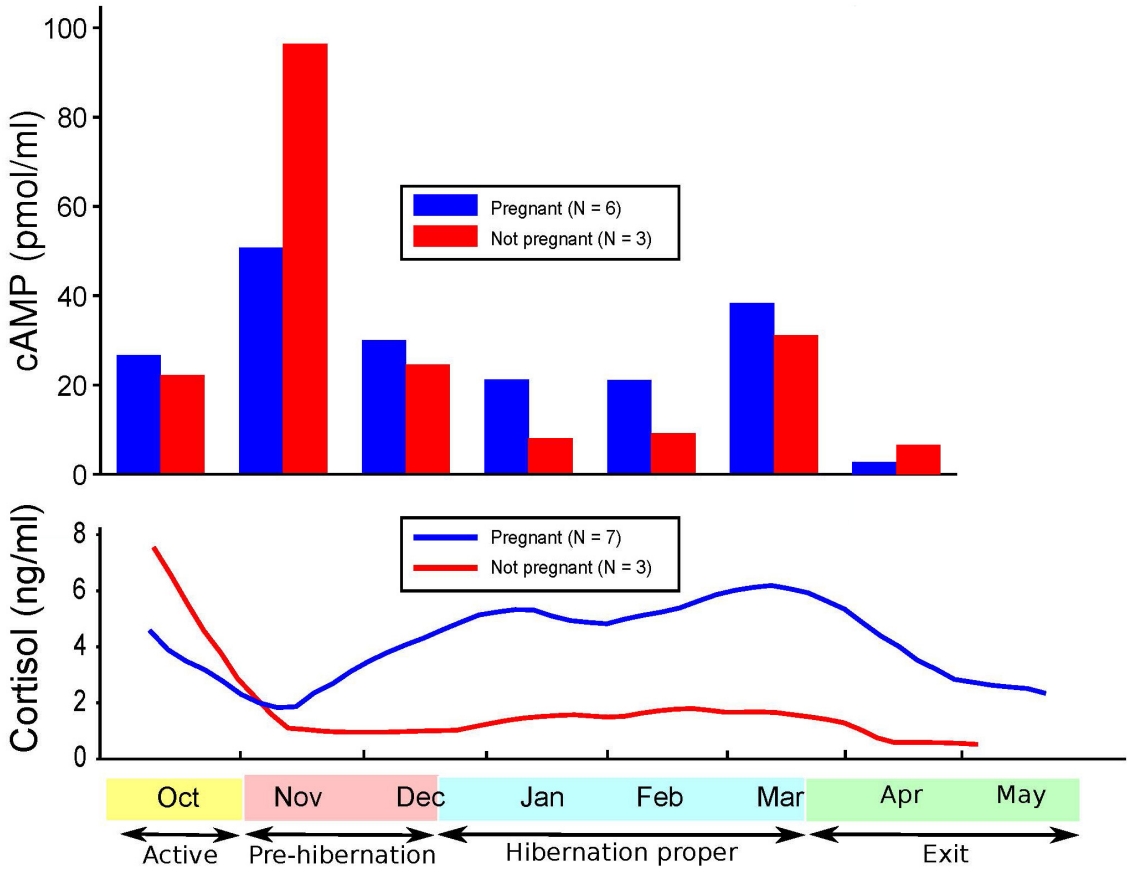

FIGURE 2
Levels of cyclic adenosine monophosphate (cAMP) and cortisol over time and pregnancy status.

in depressed patients, which are mainly related to deregulation (downregulation) or energy metabolism pathways (17).

The major characteristics of MDD in humans, as per the DSM-5 (65), are lack of energy, fatigue, lack of interest, lack of motivation, avoidance of interaction, weight loss, insomnia, and psychomotor retardation, all of which are secondary to hypometabolism and are associated with low ATP turnover (18, 19). This condition, according to Engel and Schmale (66), was called "conservation withdrawal." It appears that if untreated, some patients with MDD develop melancholic or catatonic features (the prototype of metabolic depression in MDD) or a constant state of agitation possibly dependent on their temperament (genetics), personality features, and environmental stressors. The symptoms of diminished ability to think are secondary to lack of energy, and the depressed mood, feelings of worthlessness, hopelessness, or excessive guilt appear to be secondary to the negative reevaluation of self, rumination of past actions perceived as negative due to the lack of energy and strength and to weakness, for which patients blame themselves, as often, no medical explanation for their condition is possible. The symptoms of suicidal phenomena (suicidal ideation, suicide threats/attempts, and suicide death) have been considered to be plans and actions of the person asking for help, trying to escape from or terminating the unbearable condition created by the core symptoms associated with hypometabolism. The findings of cAMP level changes in response to treatment of humans with MDD with antidepressants (12–14) and of changes in the levels of cAMP in different states (pre-hibernation, hibernation, and active) in CBBs suggest the state-dependent quality of cAMP, as was reported previously (5), and are similar to the other neurobiological changes associated with MDD in humans and with hibernation in mammals investigated to date (21). The decreased cAMP levels in CBBs during hibernation and in patients with MDD suggest similarities in the cAMP levels in the two conditions and can be added to the observations of many neurobiological changes that are similar in the two conditions (21). These findings do not support the theory of cAMP dysfunction in MDD in humans that has been proposed by Fujita et al. (11, 14).

Our study has the following limitations: the small total number of CBBs from which specimens were obtained, although the adequate number of serial specimens obtained compensated for this; the sample comprising entirely female CBBs, two-thirds of which were pregnant; the captivity status; the few specimens obtained for determination of cAMP levels during the active state after the CBBs' exit from hibernation; and that cAMP levels were analyzed for lysed leukocytes during hibernation and the states before it and after exit from it in CBBs, which was different from the methods used to determine cAMP levels in lymphoblasts, lymphocytes, and leukocytes in only one specimen obtained from patients with MDD versus euthymic patients or controls. However, the longitudinal nature of the data collected and the analysis and comparison of both cAMP and cortisol levels in this study are unusual if not unique, offering insight

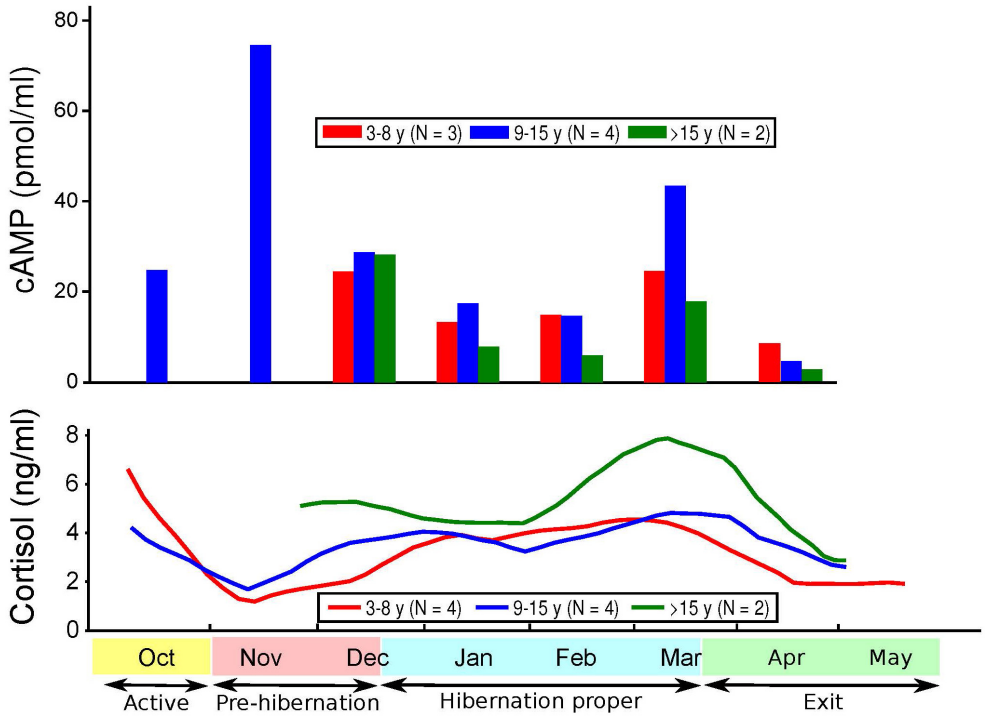

FIGURE 3
Levels of cyclic adenosine monophosphate (cAMP) and cortisol over time and age of subjects.

into both the entry into, and the emergence from, a state resembling, in some ways, MDD in humans. Also, this is the first study to document cAMP level changes in the leukocytes of black bears during active and hibernation states, revealing their similarities with the cAMP level changes reported in patients with MDD versus controls, and confirming the state-dependent changes of cAMP.

In conclusion, this study is the first to document changes in cAMP levels during mammalian hibernation and has established that the downregulation of cAMP levels is similar during hibernation of female CBBs and in patients with MDD; that there is a significant increase in cAMP levels with the entrance to the pre-hibernation state during captivity in the month of November, which corresponds to the month of entrance into hibernation proper of black bears in the wild, whereas the levels of serum cortisol are low (opposite direction); and that there is a mild increase in cAMP levels during the exit from hibernation (late March), whereas the serum cortisol levels are high, as they have been during hibernation proper. Finally, this study strongly suggests that the changes in cAMP levels in CBBs are state-dependent, as are most of the similar neurobiological findings associated with MDD in humans and mammalian hibernation. These findings dispute the theory of cAMP dysfunction as a cause of MDD, as was recently suggested (11, 14).

In-depth studies of the biological process of mammalian hibernation are under way (24, 25, 64, 67). Research on the cause of hypometabolism in MDD in humans has recently questioned the mitochondrial dysfunction theory of MDD and has suggested instead that suppression of mitochondrial function, which leads to the low ATP turnover observed in MDD, is the cause of hypometabolism in MDD (17–20). The findings of downregulation of cAMP levels during hibernation in female CBBs must be replicated in lysed leukocytes and other cells obtained through serial specimens from black bears (male and female) and from other hibernating mammals in the wild and in captivity, and from patients with recurrent MDD in different states of severity and in euthymic states. Confirmation of our findings, together with the previous findings of low ATP turnover in MDD (17–20), would offer more supportive evidence of the theory that a *form* of metabolic depression that is homologous to the one responsible for mammalian hibernation is the underlying adaptive process responsible for MDD in humans (21).

In spite of vigorous research, a full understanding of the etiology and neurobiology of MDD has been elusive to date (68), and no explanatory theory exists for most of the abnormal findings that have been proven to date to be state-dependent. The similarities in the findings of research regarding suppression of mitochondrial metabolism and neurobiological changes between human MDD and mammalian hibernation call for a paradigm shift in MDD research.

This new paradigm must seriously consider that the core symptoms of MDD are secondary to hypometabolism, a *form* of metabolic depression (21) homologous to one that is responsible for mammalian hibernation and also for torpor and estivation in many organisms (27, 64, 69, 70). It is hoped that this paradigm will inspire new basic research into the process of entering into and exiting from the state of hypometabolism in both MDD and mammalian hibernation and an extensive collaboration between researchers involved in the study of hypometabolism

in these conditions. Understanding and viewing MDD as an old adaptive process that is activated in about 20% of humans under different adverse conditions (71) could open many new pathways for research into the etiology and neurobiology of MDD. We propose again [as previously (21)] that the process responsible for the documented hypometabolism in mammalian hibernation—suppression of mitochondrial function—is partially or fully activated in 20% of humans in their lifetime (71), leading to MDD, especially in humans exposed to environmental stressors (72, 73) and predisposed to MDD by behavior inhibition by temperament (74), anxiety disorders (75), and early life traumatic experience (76).

If future research fully confirms the theory that a form of hypometabolism that is homologous to the one responsible for mammalian hibernation is the underlying old adaptive process responsible for human MDD, the stigma associated with MDD could be reduced, and our diagnostic and treatment strategies for MDD could be improved.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, United States, and the Animal Care Committee, Virginia Polytechnic Institute, Blacksburg, VA, United States.

Author contributions

JAT conceived and designed the study, obtained the blood and serum specimens, oversaw the execution of the study, and wrote and revised the first draft of the manuscript. MF analyzed the data and wrote the results section. Both authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Çiçek Hocaoğlu,
Recep Tayyip Erdoğan University, Türkiye

REVIEWED BY
Karl Friston,
University College London, United Kingdom
Ganesh Chand,
Washington University in St. Louis,
United States
Indranath Chatterjee,
Tongmyong University, Republic of Korea

*CORRESPONDENCE
Matthew Dobbertin
✉ matthew.dobbertin@boystown.org

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Neuroimaging alterations of the suicidal brain and its relevance to practice: an updated review of MRI studies

Matthew Dobbertin[1,2]*, Karina S. Blair[3], Erin Carollo[4], James R. Blair[5], Ahria Dominguez[1] and Sahil Bajaj[1]

[1]Multimodal Clinical Neuroimaging Laboratory (MCNL), Center for Neurobehavioral Research, Boys Town National Research Hospital, Boys Town, NE, United States, [2]Child and Adolescent Psychiatric Inpatient Center, Boys Town National Research Hospital, Boys Town, NE, United States, [3]Program for Trauma and Anxiety in Children (PTAC), Center for Neurobehavioral Research, Boys Town National Research Hospital, Boys Town, NE, United States, [4]Stritch School of Medicine, Loyola University Chicago, Chicago, IL, United States, [5]Child and Adolescent Mental Health Centre, Mental Health Services, Copenhagen, Denmark

Suicide is a leading cause of death in the United States. Historically, scientific inquiry has focused on psychological theory. However, more recent studies have started to shed light on complex biosignatures using MRI techniques, including task-based and resting-state functional MRI, brain morphometry, and diffusion tensor imaging. Here, we review recent research across these modalities, with a focus on participants with depression and Suicidal Thoughts and Behavior (STB). A PubMed search identified 149 articles specific to our population of study, and this was further refined to rule out more diffuse pathologies such as psychotic disorders and organic brain injury and illness. This left 69 articles which are reviewed in the current study. The collated articles reviewed point to a complex impairment showing atypical functional activation in areas associated with perception of reward, social/affective stimuli, top-down control, and reward-based learning. This is broadly supported by the atypical morphometric and diffusion-weighted alterations and, most significantly, in the network-based resting-state functional connectivity data that extrapolates network functions from well validated psychological paradigms using functional MRI analysis. We see an emerging picture of cognitive dysfunction evident in task-based and resting state fMRI and network neuroscience studies, likely preceded by structural changes best demonstrated in morphometric and diffusion-weighted studies. We propose a clinically-oriented chronology of the diathesis-stress model of suicide and link other areas of research that may be useful to the practicing clinician, while helping to advance the translational study of the neurobiology of suicide.

KEYWORDS

suicidal thoughts and behavior, depression, review, clinical relevance, task-based fMRI, resting state fMRI, brain morphometry, diffusion tensor imaging

1. Introduction

The World Health Organization (WHO) reports that suicide is the second leading cause of death among individuals aged 15–29 years (1) with an estimate of approximately 800,000 people dying from suicide each year - a global mortality rate of one person every 40 s. In the United States, the Center for Disease Control and Prevention (CDC) reports Suicide is the

12th leading cause of death for both Hispanic and non-Hispanic people of all races (2). In 2020, suicide was the second leading cause of death for children (age 10–14 years, accounting for 581 deaths) and third leading cause of death for young individuals (age 15–24 years, accounting for 6,062 deaths) (3). Suicide research has been very important in developing clinical suicide risk assessments (4). However, recent neuroimaging work with suicidal patients holds significant promise for the clinician to directly access information without it being filtered through the situation, suspicion or in fact impaired processes a suicidal individual may use to disclose the risk assessment information. This has been accelerated by parallel theories in neurobiology and cognitive neuroscience (5–7) and a clinical focus from the likes of McGirr (8) and Turecki (9). Recent reviews (10, 11) have also contributed to bridging this translational gap. In spite of this, there still is not a clinically-accessible link between witnessed patient histories, symptoms, and deficits and what is rapidly being discovered in the fields of functional, network, and morphometric neurobiology.

Multiple general theories have been developed in an attempt to understand the risk factors, thoughts, distortions, cognitive/behavioral differences, atypical brain structures, systems and functions that distinguish suicidal individuals from those without past attempts, or a high risk. As clearly laid out in Van Heeringen's book "the Neuroscience of Suicidal Behavior," (6) five main neurobiological theories precede the recent work of Schmaal, Auerbach, and others. These include the "Cry of Pain" model (12), the Interpersonal model (7), the Integrated Motivational model (13), the Clinical Stress-Diathesis model (8, 14), and Jollant's Neurocognitive model (5). The most relevant to this paper is Van Heeringen's Neurobiological model (6). This model synthesizes Molecular, Morphological, Cognitive, and Functional evidence into a theory based on predictive coding, also known as computational psychology. This model suggests that the main difference between suicidal individuals and those that are not suicidal, have an impaired system of evaluating old beliefs, evaluating the importance and certainty (precision) of new information, and appropriately changing current beliefs and strategies accordingly. Author states that learning is directly affected, proposing that humans are generally biased toward positive valenced stimuli and predictions. However, those with abnormal serotonin systems, which play a role in learning and extinction of behaviors that lead to aversive events, may be biased toward learning more negatively valenced behaviors (called Pavlovian instrumental transfer). Author further proposes that belief updating (modifying old beliefs based on new sensory information) is dependent on the right inferior frontal gyrus (IFG) and bilateral superior frontal gyrus (SFG) for positive valenced information, and on the left IFG and right inferior parietal lobule (IPL) for negative information. Lastly, as with disrupted serotonin and NMDA systems, blunted cortisol reactivity to stress creates a founding diathesis and may account for the higher rates of suicidality amongst individuals with trauma and adverse childhood events.

Our goal is to consider the current body of neuroimaging research on STBs (defined here as suicidal ideation and attempts) among those with Major Depressive Disorder (MDD) (15). Our goal is to clarify relevant concepts for the clinicians working with these patients and to propose the framework of a testable timeline of the suicidal brain in this population that may be developed into a clinical tool.

2. Methods

A search on functional, structural, and diffusion-weighted MRI studies of the suicidal brain was performed in the search engine 'PubMed' for both original and review research articles that were published before December 2021. The literature search was conducted using the following terms in the title:

((BOLD[Title]) OR (fMRI[Title]) OR (functional MRI[Title]) OR (functional magnetic resonance imaging[Title]) OR (morphometry[Title]) OR (thickness[Title]) OR (surface area[Title]) OR (volume[Title]) OR (gyrification[Title]) OR (folding[Title]) OR (MRI[Title]) OR (DTI[Title]) OR (magnetic resonance imaging[Title]) OR (diffusion tensor imaging[Title]) OR (brain connectivity[Title]) OR (connectivity[Title]) OR (brain activation[Title]) OR (neural activation[Title]) OR (neuroimaging[Title]) OR (spectroscopy[Title]) OR (white-matter[Title]) OR (gray-matter[Title]) OR (neural correlates[Title]) OR (neural representations[Title])) AND ((suicide[Title]) OR (suicidal[Title]) OR (suicidality[Title]) OR (suicide risk[Title]) OR (self-harm[Title]) OR (suicidal ideation[Title])) NOT ((Inflammation[Title]) OR (Inflammatory[Title]) OR (Plasma[Title]) OR (Tumor[Title]) OR (Immunity[Title]) OR (habenula[Title]) OR (mRNA[Title]) OR (RNA[Title]) OR (DNA[Title]) OR (Gene[Title]) OR (Genetics[Title]) OR (Glucose[Title]) OR (Brain expression[Title]) OR (Pain[Title])). The search was performed without a time limit. This resulted in a total of 149 articles. The articles were further filtered through an inspection of the abstracts. A total of 80 articles that included studies focusing on patients with clinical conditions other than MDD, studies focusing on non-suicidal self-injury, and studies relating to neuroimaging modalities other than MRI (i.e., MEG, PET) were excluded.

3. Results

A total of 69 research articles, focusing on STBs associated with depression, were identified, and reviewed in the current study (Tables 1–4).

3.1. Functional MRI (fMRI)

3.1.1. Task-based fMRI

The task-based fMRI research in STBs depends on the ability of a participant to complete a task in real time, and thus, may be a more proximally clinically important difference amongst patients. Task-based fMRI studies of the suicidal brain have focused on six primary tasks according to Dr. Van Heeringen: (1) Decision Making/Reward-Based Learning; (2) Emotional Pain and Affect Regulation; (3) Sensitivity to Social Stressors; (4) Cognitive Control/Response Inhibition; (5) Hopelessness; and (6) Impulsivity and Aggression. Unfortunately, within these 6 domains, only the first 4 have functional neuroimaging data consistent with our focused limitations.

3.1.1.1. Decision making/reward-based learning

Examining the fMRI activation differences during a learning task which requires participants to maximize rewards earned through a sequence of lever pulls (the Three-Armed Bandit Task), Brown et al. found that while non-suicidal participants showed decreased

TABLE 1 Task-based fMRI (TBfMRI) studies.

Author	Mode	Task	Findings	Population
Brown et al. (2020)	TBfMRI	Decision Making	↓ BOLD in vmPFC activity in SUIATT and impulsivity not correlated to vmPFC-FP connectivity ➔ compared to HC	Adults with and without STB (past attempts, ideation only) vs. HC
Li et al. (2020)	TBfMRI	Iowa Gambling Task (IGT), Tower of London Task, Go/No-Go task, Faces and Shapes fMRI task, and Emotion-Processing Task	↓ BOLD in fusiform gyrus but ↑ in left insula activation in SUIATT	Adolescent and adult MDD + SUIATT vs. MDD alone
Olié et al. (2017)	TBfMRI	Cyberball Game/Task	↓ BOLD in left insula and SMG in SUIATT vs. both controls	36 Women with MDD + STB vs. 41 with history of MDD vs. 28 HCs
Cáceda et al. (2020)	TBfMRI	Cyberball Game/Task	No group differences in activation, but with social exclusion: 1. Suicide risk correlated with BOLD in superior insula 2. Depression severity and psychological pain correlated with BOLD in superior insula 3. BOLD in dACC correlated with physical pain severity	Adults with MDD and SUIATT vs. MDD + SI vs. MDD vs. HCs
Miller et al. (2018)	TBfMRI	Facial Affective Task requiring regulation of response before stimuli presentation	↑ BOLD in dlPFC among SUI vs. HCs	Adolescents with SI vs. HCs
Davis et al. (2014)	TBfMRI	Emotion Regulation-Reappraisal	↑ BOLD in amygdala vs. controls	Adults with STB (no distinction) vs. Adults with Depression and Anxiety without STB vs. HCs
Jollant et al. (2008)	TBfMRI – Passive Task	Visual Affective Valence Task	↑ BOLD in lateral OFC and ↓ BOLD in SFG during angry stimuli, ↑ BOLD ACC to happy stimuli, and ↑ BOLD in cerebellum to mild angry stimuli in the MDD + STB group	Adult men with MDD + STB vs. MDD vs. HCs
Richard-Devantoy et al. (2016)	TBfMRI	Go/No-Go Response Inhibition	No difference between SUIATT and controls; No association between SUIATT and BOLD	Adults with MDD + SUIATT vs. MDD vs. HCs
Pan et al. (2013)	TBfMRI	Emotionally Valenced Gender Discrimination Task	SUIATT ↑ BOLD in right ACC, bilateral primary sensory cortex, left dlPFC, and right MTG during angry faces; SUIATT ↓ BOLD in left fusiform gyrus during neutral faces compared to MDD. ↑ BOLD in primary sensory cortex during angry compared to HCs	Adolescents with SUIATT + MDD vs. MDD vs. HCs
Ai et al. (2018)	TBfMRI	Emotionally Valenced Gender Discrimination Task	SUIATT ↓ BOLD in fusiform gyrus across all emotional valences vs. controls	Adults with SUIATT + MDD vs. SI + MDD vs. MDD
Alarcón et al. (2019)	TBfMRI/FC	Emotional Self-Face Recognition Task	↑ FC between amygdala and dlPFC, dmPFC, and precuneus in SUIATT + MDD vs. HCs	Adolescents with SUIATT + MDD vs. high SI + MDD vs. low SI + MDD vs. HCs
Malhi et al. (2019)	TBfMRI/FC	Emotional Face-Word Stroop Task	↑ BOLD in PFC, frontopolar cortex, ACC, and posterior parietal cortex; and ↑ activity among basal ganglia structures with increasing suicide risk	Adults with STB (both SI and SUIATT) + Mood Disorder vs. HCs
Just et al. (2017)	TBfMRI Machine Learning	Neurosemantic (Presentation of words associated with life and death)	Areas found to be significantly associated with suicidal ideation = medial superior frontal, inferior parietal, medial temporal, anterior cingulate, and inferior frontal cortices	SUI vs. HCs

impulsivity with increasing connectivity between the ventromedial prefrontal cortex (vmPFC) and parietal cortex, suicidal participants had *increasing* impulsivity with increased connectivity between these regions (16).

Suicide attempts have been found to be associated with greater activation in the right lateral orbitofrontal cortex (OFC) and decreased activation in the right superior frontal gyrus (SFG) while performing decision-making tasks in response to prototypical angry versus neutral faces (17).

In a recent meta-analyses that included work on decision making/reward-based learning, Li et al. concluded that brain activation in suicide attempters increased in the left insula but decreased in the

TABLE 2 Resting-state fMRI studies.

Author	Mode	Findings	System interactions	Population
Qiu et al. (2020)	RSFC	↑ SI = ↓ RSFC between pregenual ACC and SFG	↑ SI = ↓ between**M-CIN/SN** and**M-FPN/DMN**	Adults with MDD + SUIATT vs. MDD
Du et al. (2017)	RSFC	↓ RSFC between ACC (**M-CIN/SIN**) and orbito-medial PFC (**M-FPN/DMN**) in MDD + SI	↓ RSFC between**M-CIN/SN** and**M-FPN/DMN**	Adults with MDD + SI vs. MDD vs. HCs
Yang et al. (2020)	RSFC/ Morphometric	↓ RSFC in right inferior Orbitofrontal gyrus; ↓ GMV in right IFOG and left caudate	↓RSFC between**M-FPN/DMN** and**M-CIN/SN**	Adults with MDD + SUIATT vs. MDD
Stange et al. (2019)	RSFC	↓ RSFC in rMFG/SFG and**M-FPN/DMN;** ↓ RSFC between precuneus and**M-CIN/SN**	↓ RSFC between**L-FPN** and**M-CIN/SN**, ↓ RSFC between**L-FPN/CCN** and**M-FPN/DMN**	Adults with Mood Disorders + SUIATT vs. Mood Disorders vs. HCs
Cao et al. (2016)	RSFC/Low Frequency Resting Activation	↑ fALFF in right STG, left MTG, and left MOG	*N/A	Adolescents and young adults with MDD + SUIATT vs. MDD vs. HCs
Cao et al. (2021)	RSFC	↓ RSFC between left MFG and left SPG	↓ RSFC between**L-FPN/CCN** and left**D-FPN/AN**	Young adults with MDD + SUIATT vs. MDD vs. HC
Zhang et al. (2020)	RSFC	↑ RSFC between bilateral amygdala and bilateral paracentral lobule/precuneus in SUIATT and SI vs. HCs	↑ RSFC between**M-FPN/DMN** and**M-CIN/SIN** in STB groups vs. HCs	Adolescents and young adults with Mood Disorders + SUIATT vs. Mood Disorders + SI vs. Mood Disorders vs. HCs
Kang et al. (2017)	RSFC	↑ RSFC from left amygdala to the right insula and left superior OFC and increased FC of the right amygdala with the left middle temporal area	↑ RSFC between**M-CIN/SN** to**M-CIN/SN** and**M-FPN/DMN**	Adults with MDD + SUIATT vs. MDD
Wei et al. (2018)	RSFC	↑ RSFC amygdala to precuneus/cuneus compared to non-suicidal and HCs	↑ RSFC between**M-CIN/SN** to**M-FPN/DMN**	Adults with MDD + SI vs. MDD vs. HCs
Cao et al. (2020)	RSFC	↓ RSFC between (superior frontal gyrus and medial frontal gyrus) and (bilateral anterior insular and anterior cingulate cortices, and the temporal–parietal junction area); ↑ RSFC between (bilateral anterior insular and anterior cingulate cortices and the temporal–parietal junction area) and (precuneus, inferior parietal lobule, middle frontal gyrus, and superior parietal lobule)	↓ RSFC between**M-FPN/DMN** and**L-FPN/CCN**, ↑ RSFC between**L-FPN/CCN → M-CIN/SN**	Adolescents and young adults with MDD + SUIATT vs. MDD vs. HCs
Shu et al. (2020)	RSfALFF	↑ fALFF in posterior cerebellum, right ACC, left caudate and left SFC; ↑ fALFF in left middle occipital cortex and left precuneus after treatment vs. HCs	↑ fALFF within **M-FPN/DMN**, **L-FPN/CCN**, and **M-CIN/SN** in SUIATT; ↑ fALFF in **L-FPN/CCN** after treatment	Adults with SUIATT + MDD vs. HCs
Zhang et al. (2016)	RSFC	↑ RSFC in cerebellum; ↑ between frontal and parietal lobes within **M-FPN/DMN**	↑ RSFC between areas within **M-FPN/DMN** but ↓ RSFC between others within **M-FPN/DMN**	Adolescents and adults with MDD + SUIATT/SI vs. HCs
Chen et al. (2021)	RSFC, Correlation analysis, fALFF, ReHO	In MDD + SI vs. MDD: ↑ RSFC in right and left hippocampus; ↓ fALFF in left cuneus; ↑ fALFF in right MTP; ↓ ReHO in right cuneus; ↑ ReHO in left MTG. In MDD vs. HC: ↓ in right and left thalamus and both right and left MC	↑ RSFC between regions within **M-FPHN/DMN**	Adults with MDD + SI vs. MDD vs. HCs
Barredo et al. (2019)	RSFC and Morphometric (cortical thickness)	↑ RSFC in pars orbitalis, striatum, and thalamus = ↑ cortical thickness = ↑ self-reported suicidality	↑ RSFC between regions within **M-FPN/DMN** correlates with cortical thickness	Adults with PTSD with scale of varying depression scores vs. HCs

(Continued)

TABLE 2 (Continued)

Author	Mode	Findings	System interactions	Population
Lee et al. (2019)	RSFC	↑ RSFC between anterior right parahippocampal gyrus to posterior parahippocampal gyrus	↑ RSFC within **M-FPN/DMN** in MDD + SUIATT vs. HCs	Adults with MDD + SUIATT vs. HCs
Schreiner et al. (2019)	RSFC	↑ RSFC between right precuneus and right IFG and cerebellum and between left PCC, left cerebellum, and cingulate gyrus	↑ RSFC between components of **M-FPN/DMN**	Adolescents with MDD with vs. without medication treatment
Kim et al. (2017)	RSFC	↓ RSFC in SFG, pars orbitalis, left thalamus, and right thalamus compared to the whole brain among MDD + SI vs. HCs	↓ RSFC in **M-FPN/DMN** to whole brain in MDD + SI vs. HCs	Adults with MDD + SI vs. MDD vs. HCs
Gosnell et al. (2019)	ML RSFC	↓ RSFC between rSFG and insula; ↑ RSFC between left habenula and right parahippocampus; ↑ RSFC between left MFOG and left Rolandic operculum; ↑ RSFC between left putamen and cerebellar vermis; ↓ RSFC between amygdala and MTP	↓ RSFC in **M-FPN/DMN** and **M-CIN/SN**; ↑ RSFC between **M-CIN/SN** and **M-FPN/DMN**; ↑ RSFC between **M-FPN/DMN** and **L-FPN/CCN**; ↑ RSFC between left putamen and cerebellar vermis; ↓ RSFC between **M-CIN/SN** and **D-FPN/AN**	Adult inpatient psychiatric patients with SI and/or SUIATT vs. without
Dai et al. (2020)	ML RSFC	Significant areas distinguishing high suicide risk = right inferior temporal gyrus, left inferior frontal gyrus, right anterior angular gyrus, left inferior parietal cortex, left Rolandic operculum, and right dorsolateral superior frontal gyrus	Significant areas were found in **L-FPN/CCN**, **M-FPN/DMN** primarily	Adults with MDD + SUIATT/SI vs. MDD
Stumps et al. (2020)	ML RSFC	Right amygdala and right MTG specifically correlated to high suicide risk group	**M-CIN(SN)**, cognitive-control **(L-FPN)**, **M-FPN**, and visual networks	Adults with trauma with SUIATT vs. Clinical vs. Trauma-exposed
Chase et al. (2017)	RSFC	↑ RSFC between dorsal PCC and MTG	↑ RSFC between**M-FPN/DMN** and**D-FPN/**Attn	Adults with MDD + SI vs. HCs
Serafini et al. (2016)	RSFC Review	Activity mixed among networks, no distinction between pathologies	Activity mixed among networks, no distinction between pathologies	Review

bilateral fusiform gyrus compared to non-attempters across multiple learning-based fMRI tasks (18).

3.1.1.2. Emotional pain, affect regulation

As a proximal and distal risk factor for suicide, social exclusion is of immediate importance to the suicidal patient. This is consistent with the concepts of "thwarted belongingness" in Joiner/Van Orden's interpersonal theory of suicide, shining light on the vital importance of social support amongst persons at high risk for suicide.

Two fMRI studies (19, 20) have used the Cyberball task (where the participant is progressively excluded from a game) to examine social exclusion in suicidal populations. Both found a decreased activation in the anterior cingulate cortex (ACC) in their higher suicide risk groups. Specifically, Olie et al. found that suicide attempters displayed decreased activation in the left insula (as well as supramarginal gyrus) when compared to patients without any history of suicide attempt and healthy controls (19). Caceda et al. (20) found that the activation of the anterior insula during inclusion trials in suicide attempters was significantly decreased compared to depressed patients with and without suicidal ideation.

Emotion regulation is clinically relevant to multiple conditions, from self-injurious behavior to PTSD. Supportive of the clinical impression that emotion regulation is important in STBs, Miller et al. found that adolescents with suicidal ideation (SUI) showed increased activation in the dorsolateral prefrontal cortex (dlPFC) compared to healthy controls (21).

3.1.1.3. Sensitivity to social stressors

Many studies have tried to examine the connection between the structures involved in affective processing and regions of interest in the suicidal brain. Clinically, this may be consistent with the concept of a cognitive distortion and related to such possible risks as low self-esteem, isolation, and unwillingness to seek help, though a comparison of the neurobiological changes associated with Cognitive Therapy is beyond the scope of this review.

In a study by Pan et al. participants made a gender selection for images of faces with or without affective valences (22). Consistent with the idea of a sensitivity to social stressors, adolescents with past suicide attempts showed an increased activation in ACC, dlPFC, sensory cortex, and temporal cortex during *angry* trials but a decreased activation in the same areas during neutral or happy face trials.

Ai et al. similarly utilized a gender discrimination task with individuals with past suicide attempts. Authors found that they had lower activation within the fusiform gyrus during emotional face processing across all stimulus types: happy, angry, sad, and scared (23).

Two major studies mixed resting state data with task-based functional tasks. Alarcon et al. found that depressed participants who had attempted suicide or had high suicidal ideation showed greater functional connectivity between the amygdala, dlPFC, dorsomedial prefrontal cortex (dmPFC), and precuneus compared to controls completing an emotional self-face recognition task where they considered if the faces looked like them, with valence varying between happy, sad, and neutral (24). Malhi et al. examined resting state

TABLE 3 Morphometric studies.

Author	Mode	Findings	Population
Hwang et al. (2010)	Cortical Thickness	Cortical thinning in the left dlPFC, vlPFC, and ACC in MDD + SUIATT	Adults with MDD + SUIATT vs. MDD
Wagner et al. (2012)	Cortical Thickness	Cortical thinning in the left dorsolateral, ventrolateral prefrontal, and ACC in MDD + STBs	Adults with MDD + high risk vs. MDD without high risk for suicide
Huber et al. (2021)	Cortical thickness and volume, RSFC	Cortical thickness of the anterior cingulate/paracingulate cortex was shown to predict the functional connectivity between the lateral pars orbitalis and anterior cingulate/paracingulate	Adult veterans with SUIATT vs. SI
Wang et al. (2020)	GMV	Reduced GMV in left and right MFG among MD + SAs compared to other groups	Adolescents and adults with MDD/BD + SUIATT vs. MDD/BD + SI vs. MDD vs. HCs
Ding et al. (2015)	GMV	↓ GMV in left vlPFC in suicide attempters	Adults with Mood Disorders + STB vs. Mood Disorders vs. HCs
Fan et al. (2019)	Morphometric and DTI	↓ GMV in left vlPFC and left dlPFC; ↑ GMV in the left vlPFC compared to depressed but non-suicide attempters	Adolescents and adults with MDD + SUIATT vs. BD + SUIATT vs.
Lippard et al. (2019)	Morphometric	Lower baseline ventral and rostral prefrontal GMV compared to those who did not attempt	Adolescents and adults with Mood Disorders + SUIATT vs. Mood Disorders + future SUIATT vs. Mood Disorders
Segreti et al. (2019)	Morphometric	↓ GMV in left MFG; ↓ Cortical thickness within the posterior frontal lobe including the bilateral precentral gyrus	Adults with SI vs. HCs
Bajaj et al. (2019)	Morphometric	↓ Cortical surface area and volume within the left dlPFG with ↑ SI	Non-clinical adults
Kang et al. (2020)	Morphometric	↑ CSA in left postcentral and left lateral occipital areas and ↑ CV in left postcentral and left lateral OFC, but ↓ CSA in left SFG among MDD + SUIATT	Adults with MDD + SUIATT vs. MDD
Harenski et al. (2020)	Morphometric	SUIATT ↓ GMV in PCC/precuneus, IPC, dorsal prefrontal cortex, amygdala, insula, superior occipital gyrus, cuneus, and cerebellum	Adult criminal offenders with SUIATT vs. no SUIATT vs. HCs
Kang et al. (2020)	Morphometric	↑ GSA in left postcentral area and left lateral occipital area and a larger CV in the left postcentral area and left lateral orbitofrontal area among SUIATT; ↓ CSA in left superior frontal area than suicide non-attempters	Adults with MDD + SUIATT vs. MDD
Gosnell et al. (2016)	Morphometric	↓ Volume of the right hippocampus	Adults with MDD + SUIATT vs. MD
Chen et al. (2020)	Morphometric and Cell Type Analysis	↑ Neuron number in CA2/3 subregions of the hippocampus gyrus	Post-mortem MDD + suicide vs. MDD vs. Schizophrenia + suicide vs. Schizophrenia vs. HCs
Jollant et al. (2018)	Morphometric	Association between family history of suicide and ↓ volume within the bilateral temporal regions, right dlPFC, and left putamen, as well as between violent method of attempt and increased bilateral caudate and left putamen volumes	Adults with SUIATT vs. Patient Controls vs. HCs
Ho et al. (2018)	Morphometric	↓ GMV in the dorsal striatal structures, particularly bilateral putamen and caudate, were associated with greater implicit SI observed from suicide-related outcomes from the death version of the Implicit Association Test	Adolescent Clinical vs. HCs
Ho et al. (2021)	Morphometric	↓ GMV in the dorsal striatal structures, particularly bilateral putamen and caudate, were associated with greater implicit SI observed from suicide-related outcomes from the death version of the Implicit Association Test	Adolescent Clinical vs. HCs
Pan et al. (2015)	Morphometric	↓ GMV in right STG	Adolescents with MDD + SUIATT vs. MDD
Vidal-Ribas et al. (2021)	Morphometric	↓ GMV in superior temporal sulcus in children aged between 9 and 10 years	Children with no previous diagnosis or STB
McLellan et al. (2018)	Morphometric	↓ of the right STG in adolescents with MDD	Adolescents and adults with MDD(TRD) + SUIATT vs. MDD(TRD) vs. HCs
Peng et al. (2014)	Morphometric	MDD + SUIATT showed ↓ GMV within the right MTG and ↑ GMV within the right parietal lobe vs. HCs	Adults with MDD + SUIATT vs. MDD vs. HCs

(Continued)

TABLE 3 (Continued)

Author	Mode	Findings	Population
Lee et al. (2016)	Morphometric	↓ GMV in the left anterolateral region of the parietal lobe as well as in the right cerebellum in MDD + SUIATT	Adults with MDD + SUIATT vs. MDD
Campos et al. (2021)	Morphometric	↓ GMV of thalamus and right pallidum significantly smaller in MDD + SUIATT vs. MDD and HCs; ↓ CSA of the left cuneus, left inferior parietal, left rostral middle frontal, and right pericalcarine cortex in MDD + SUIATT vs. HCs; MDD + SUIATT ↓ Cortical thickness in left rostral middle frontal cortex	Adults Enigma Metanalysis MDD + SUIATT vs. MDD vs. HCs
Sarkinaite et al. (2021)	Morphometric	↓ Thickness of temporal cortex in inferior middle and temporal cortex as number of SUIATT ↑	Hospitalized adults with first SUIATT vs. > 1 SUIATT vs. HCs

functional connectivity (RSFC) in suicidal adults using an emotional face-word stroop paradigm in which congruent and incongruent images were flanked by the word "happy" or "sad." During negative valenced incongruent trials, depressed participants (with and without suicidal thoughts and behaviors) had increased activity relative to healthy controls in the prefrontal cortex, frontopolar cortex, ACC, and posterior parietal cortex. At the same time, participants with STB's showed increased activity among basal ganglia structures but decreased activity among the Medial Frontoparietal Network/Default Mode Network (M-FPN/DMN) structures with increasing suicide risk on measures, including the Columbia-Suicide Severity Rating Scale (C-SSRS) (25).

A recent machine learning study by Just et al. supported the involvement of structures important to all these processes among participants with suicidal ideation. When presented with affectively valenced verbal stimuli, specifically the words death, cruelty, trouble, carefree, good, and praise, group differences in activation in the medial superior frontal cortex, inferior parietal, medial temporal, ACC, and inferior frontal gyrus (IFG) were found (26).

3.1.1.4. Cognitive control/response inhibition

Impairments in top-down cognitive control and response inhibition have clear clinical relevance to suicide but have been studied very little in task-based fMRI research in this population. However, Richard-Devantoy et al. used a Go-No-Go task and found that deficits in cognitive inhibition (in relation to the IFG, thalamus, OFC, and parietal cortex) were related to the depressive, but not specifically, STB vulnerability risk (27). In contrast, the meta-analysis involving neuroimaging studies using the monetary incentive delay task and the stop signal task with over 5,000 participants aged 9–11 could not delineate between those with suicidal ideation from those with suicidal behaviors (28). Although our belief is that there is a difference in this domain between those with suicidal ideation and those who attempt, evidence is scant and will depend on future work of our own and others.

3.1.2. Resting-state fMRI

While performance on fMRI tasks and task-based connectivity studies can show abnormal/atypical recruitment of structures theorized to be essential in relevant cognitive tasks, resting-state fMRI (rsfMRI) studies allow a view of default self-referential thought processes while the participant is not engaged in a specific task. It, therefore, is used to analyze which relevant systems have robust or weakened 'default' connections or communications (29–31) within and between networks, defined as the level of increased, decreased, or mixed functional connectivity between them, or RSFC. Each defined network is organized based on theoretical common functions. In the interest of clarity, we will use Uddin et al.'s (32) definitions of major networks as a reference for the resting-state studies in our review, as they clarify the involved neuroanatomy and are analogous to established networks familiar in the research domain.

Uddin proposes the following six main networks and their primary functions: (1) the Lateral Fronto-Parietal Network/Cognitive Control Network (**L-FPN/CCN**) = *functions include executive functions, such as goal-oriented cognition, working-memory, inhibition, and task switching*; (2) the Pericentral/Somatomotor Network (**PN**/Somatomotor) = *functions include involvement in motor processes and somatosensory processing*; (3) Occipital Network/Visual Network (ON/VN) = *functions include visual processing*; (4) Dorsal Frontoparietal Network/Attention Network (**D-FPN/AN**) = *plays a broad role in visuospatial attention. The functions of this system are to prepare and apply top-down selection for stimuli and responses*; (5) The Midcingulo-insular Network/Salience Network (**M-CIN/SN**) = *has a broad role in identifying important, or salient, information. Salience processing involves the detection of behaviorally-relevant environmental stimuli and may include internally-generated (i.e., remembered) information*; and the (6) **M-FPN/DMN** = *functions likely involve formation, temporal binding, and dynamic reconfiguration of associative representations based on current goal-states, detecting the associative relevance of internal and external stimuli, and providing value coding and elaboration to perceived events. Other accounts suggest M-FPN function accommodates predictive coding, semantic associations, and plays a role continuously monitoring the environment.*

Though abnormal RSFC can be complicated, ranging from nodal (i.e., region to region) to whole brain (as it sounds) analysis and involving established networks or networks defined within each individual study, it may become increasingly relevant to clinical practice. One limitation may be the inherent assumption of the specific functions of each interconnected area. We present RSFC studies grouped according to main findings. The most consistent findings among suicidal participants seem to occur between the M-FPN (default network/DMN) and the M-CIN (salience network/SN). Many studies showed decreased RSFC between M-FPN/DMN and M-CIN/SN. When we talk about connections between networks, we clearly mean connections between the regions or nodes that comprise networks. In other words, resting state or intrinsic brain networks in fMRI are best thought of as a collection of regions that show correlations in terms of their fluctuating activity.

TABLE 4 Diffusion tensor imaging (DTI) studies.

Author	Mode	Findings	Population
Jia et al. (2010)	DTI	↓ FA in left anterior limb of the internal capsule (ALIC) among MDD + SUIATT; ↓ FA in right frontal lobe vs. HCs, and ↓ FA in right lentiform nucleus (putamen) vs. MDD	Adults with MDD + SUIATT vs. MDD vs. HCs
Jia et al. (2014)	DTI	MDD + SUIATT showed ↓ MPF from the ALIC to the left medial frontal cortex, left OFC, and left thalamus.	Adults with MDD + SUIATT vs. MDD vs. HCs
Kim et al. (2015)	DTI	↑ FA among PD + SA vs. PD in retrolenticular part of the internal capsule, splenium of the corpus callosum, superior and posterior corona radiata, posterior thalamic radiations, sagittal stratum (including the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), and superior longitudinal fasciculus	Adults with PD + SUIATT vs. PD vs. HCs
Myung et al. (2016)	DTI	MDD + SI had ↓ SC/EW across cortical (i.e., rostral middle frontal cortex, superior parietal cortex, subdivisions of the inferior frontal cortex [pars triangularis and pars orbitalis, frontal pole, and lateral occipital cortex]) and subcortical (i.e., pallidum, thalamus, putamen, and caudate) regions in the left hemisphere	Adults with MDD + SI vs. MDD vs. HCs
Olvet et al. (2014)	DTI	↓ FA among MDD + SUIATT vs. MDD vs. HCs in right dmPFC and white-matter bundles in several regions including the bilateral inferior fronto-occipital fasciculus, bilateral uncinate fasciculus, body of corpus callosum, right anterior limb of internal capsule, right external capsule, left posterior thalamic radiation, and bilateral posterior corona radiata	Adults MDD + SUIATT vs. MDD vs. HCs
Wei et al. (2020)	DTI	↓ FA among MDD + SUIATT compared to non-attempters with MDD and healthy controls in right dmPFC and bilateral inferior fronto-occipital fasciculus, bilateral uncinate fasciculus, body of corpus callosum, right anterior limb of internal capsule, right external capsule, left posterior thalamic radiation, and bilateral posterior corona radiata	Adults with MDD + SUIATT vs. BD + SUIATT vs. MDD vs. BD vs. HCs
Bijttebier et al. (2015)	DTI	↓ Structural connectivity between left olfactory cortex and left anterior cingulate gyrus; ↓ connectivity between the right medial orbital, SFG and the right rectal gyrus, and between the right calcarine fissure and both the left superior and middle occipital gyrus	Adults with MDD + SUIATT vs. MDD vs. HCs
Hwang et al. (2018)	DTI	↑ Edge weight in the left PCC and ↑ structural connectivity of local connections among MDD + SUIATT vs. MDD + SUI	Adult veterans with SUIATT vs. SUI
Chen et al. (2021)	DTI	↓ White matter integrity in MDD + SUI, specifically in the corpus callosum and the anterior cingulate cortex compared to MDD and HCs. On network-based analysis, ↓ connections within subnetworks of the frontal lobe among MDD + SUI vs. HCs	Adults with MDD + SUI vs. MDD vs. HCs
Chen et al. (2021)	DTI	Significantly ↓ white matter compactness and integrity in the corpus callosum, cingulate gyrus, and caudate among MDD + SUIATT vs. both the depressed non-attempt and HCs	Adults with MDD + SUIATT vs. MDD vs. HCs

Qiu et al. (33) looked at depressed participants with a history of suicide attempts compared to those without and found that in both groups, as suicidal ideation increased, functional connectivity decreased between the pregenual anterior cingulate cortex (pgACC part of M-CIN/SN) and the superior frontal gyrus (M-FPN/DMN). Among depressed suicidal adults, Du et al. (34) found that the SUI group exhibited *decreased* functional connectivity between the right ACC (M-CIN/SN), the orbito-medial prefrontal cortex (M-FPN/DMN), and the right middle temporal pole (within the D-FPN/AN) compared to non-suicidal depressed and control groups. Yang et al. (35) found that between depressed participants with past attempts and those without attempts, those with past attempts showed decreased RSFC (decreased positive correlation) in the right inferior front orbital gyrus (within the M-FPN/DMN) to the left inferior parietal lobule (within the M-CIN/SN). They also found that compared with non-attempters, those with past attempts had decreased gray matter volume (GMV) in the right inferior frontal orbital gyrus (IFOG) and left caudate (CAU) but increased GMV in the left calcarine fissure.

In a study by Stange et al. (36), suicidal participants showed decreased connectivity between the right middle frontal gyrus/SFG (L-FPN/CCN) and the M-FPN/DMN and decreased connectivity between the precuneus (L-FPN/CCN or M-FPN/DMN) and the Salience Network (SN). The difference in RSFC within areas of M-FPN/DMN was greater than that between M-FPN/DMN to M-CIN or to L-FPN/CCN.

Cao et al. (37) analyzed low frequency RSFC and found participants with STB's had increased connectivity in the right superior temporal gyrus (STG) (M-FPN/DMN), left MTG (M-FPN/DMN), and left middle occipital gyrus (ON/VN) but decreased connectivity in the left SFG (M-FPN/DMN) and left MFG (M-FPN/DMN), at least compared to non-suicidal clinical participants. Another study by this group (38) found that participants with past attempts had decreased RSFC between the left MFG (L-FPN/CCN) and the left SPG (D-FPN/AN) compared to the non-attempt group and decreased RSFC between the left superior frontal gyrus (M-FPN/DMN) and the right ACC (M-CIN/SN).

Several studies showed an increase in connectivity between the M-FPN/DMN and M-CIN/SN. Zhang et al. (39) specifically focused on RSFC between the bilateral amygdala and whole-brain activation and found increased connectivity between the right amygdala (M-CIN/SN) and bilateral paracentral lobule/precuneus (part of M-FPN/DMN) in a suicidal behavior (suicidal ideation and/or past

suicide attempt) group relative to non-suicidal and healthy-control groups.

Kang et al. (40) found mixed results, with suicide attempters displaying significantly increased functional connectivity of the left amygdala (within the M-CIN/SN) with the right insula (within the M-CIN/SN) and the left superior orbitofrontal area (within the DMN) and increased functional connectivity of the right amygdala (within the M-CIN/SN) with the left middle temporal area (within the D-FPN/Attn). Wei et al.'s (41) study similarly found that suicidal patients with depression showed greater amygdala (within the M-CIN/SN) to precuneus/cuneus (within the M-FPN/DMN) RSFC compared with non-suicidal patients and healthy controls.

Cao et al. (42) showed that a suicidal (history of an attempt) depressed group demonstrated decreased RSFC connectivity between the anterior M-FPN/DMN and left L-FPN/CCN but *increased* connectivity between the L-FPN/CCN and M-CIN/SN.

The next most common findings were abnormal RSFCs between the M-FPN/DMN and L-FPN (CCN), adding to the findings of Stange, Cao and others.

An RSFC analysis of treatment changes by Shu et al. (43) showed that prior to treatment, participants showed increased baseline activity in the left posterior cerebellar lobe, right ACC (within the M-FPN/DMN), left caudate (within the L-FPN/CCN) nucleus, and left superior frontal cortex (within the M-CIN/SN). After combined treatment, patients showed increased activity in the left middle occipital cortex and left precuneus (within the L-FPN/CCN).

After this, intra-network abnormalities show up in multiple studies, focusing on the M-FPN/DMN.

Zhang et al. (44) used an independent component analysis to show that RSFC within the M-FPN/DMN was increased in the left cerebellum but decreased in the posterior cingulate cortex (PCC) and right precuneus among suicidal (SUI & STBs) versus healthy controls. Network analysis by Chen et al. (45) found increased connectivity between the frontal (M-FPN/DMN) and parietal lobes in comparison to the healthy controls.

Yang's work (35), mentioned above, also found participants with past attempts had increased RSFC between the right IFOG and left rectus gyrus (both in M-FPN/DMN).

In a study examining trauma and suicide in adults with PTSD, increased functional connectivity between reward and control regions (primarily under the M-FPN/DMN of Uddin's definition) was found to be positively correlated with suicidality (46).

Lee et al. (47) found that suicidal patients (past attempts) with depression had significantly increased RSFC in tracts from an anteriorly defined division of the right parahippocampal gyrus (within the M-FPN/DMN) to a posteriorly defined division of the left parahippocampus.

Schreiner et al. (48) examined suicidal adolescents and found more evidence for involvement of the precuneus/cuneus (within the M-FPN/DMN) in the suicidal mind. They showed that in suicidal participants, as suicidality increased, RSFC increased between the right precuneus (M-FPN/DMN), right IFG (M-FPN/DMN), and cerebellum; and between the left PCC (M-FPN/DMN), left cerebellum, and cingulate gyrus.

Using whole brain analysis, Kim et al. (49) proposed a subnetwork of decreased RSFC among participants with suicidal ideation consisting of the "orbitofrontal cortex (within the M-FPN/DMN), especially the left SFT (M-FPN/DMN), pars orbitalis, left MFG, and right olfactory cortex."

Most promising may be the recent attempts to apply machine learning to one or more MRI modalities. Gosnell et al. (50) distilled five prominent RSFC patterns amongst participants with suicidal ideation or past attempts, including: (1) decreased RSFC between the rSFG (M-FPN/DMN) and insula (M-CIN/SN); (2) increased RSFC between the left habenula (possibly M-CIN/SN) and right parahippocampus (M-FPN/DMN); (3) increased connectivity between the left frontal middle orbital gyrus (M-FPN/DMN) and left rolandic operculum (L-FPN/CCN); (4) increased connectivity between the left putamen (within the FPN) and the cerebellar vermis; and (5) decreased connectivity between the amygdala (within the SN) and middle temporal pole (within the D-FPN/AN).

Dai et al. (51) used ICA (machine learning) to conclude that the relevant structures were the right inferior temporal gyrus (within the L-FPN/CCN), left IFG (within the DMN), right angular gyrus (within the L-FPN/CCN), left inferior parietal cortex (IPC) (within the L-FPN/CCN), left rolandic operculum (within the L-FPN/CCN), and right dorsolateral superior frontal gyrus (within the DMN-M-FPN).

Suicide attempt-related altered RSFC was also observed in a Graph Analytics analysis (machine learning) by Stumps et al. (52) within the M-CIN(SN), cognitive-control (L-FPN), M-FPN, and visual networks.

There were a variety of studies showing abnormal connections between other networks, including the D-FPN/Attention Network, PN/Somatomotor Network, and ON/Visual Network.

In line with the research of Du and Kang above, Chase et al. (53) found that patients with SUI (but not necessarily historical attempts) had increased connectivity between the dorsal PCC(M-FPN/DMN) and MTG (D-FPN/Attn).

Serafini et al. (54) in a review of RSFC work showed a mixed increased connectivity/decreased connectivity pattern among networks but could not distinguish findings between pathologies.

Along with abnormalities in the M-FPN/DMN above, Lee also found increased RSFC in tracks from the temporooccipital part of the right inferior temporal gyrus (within the L-FPN/CCN) to the frontal eye fields of the Dorsal Attention Network (i.e., within the D-FPN). They also found decreased RSFC between the medial frontal cortex (within the M-FPN/DMN) and the right supplementary motor cortex (within the PN/Somatomotor network).

3.2. Brain morphometry

Another way to examine the suicidal brain is through morphometric analysis. Here, we try to make it more directly accessible to the clinician. This modality measures the physical makeup of brain structures by examining measures such as cortical thickness, cortical surface area, and/or cortical volume of the relevant brain areas. The implication is that the neural systems which may be hypo/hyperactive during functional processing may have altered physical attributes. Many morphometric studies have been done to find alterations in those with STBs.

The current review identified such studies which reported associations between these morphometric measures and suicidal behavior.

One of the earlier studies addressing the association between history of suicidal attempts in elderly, depressed individuals and both cortical and sub-cortical abnormalities was attempted by Hwang et al. (55). In that study, authors used voxel-based analysis and were able to show widespread gray matter volume (GMV) reduction in the frontal (i.e., left medial, bilateral superior, right middle, right inferior, and left posterior frontal cortices), parietal (i.e., left superior, right inferior, and left lateral parietal cortices), occipital gyrus (i.e., left cuneus), left STG, and sub-cortical (i.e., bilateral insula, left lentiform nucleus, right claustrum, bilateral midbrain, bilateral culmen, and right inferior and bilateral superior semilunar lobules) brain regions in late-onset geriatric depressed individuals with a history of suicide attempts compared to those without previous attempts. Here, volume reduction was most prominent within the dmPFC, consistent with impairment in reward-based learning and top-down executive control.

Wagner et al. reported cortical thinning in the left dorsolateral, ventrolateral prefrontal, and ACC in depressed adults with documented suicidal behavior, i.e., high-risk group of suicide as compared to depressed adults with a non-high risk for suicide (56).

A study by Huber et al. specifically found white-matter volume differences in the left ACC between veterans with a history of attempting suicide relative to veterans with a history of SUI (57). Along with RSFC data previously mentioned, the work by Barredo and colleagues found that cortical thickness of the ACC/PCC was shown to predict the functional connectivity between the lateral pars orbitalis and anterior cingulate/paracingulate control regions (46).

Wang et al. specifically reported significant differences in GMV in the bilateral MFG across patients with mood disorders and suicidal behavior, patients with mood disorders without suicidal behavior, and healthy controls (58). However, they did not find significant differences between participants with SUI and those with a history of actual suicide attempts.

Ding et al. used a region-specific approach to study differences between suicide attempters with a past history of mood disorders and suicidal behavior, participants with a mood disorder but not suicidal behavior, and healthy controls with neither (59). Reduced cortical volume was observed within the left ventrolateral prefrontal cortex in suicide attempters compared to both control groups. In addition, the orbitofrontal and dorsal prefrontal cortices (but not medial prefrontal cortex) also showed reduced cortical measures in suicide attempters compared to healthy controls. This is consistent with task-based and resting-state fMRI studies showing generally both reduced top-down executive control and impairment in reward-based learning regions and networks. Structurally, there were significant GMV decreases among suicide attempters across clinical conditions compared to non-attempters. Diffusion Tensor Imaging (DTI) findings also showed significantly reduced fractional anisotropy among those with past attempts versus those without (60). In a study of future suicide attempters (i.e., individuals attempting suicide between baseline and follow-up assessment) with mood disorders, participants showed lower baseline ventral and rostral prefrontal GMV compared to those who did not attempt (61). Besides the studies examining participants with depression and/or previous suicide attempts, distinct markers that included an involvement of frontal regions, particularly reduced cortical volume within the left MFG and cortical thinning within the posterior frontal lobe including the bilateral precentral gyrus, were also found in individuals with current SUI as compared to healthy controls without even a family history of psychiatric disorders or suicide attempts (62). Interestingly, greater cortical surface area and cortical volume within the left dorsolateral prefrontal gyrus were reported to be associated with reduced SUI in a non-clinical population with mild levels of stress and perceived lack of social support (63). This would be consistent with increasing behavioral control and top-down influence on impulsivity with decreasing pathology.

In a recent study by Yang et al. authors found that suicidal depressed patients had reduced GMV in the right IFG and left caudate but increased GMV in the left calcarine fissure (35), areas associated with visual processing not irrelevant to potential affective or social stimuli.

A recent study by Kang et al. involving individuals with depression with and without a history of suicide attempts showed altered morphometry in the lateral parietal and occipital brain regions along with frontal areas. In that study, depressed patients with past suicide attempts were found to have larger surface area within the left postcentral and left lateral occipital areas and large cortical volume within the left postcentral and left lateral orbitofrontal areas, whereas smaller surface area within the left SFG was found (64). In another recent study by Harenski et al. criminal offenders with a history of suicide attempts had widespread decreased gray matter within both cortical and sub-cortical regions, including the PCC/precuneus, IPC, dorsal prefrontal cortex, amygdala, insula, superior occipital gyrus, cuneus, and cerebellum (65). Using local shape volume analysis, researchers specifically found significant volumetric differences between suicidal and non-suicidal depressed individuals in the left amygdala, left hippocampus, left putamen, bilateral pallidum, and bilateral thalamus (66). In another study however, it was only the reduced volume of the right hippocampus that was most prominent in participants with a recent history of suicide attempts within the past 2 months as compared to healthy individuals (67). This may represent limited or impaired processing of new information relative to old beliefs and memories, consistent with Van Heeringen's framework. Interestingly, in a postmortem study, compared to healthy controls, the suicidal depressed participants had an increased neuron number in CA2/3 subregions of the hippocampus gyrus (68).

In a study of suicide attempters with a family history of suicide and personal history of violent suicide attempts, Jollant et al. found an association between family history of suicide and reduced volume within the bilateral temporal regions, right dlPFC, and left putamen, as well as between violent methods of attempt and increased bilateral caudate and left putamen volumes (69). Reduced GMV in the dorsal striatal structures, particularly bilateral putamen and caudate, were associated with greater implicit SUI observed from suicide-related outcomes from the death version of the Implicit Association Test (IAT) (70, 71).

Several studies also reported cortical alterations within the temporal and parietal lobes but not the frontal lobe.

Reduced GMV within the right STG was observed in adolescents with MDD and a history of suicide attempts compared to adolescents with MDD but without any history of suicide attempts (72), whereas care-giver reported STBs were also associated with decreased volume at the left bank of the superior temporal sulcus in children (73). In another study on adolescents, McLellan et al. reported reduced volume of the right STG in adolescents with treatment-resistant depression and a history of suicide attempts as compared to healthy adolescents (74). Compared to healthy controls, patients with MDD

and a history of suicide attempts in Peng et al.'s work showed decreased GMV within the right MTG and increased GMV within the right parietal lobe (75). Authors reported decreased GMV in the left limbic cingulate gyrus for the depressed suicidal group compared to the depressed non-suicidal group. Somewhat contrary to Peng's work, patients with an attempt history have also been shown to have decreased GMV in the left anterolateral region of the parietal lobe as well as in the right cerebellum (76).

A recent study by the ENIGMA-MDD working group of over 18,925 participants examined morphometric differences between healthy controls, depressed participants, and participants with a history of attempted suicide and found multiple differences between the groups (77). Regarding volumetric differences, the thalamus and right pallidum were significantly smaller in depressed attempters compared to depressed and healthy controls. Regarding cortical surface area, depressed attempters had smaller cortical surface area of the left cuneus, left inferior parietal, left rostral middle frontal, and right pericalcarine cortex compared with healthy controls, but only the inferior parietal cortex was clinically distinct from depressed clinical controls. Lastly, in terms of cortical thickness, although there was not a significant difference between depressed attempters and clinical controls, attempters did display significantly lower cortical thickness in the left rostral middle frontal region. The authors concluded that these findings suggested impairment in decision making, impulsivity, and planning as well as attention and the concept of self (77). However, please note that a significant difference in such large studies does not mean the effect size is clinically meaningful. In other words, a clinically insignificant volumetric difference could be statistically significant due to the large number of subjects studied. For example, in this study, for the left pallidum and right nucleus accumbens subcortical volumes, the difference between clinical and healthy controls did not reach statistical significance after correction for multiple comparisons. Therefore, statistically significant differences may not necessarily translate to clinical significance, but it can inform next steps and build a future-focused plan for translational researchers.

Most recently, Sarkinaite et al. (78) published findings that showed volumetric differences between participants with past suicide attempts and healthy controls in the frontal and temporal cortex thickness and volume of the hippocampus. Notably, with number of attempts as a covariate, participants with increasing number of past suicide attempts showed decreasing thickness of temporal cortex in the inferior middle and temporal cortex.

In Figures 1, 2, we provide an overview of brain regions (Figure 1) and networks (Figure 2) that are most commonly found to be involved in functional MRI and brain morphometry research of suicidal thoughts and behavior. Both the figures are generated through FreeSurfer 7.3.2 (82, 83) and Yeo's 17-network atlas (84).

3.3. Diffusion-weighted MRI

The fourth neurobiological modality that we included in this study was Diffusion Tensor Imaging (DTI). This method analyzes the robustness of water diffusion within white-matter structures of the brain to find associated differences between patient populations and healthy controls or other cohorts. DTI also examines the physical "highways" within and between significant structures. While fMRI gives information on "in the moment" electrical communication that could conceivably indicate functional robustness of structures and pathways, DTI is a direct measure of the physical robustness of those structures and pathways. To that end, it may be considered as a more concrete/persistent measure to estimate the difference between healthy controls and the suicidal patients. Again, most of the modalities can be accomplished in a relatively short scanning session and are more potentially accessible to the working clinician.

Recent advancements in imaging have allowed the scientists to study differences in white-matter integrity, compactness, or structural connectivity in clinical populations – the "quality of the highways" so to speak. These studies use parameters such as apparent diffusion coefficient (ADC-speed of water flow regardless of direction), fractional anisotropy (FA-diffusion of water molecules in a particular direction), and edge-weight (white-matter structural connectivity) to measure connections between regions of interest (85, 86). Edge weight has been considered a potentially more appropriate parameter to measure the strength of structural connectivity because it takes into account both the number of white-matter fibers and the size of the regions of interest (87). Our focused review identified studies which reported associations between these measures and suicidal behavior.

In a study of young adult healthy controls and young adults with MDD with and without a history of suicide attempts conducted by Jia et al. reduced FA was found in the (a) left anterior limb of the internal capsule (ALIC) for suicide attempters compared to non-attempters and healthy controls, (b) right frontal lobe (subgyral) for suicide attempters compared to healthy controls, and (c) right lentiform nucleus (putamen) for suicide attempters compared to non-attempters (88). In another similar study by Jia et al. it was also found that compared to healthy controls, depressed suicide attempters had significantly lower mean percentage of fibers projecting from the ALIC to the left medial frontal cortex, left OFC, and left thalamus. Compared to depressed non-suicide attempters, depressed suicide attempters had significantly lower mean percentage of fibers projecting from the ALIC to the left OFC and left thalamus (89). However, in a study involving panic disorder and suicide attempt, several regions, including the retrolenticular part of the internal capsule, splenium of the corpus callosum, superior and posterior corona radiata, posterior thalamic radiations, sagittal stratum (including the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), and superior longitudinal fasciculus, showed increased FA in individuals with panic disorder and history of suicidal attempt (PD + SA) compared to individuals with panic disorder but without any history of suicidal attempt (90). For the PD + SA group, Kim et al. also found that for two regions (i.e., right retrolenticular part of the internal capsule and bilateral posterior thalamic radiations), there was a significant positive association between FA and SUI.

In another study, lower baseline FA was found in the left ALIC, bilateral dmPFC, and right dorsal cingulum for future suicide attempters (i.e., who attempted suicide between the baseline and follow-up assessment) compared to non-attempters (61). In that study, compared to the non-future suicide attempt group, both future suicide attempters with or without a history of suicide attempts had lower FA for the left dmPFC, right dlPFC, and left ALIC. Future suicide attempters with a history of suicide attempts also showed lower FA in the right dmPFC and right dorsal cingulum. Authors found that after an exclusion of four participants with alcohol/substance use disorder, the left ventral prefrontal cortex also had lower FA for the future suicide attempters relative to non-attempters.

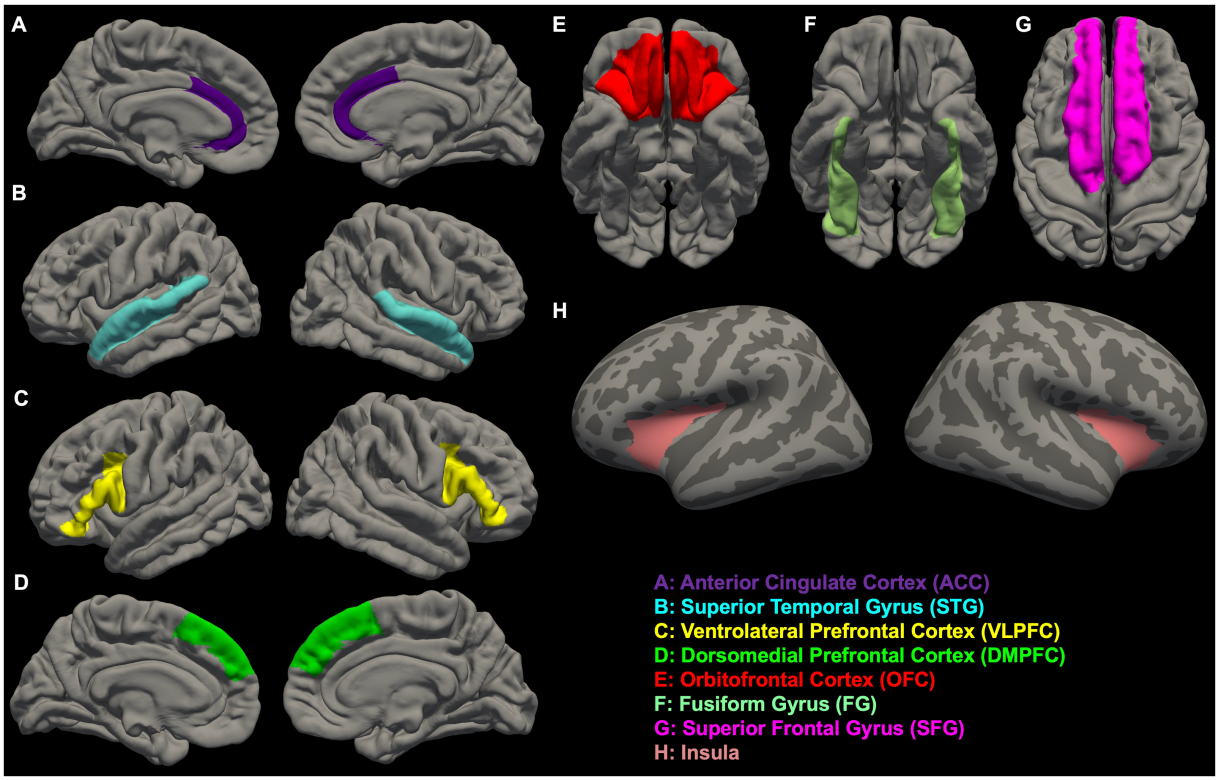

FIGURE 1
Overview of brain regions **(A–H)** that are most commonly found to be involved in functional MRI and brain morphometry research of suicidal thoughts and behavior.

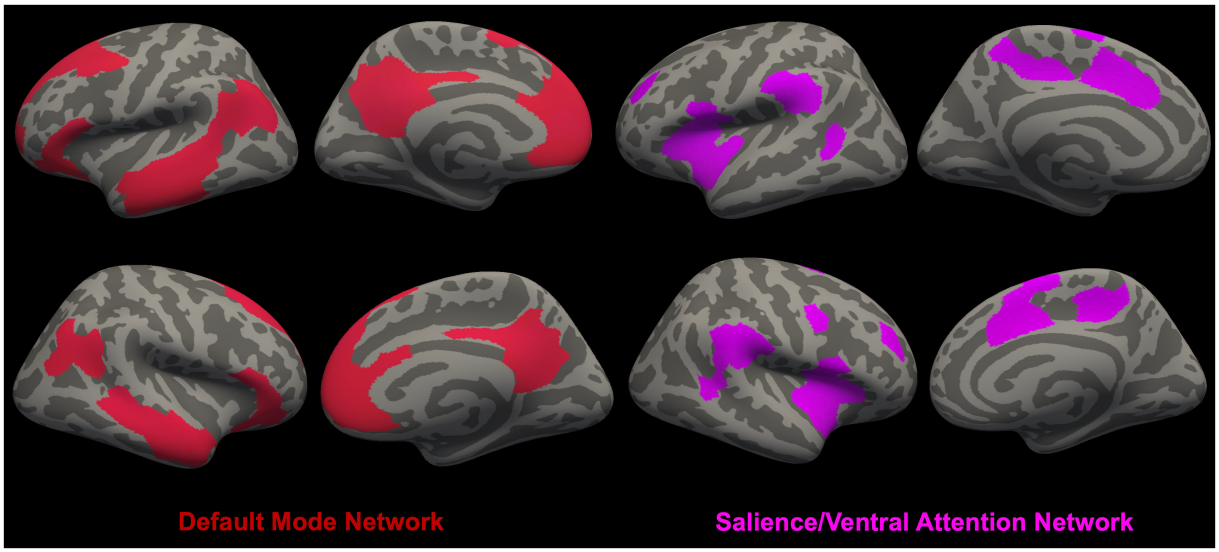

FIGURE 2
Overview of brain networks [i.e., Default Mode Network (DMN) (79) and Salience/Ventral Attention Network (SN/VAN) (80)] (81) that are most commonly found to be involved in functional MRI and brain morphometry research of suicidal thoughts and behavior.

Fan et al. also found lower FA in the dorsal and ventral frontal regions that included the uncinate fasciculus for individuals with MDD and a history of suicide attempts as compared to non-suicide attempters (60).

In terms of structural connectivity parameters, it was determined that compared to individuals with MDD without SUI, individuals with MDD and SUI had reduced structural connectivity/edge weights across cortical (i.e., rostral middle frontal cortex, superior parietal

cortex), subdivisions of the inferior frontal cortex (i.e., pars triangularis and pars orbitalis, frontal pole, and lateral occipital cortex), and sub-cortical (i.e., pallidum, thalamus, putamen, and caudate) regions in the left hemisphere (91). In terms of FA also, the frontal areas, especially right dmPFC and white-matter bundles in several regions, including the bilateral inferior fronto-occipital fasciculus, bilateral uncinate fasciculus, body of corpus callosum, right anterior limb of internal capsule, right external capsule, left posterior thalamic radiation, and bilateral posterior corona radiata, showed lower FA amongst suicide attempters with MDD compared to non-attempters with MDD and healthy controls (92, 93).

Another structural connectivity study showed that compared to euthymic non-attempters and healthy controls, there was significantly decreased structural connectivity in euthymic suicide attempters in the connections between the left olfactory cortex and left anterior cingulate gyrus, as well as a clear trend of decreased connectivity between the right medial orbital, SFG, and the right rectal gyrus and between the right calcarine fissure and both the left superior and middle occipital gyrus (94). Hwang et al. reported greater edge weight in the left PCC and greater structural connectivity strength of local connections amongst participants who were military veterans with prior suicide attempts in comparison to those with SUI only and with no suicidal behavior (95).

A 2021 study by Chen et al. evaluated white-matter integrity (generalized fractional anisotropy) and white-matter compactness (normalized quantitative anisotropy) among depressive patients with and without past suicide attempts (96). On a voxel-based (region of interest) analysis, participants with past suicide attempts had significantly lower white matter compactness and integrity in the corpus callosum, cingulate gyrus, and caudate than both the depressed non-attempt and the healthy control groups, with differences between the attempt group and healthy control group reaching statistical significance (96).

The same researchers evaluated white matter density and integrity among depressed patients with suicidal ideation but no history of attempts (97). In the voxel-based analysis, white matter integrity was found to be decreased in the suicidal ideation group, specifically in the corpus callosum and the ACC compared to depressed, non-SI, and healthy control participants. On RSFC, the suicidal ideation group had weaker connections within subnetworks of the frontal lobe compared to healthy controls but did not find differences between suicidal ideation and depression in suicidal participants.

4. Discussion

The concept of maladaptive thinking in depression is well understood by most clinicians (98). The notion that patients may develop maladaptive thinking in/or about social interactions is likely not surprising. However, to grasp the comprehensive picture of what is happening neurobiologically, providers must look to the evolving literature in neuroscience and neurobiology. Among our sample we have found many indications that functional, structural, RSFC, and diffusion-weighted MRI studies are beginning to bridge this translational gap well.

Task based fMRI studies show abnormal activation in prefrontal, subcortical, and limbic regions. Specifically, areas important for emotional processing, reward-based learning (value estimation), emotional regulation/social exclusion, relative representation/sensitivity to affective stimuli, and cognitive control/response inhibition show abnormal activation, though in some cases (18), they contradict other studies. It may be that the same regions (e.g., left insula) are increasingly active in some cognitive challenges but less activated than controls in others, but this would not be contradictory to Van Heeringen's model. Complicating the current growing body of research is the comparison of suicidal individuals with past attempts, versus those without, versus those with ideation and those without. At this stage it may simply be important to keep the focus on what regions and processes are relevant as data grows and models continue to develop.

Among our sample, rsfMRI enriches the functional data by showing the major networks with abnormal connectivity among patients with MDD and STBs. From machine learning to strictly RSFC studies, the most relevant networks are clearly the M-FPN/DMN and M-CIN/SN and their communication within and between each other and with top-down control areas of the L-FPN/CCN. With the vast and complex roles of the M-FPN/DMN and M-CIN/SN, it is clear that even in the resting state, areas important for learning, affective and social processing, and cognitive control are affected, but this research also lends depth to the increased weight of an abnormally functioning "salience judge" at the cost of new information coming in from all sides. The mix of participants (adults, adults and adolescents, older adults, combat veterans, and convicted criminals) and type of STB being studied (standard scale score, suicide attempt, or suicidal ideation) of course complicates these already complicated findings, but data continues to grow.

Helping to enlighten a picture of abnormal communication amongst regions and networks, DTI data among our sample similarly supported differences in major tracts such as the ALIC and uncinate fasciculus (UF), important in communicating between structures of the reward-based learning network, along with differences in edge weight and FA among and between structures important for emotional processing, reward-based learning (value estimation), emotional regulation/social exclusion, relative representation/sensitivity to affective stimuli, and cognitive control/response inhibition. The clear difference among our DTI sample and the other methodologies, however, is that among participants with MDD and STBs, all of these measures were found to be decreased in comparison to control groups.

This is further supported in our sample by the morphometric studies generally showing that structures involved in both top-down and bottom-up emotional processing, visual and language processing, impulse control, and affective processing are atypical across the board. Decreased GMV/thickness/area were found in frontal systems such as the IFG and OFC, ventral-lateral prefrontal cortex, dlPFC and temporal regions, and in suicidal individuals, there are clear reductions in GMV in subcortical (putamen and caudate) and limbic (hippocampus-MFPN/DMN) areas as well. Intuitively, these measured differences represent more long-term changes among the relevant structures and networks that a patient would depend on as stressors and, hence, the risk of STBs accumulate.

Previous literature reviews are generally consistent with our results, though many have incorporated different samples with different conditions that inhibit direct comparison. Especially relevant to our review are the work of Jollant (5), Desmyter (99), Zhang (100), Martin (101), Schmaal (10), and Auerbach (11), among others (102–106). Studies over the last 20 years have increasingly showed a relation between emotional pain and physical pain (107–109). Work by Olie et al. has specifically examined the increasing relevance of social exclusion to affective pain and suicide and further discussed the association between neuroimaging findings of social exclusion and suicide risk (110). They found that while the normal response to the

affective pain of social exclusion increases activity in the anterior insula, ACC, and inferior OFC in normal controls, suicidal individuals show a decreased activation in these same regions, even compared with non-suicidal patients with a mood disorder.

In short, we are not proposing a grand new theory that is all encompassing, for that would take many more variables into account, which have their own emerging literature, such as genetic, socioeconomic, and cultural factors. Also biochemical, MEG, SPECT, and PET scanning and incorporating the rich and ever evolving psychometric data would also need to be considered. We are simply proposing a framework to begin applying emerging neurobiological data in a clinical and chronological way in conjunction with already used measures, such as psychometrics and clinical assessments, so that as a patient encounters various diatheses and stressors, their clinician will be able to look to this framework to address a complex problem in comprehensive but clinically feasible way. With genuine and earnest collaboration in translational medicine, imaging, and neuroscience, combined with machine learning and worldwide research consortiums focusing on suicidal thoughts and behaviors, and replication of findings, especially in these diverse and complicated modalities, collaboration can shrink the time from new discoveries to clinical intervention. There are few things more urgent than attempting it.

Our simple framework is this: First, morphometric changes may be more observable early on from genetic and environmental stressors but also long standing atypical cognitive processing. Second, abnormalities in diffusion-weighted projections will become apparent, implying increasingly longstanding atypical networks and relevant ROI communication, and demonstrable on scanning. Third, abnormalities in processing new information, especially negative social and affective valenced-relevant stimuli tethered to language and facial processing, will be demonstrated on rsfMRI/RSFC analysis, as evident by increased communication between networks (M-CIN/SN to L-FPN/CCN), implying maladaptive rumination of faulty negative information and decreased communication between new, contradicting affective/relevant processing areas and value estimation/strategy adjustment networks (M-CIN/SN TO M-FPN/DMN). Fourth, the gap between value and risk estimation will widen on fMRI tasks immediately prior to the STBs.

Ultimately, we hope to start to construct a chronological framework of early diatheses, developing stressors, whether distal or proximal, and correlating their neurobiological fingerprint across MRI modalities and behavioral task performance. We will do this through continued task/theory-based fMRI and network studies, structural/morphometric, RSFC, and DTI research. We will continue to develop machine learning evaluations through each modality and across them first using classification and machine learning techniques to quickly determine biosignatures that directly affect suicide risk and improve our model. We will then use a regression analysis to analyze level of risk and sequence mining to predict proximal neurobiological changes. Through this comprehensive and accelerated approach, we hope to begin to capture a clinically relevant and useful point-of-care tool that can accurately and thoroughly assess risk of suicidal ideation and attempt. Then, with extensive collaboration, those in the field of neurobiological suicide research can shift into evaluating the most effective interventions at each specific time that will prevent it. Lastly, given that functional connectivity studies and diffusion tensor imaging have a particular drawback: neither are in a position to assess directed functional or effective connectivity (111). In other words, one gets a single number for the connectivity between two regions – as opposed to separate estimates of the directed influence of one region on another, and the reciprocal influence. This is important when talking about the distinction between bottom-up and top-down processes in functional brain hierarchies. In consequence, given our expertise in cutting-edge directed functional (e.g., Granger causality) and effective (e.g., dynamic causal modeling) brain connectivity techniques (29–31, 112–117), we will aim to see how analyses of directional connectivity nuance the emerging picture of suicidal thoughts and behavior described above. Emerging research in directed functional and effective connectivity will surely prove invaluable.

Author contributions

MD conceived the presented idea, performed the literature search and wrote the initial draft. KB substantially contributed to interpreting the relevant literature and writing the manuscript. EC performed the literature search and contributed to writing of the manuscript. JB substantially contributed to the conception, interpretation, and writing of the manuscript. AD contributed to the writing of the manuscript and edited various versions of the draft. SB conceived the presented idea, performed literature search, wrote the initial draft, and supervised all aspects of the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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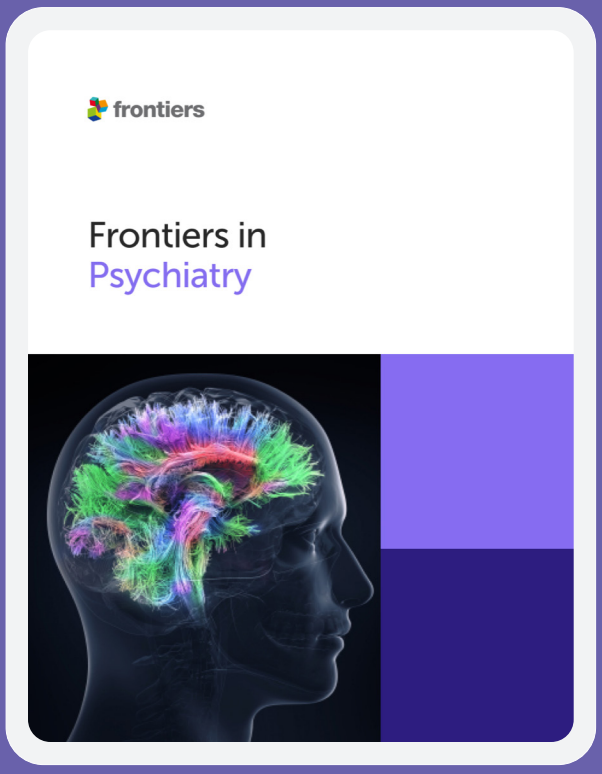

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