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Exploration of major depressive disorder among children and adolescents: From pathogenesis to intervention

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Exploration of major depressive disorder among children and adolescents: From pathogenesis to intervention

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Editorial: Exploration of major depressive disorder among children and adolescents: from pathogenesis to intervention

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Editorial on the Research Topic
Exploration of major depressive disorder among children and adolescents: from pathogenesis to intervention

Major depressive disorder (MDD) is mainly characterized by persistent depression, loss of interest or joy in previously enjoyable activities, recurrent thoughts of death, and physical and cognitive symptoms, which is a serious and highly disabling mental disorder that can cause severely long-term psychosocial impairment (1). MDD among children and adolescents is relatively common. The point prevalence of MDD in children and adolescents was 1.3% in China (2). Childhood depression disorder would increase the probability of depression in adults (3). In addition, plant/body disorders were more common in children and adolescents with MDD (4). Suicide is also a serious issue worth paying attention to in MDD. Among children and adolescents, MDD has the highest mortality risk, with a global incidence rate of 1.3% (5). The average attempted suicide rate of children and adolescents with MDD was 6.27% per year (6). Therefore, there is a high unmet need for exploring prevention and intervention mechanisms for MDD among children and adolescents.

As the guest editors for the Research Topic on the "*Exploration of major depressive disorder among children and adolescents: from pathogenesis to intervention*", we would like to highlight some research articles here. These articles covered the symptom characteristics, neural characteristics, and interventions of MDD among children and adolescents.

Liu et al. reported that Children and adolescents with MDD had a higher prevalence of underweight, obesity, suicidal ideation, and attempted suicide. When it comes to neural characteristics, Zhang et al. demonstrated that changes in gray matter volume were found in the frontotemporal parietal lobe and subcortical brain regions of MDD adolescents, which have been proven to be related to the severity of depression. In terms of suicidal behavior, Ma et al. have found evidence from neuro-electrophysiology suggested that depressed adolescents who participate in self- injury may experience impaired behavior inhibitory control (BIC) when exposed to self-injury cues.

Wang et al. showed that the prescription and treatment costs of adolescent depression patients have been increasing rapidly, which should arouse our attention. Current

antidepressants can improve the function of adolescent MDD patients, but can't improve their quality of life (7). Therefore, there is an urgent need for new and effective treatment methods for children and adolescents with MDD.

Repetitive transcranial magnetic stimulation (rTMS) is a relatively new treatment modality that is gaining attention in the treatment of adolescent depression (8). Zheng et al. demonstrated that Low-frequency rTMS could benefit children and adolescents with MDD. Besides that, Zhao et al. also found that LF-rTMS could improve the NSSI performance and abnormal EEG microstate in children and adolescents with depressive disorders. In addition, formulating treatment plans, Zou et al. demonstrated that it was also necessary to consider the combined effects of sleep and exercise on adolescent depression.

In terms of prevention, Xin et al. stated that actively participating in helping others (this psychological quality) was an important way to prevent and eliminate adolescent depression. In the process of helping others, adolescents enrich their inner emotional experience and construct positive psychological quality, which may form immunity to depression.

Based on the findings of this Research Topic, it is necessary to consider the psychological quality of MDD adolescents in the process of prevention. In addition, when formulating intervention measures, medical personnel need to consider both pharmacological and non-pharmacological treatments such as rTMS, and include consideration of the impact of sleep and exercise on MDD adolescents in the development of treatment plans.

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Low-frequency repetitive transcranial magnetic stimulation for children and adolescents with first-episode and drug-naïve major depressive disorder: A systematic review

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Objective: This systematic review of randomized controlled trials (RCTs) was conducted to explore the therapeutic effects and safety of active low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) versus sham LF-rTMS in children and adolescent patients with first-episode and drug-naïve (FEDN) major depressive disorder (MDD).

Methods: A systematic literature search was performed, and data were extracted by two independent researchers. The coprimary outcomes were study-defined response and remission.

Results: A systematic search of the literature yielded 442 references, of which 3 RCTs (130 children and adolescents with FEDN MDD, 50.8% male, and mean age range from 14.5 to 17.5years) met the inclusion criteria. Among the two RCTs (66.7%, 2/3) examining the effects of LF-rTMS on study-defined response and remission and cognitive function, active LF-rTMS was more efficacious than sham LF-rTMS in terms of study-defined response rate and cognitive function (all $p<0.05$) but not regarding study-defined remission rate (all $p>0.05$). No significant group differences were found with regard to adverse reactions. None of the included RCTs reported the dropout rate.

Conclusion: These findings preliminarily found that LF-rTMS could benefit children and adolescents with FEDN MDD in a relatively safe manner, although further studies are warranted.

KEYWORDS

rTMS, major depressive disorder, first episode, children, adolescents

Introduction

Major depressive disorder (MDD), as a leading cause of global disease burden (1), affects approximately 5–15% of children and adolescents (2). Children and adolescents with MDD are usually related to school dropout, pregnancy/parenthood, and unemployment (3). Furthermore, individuals suffering from MDD in childhood and adolescence have a relatively high risk for chronic

recurrence, suicide, and long-term psychosocial impairment in adulthood (2, 4–6). Therefore, improvements in treating MDD among children and adolescents should positively affect public health.

Initial treatment of children and adolescents with MDD may include a selective serotonin reuptake inhibitor (SSRI) or cognitive-behavioural therapy (CBT) (7). A Treatment for Adolescents with Depression Study (TADS) randomized controlled trial (RCT) found that CBT combined with fluoxetine provided a more favorable tradeoff between risk and benefit in adolescent patients with MDD than either treatment alone (7). However, up to 40% of adolescents suffering from MDD fail to respond to traditional treatment (8, 9). As a result, new and effective treatment approaches for MDD patients among children and adolescents are urgently needed.

Repetitive transcranial magnetic stimulation (rTMS), as a noninvasive brain stimulation, is gaining attention in treating adults suffering from various conditions, including MDD and obsessive–compulsive disorder (OCD) (10–12). Repetitive transcranial magnetic stimulation uses a magnetic field to stimulate the cortex and depression-related areas with electrical currents and alter dysfunctional brain patterns (13, 14). Numerous RCTs have demonstrated the therapeutic effects of rTMS in adult patients with treatment-refractory depression (TRD) (15, 16). The utility of rTMS for adult patients with MDD and OCD who did not respond to medications has been approved by the US FDA (9, 17). Accumulating evidences found that rTMS also could accelerate the rapidity of the antidepressant response in adult patients suffering from first-episode MDD (18, 19). Case reports/series (20–22) and observational studies (23–28) reported that rTMS appeared to be suitable for children and adolescents diagnosed with MDD. However, the findings of RCTs (29–31) examining the therapeutic effects and safety of active low-frequency rTMS (LF-rTMS) versus sham LF-rTMS for children and adolescents with first-episode and drug-naïve (FEDN) MDD have been inconsistent.

Therefore, the primary aim in this systematic review of RCTs was to investigate the therapeutic effects and safety of active LF-rTMS versus sham LF-rTMS for children and adolescents with FEDN MDD. We hypothesized that active LF-rTMS would be more efficacious than sham LF-rTMS in ameliorating depressive symptoms in FEDN MDD patients among children and adolescents.

Methods

Search strategy and selection criteria

To identify studies for inclusion in this systematic review, two researchers (ZJQ and XJL) independently searched Chinese Journal Net, WanFang databases, PsycINFO, Cochrane Library, PubMed, and EMBASE through November 4 2022. The search terms are listed in Appendix S1. Additionally, we manually searched reference lists of previous reviews (2, 9, 32) and the included RCTs (29–31) on active LF-rTMS versus sham LF-rTMS for children and adolescent patients with FEDN MDD.

In accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines (33), we included studies that fulfilled the following *PICOS* criteria. *P*articipants: Children (6–11 years) (34) and adolescents (12–25 years) (35) with a diagnosis of first-episode MDD who did not receive any antidepressant treatment. In line with the methodology of a recent systematic review (35), adolescents were defined as those who are 12–25 years old rather than 13–18 years old. ***I***ntervention versus ***C***omparison: active LF-rTMS versus sham LF-rTMS. Outcomes: The coprimary outcomes were study-defined response (i.e., at least 50% reduction in Hamilton Depression Rating Scale (HAMD) scores) and remission (i.e., at least 75% reduction in HAMD scores). Additional outcomes were cognitive function, dropout rate, and adverse events. ***S***tudy: Only published RCTs on active LF-rTMS versus sham LF-rTMS for children and adolescents (6–25 years) with FEDN MDD were eligible for inclusion. Studies focusing on active LF-rTMS versus antidepressants (36) or high-frequency rTMS (HF-rTMS) combined with antidepressants versus antidepressant monotherapy (14) were excluded. Review articles and case reports/series were also excluded.

Data extraction

Two independent researchers (ZJQ and XJL) performed the data extraction from each included RCT, and any disagreements were resolved by joint discussion. We extracted data using a standardized form including author, year of publication, study design, rTMS protocol, and primary and secondary outcomes. Additional data were requested by contacting the original study author(s), if necessary.

Study quality assessment

The quality of the RCTs was independently assessed by the same two researchers (ZJQ and XJL) using the Jadad scale (37) and the Cochrane risk of bias (38). As reported previously (39), RCTs were considered "high quality" when the Jadad score was ≥3.

Results

Study selection

Our initial search of the above English and Chinese databases retrieved 442 references (Figure 1). Finally, 3 RCTs (29–31) conducted in China met the inclusion criteria of this systematic review. The screening process for the literature is presented in Figure 1.

Study characteristics

The participant characteristics and LF-rTMS parameters of the three included RCTs (29–31) are summarized in Table 1. The studies ($n = 130$) were conducted between 2015 and 2019, comparing active LF-rTMS ($n = 65$) and sham LF-rTMS ($n = 65$) for children and adolescents with FEDN MDD. Their mean ages ranged from 14.5 to 17.5 years, and more than half (50.7%) of the children and adolescents with FEDN MDD were male. The LF-rTMS treatment duration varied from 10 days (2 RCTs (29, 30)) to 20 days (1 RCT (31)). The detailed LF-rTMS protocol of each included RCT is summarized in Table 1.

Assessment of study quality

As shown in Table 1, the Jadad score ranged from 1 (2 RCTs (29, 31)) to 2 (1 RCT (30)); thus, none of the included RCTs fulfilled the

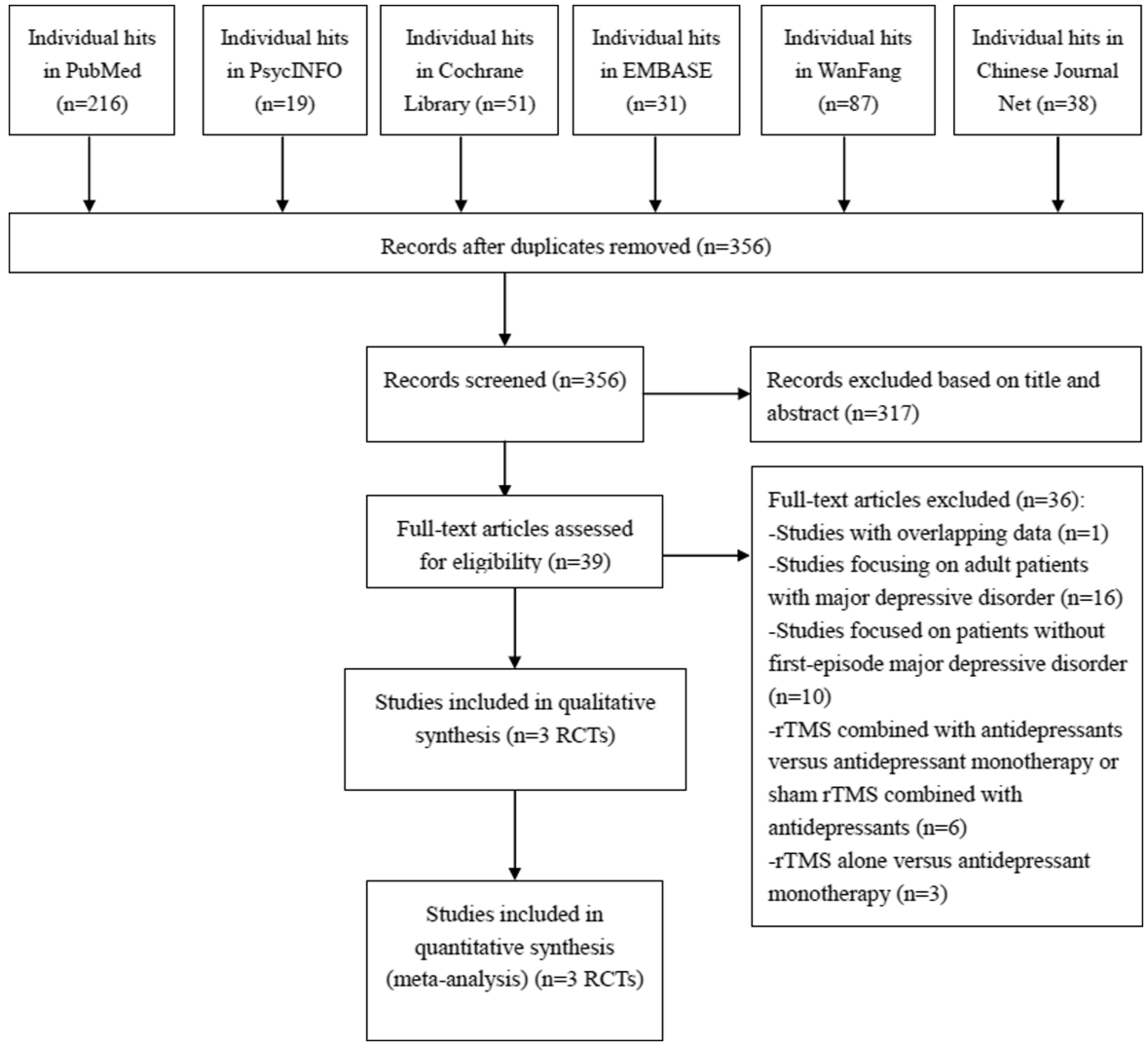

FIGURE 1
PRISMA flow diagram.

criteria of high quality. All RCTs were rated as low risk regarding attrition and reporting bias according to the Cochrane risk of bias (Figure 2).

Study-defined response and remission

Among the included three RCTs, one RCT (33.3%, 1/3) (29) did not report the rates of study-defined response and remission (Table 2) and found a significant superiority of active LF-rTMS over sham LF-rTMS in improving the depression subfactor scores of the Children's depression inventory (CDI; all $p < 0.05$). In Han et al.'s study (31), a significant superiority of active LF-rTMS over sham LF-rTMS was found for study-defined response (40.0 vs. 13.3%; $p < 0.05$) between active LF-rTMS and sham LF-rTMS but not for study-defined remission (13.3 vs. 3.3%; $p > 0.05$). Similarly, a significant superiority of active LF-rTMS over sham LF-rTMS was found for study-defined response (46.7 vs. 0%, $p < 0.05$) but not for study-defined remission (0 vs. 0%, $p > 0.05$) in Zhang et al.'s study (30).

Cognitive function

Although 66.7% (2/3) of RCTs investigated the cognitive effects of active LF-rTMS versus sham LF-rTMS (Supplementary Table 1), their data measured by using different measures were not pooled. As shown in Supplementary Table 1, two RCTs consistently found that active LF-rTMS provided a significant improvement in cognitive function over sham LF-rTMS as measured by the Wisconsin Card Sorting Test (WCST) (31) and the cognitive subscale of HAMD (30), respectively.

Dropout rate and adverse events

As depicted in Supplementary Table 2, none of the included RCTs reported the dropout rate. Only one RCT (30) (33.3%, 1/3) reported adverse events, finding no significant difference regarding dizziness, nausea, or insomnia between the two groups (all $p > 0.05$; Supplementary Table 2).

TABLE 1 Participant characteristics and low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) parameters of each study included in this systematic review.

Study (country)	Number of patients[a]	Participants: -Diagnosis -Diagnostic criteria -Setting	-Illness duration (months) -Male (%)	Mean age (years) (range)	LF-rTMS treatment duration (days)	Intervention versus control groups; number of patients (*n*)	-Intensity (%MT) -Frequency (Hz)	-Site	-Number of trains per day -Train duration (s) -Intertrain duration (s)	-Pulses per session -Number of sessions -Total pulses	Jadad score
(29) (China)	40	-FEDN MDD -DSM-IV -NR	–1.1 –45	14.8 (12–18)	10	1.Active LF-rTMS; $n=20$ 2.Sham stimulation; $n=20$	–70 –0.5	R-DLPFC	–40 –10 –2	–200 –10 –2000	1
(31) (China)	60	-FEDN MDD -CCMD-3 -NR	-NR –55	14.5 (10–16)	20	1.Active LF-rTMS; $n=30$ 2.Sham stimulation; $n=30$	–100 –1	R-PFC	–80 –10 –5	–800 –20 –16,000	1
(20) (China)	30	-FEDN MDD -DSM-IV -NR	–6.3 –50	17.5 (15–21)	10	1.Active LF-rTMS; $n=15$ 2. Sham stimulation; $n=15$	–80 –1	R-DLPFC	–15 –40 –20	–600 –10 –6,000	2

[a]Overall number of participants.
CCMD-3 = Chinese Classification and Diagnostic Criteria of Mental Disorders 3rd edition; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; FEDN = first-episode and drug-naïve; MDD = major depressive disorder; MT = motor threshold; NR = not reported; R-DLPFC = right dorsolateral prefrontal cortex; R-PFC = right prefrontal cortex; LF-rTMS = low-frequency repetitive transcranial magnetic stimulation.

Discussion

To the best of our knowledge, this article is the first systematic review of RCTs to investigate the effectiveness and safety of active LF-rTMS versus sham LF-rTMS for children and adolescents (6–25 years) with FEDN MDD. Only three RCTs (29–31) involving 130 subjects with FEDN MDD among children and adolescents were included in this systematic review. The major findings of this systematic review were as follows: (1) active LF-rTMS was more efficacious than sham LF-rTMS in terms of the study-defined response rate and the improvement of cognitive function; and (2) there is a strong indication that LF-rTMS was relatively safe and well tolerated in subjects with FEDN MDD among children and adolescents, although better quality studies are warranted.

In this systematic review, LF-rTMS as a stand-alone treatment appears to be effective for children and adolescents with FEDN MDD, although long-term efficacy was not reported. A recent RCT ($n = 103$) examining the potential therapeutic role and safety of active LF-rTMS versus sham LF-rTMS for adolescents with TRD found that 41.7% responded, and 29.2% met the criteria of remission with active LF-rTMS (40). Numerous RCTs (14) and meta-analyses (2) found that rTMS as an adjunctive therapy is safe and effective in children and adolescents with MDD. Importantly, several recent studies found that LF-rTMS and antidepressants were equally efficacious in reducing depressive symptoms in children and adolescents with MDD (41). Taken together, these findings provide preliminary support for the utility of LF-rTMS in children and adolescents with MDD.

For other noninvasive brain stimulations, such as transcranial direct current stimulation (tDCS) (42–44) and electroconvulsive therapy (45, 46), another objective is to monitor the cognitive effects of rTMS. Consistent with previous meta-analyses focusing on adult patients with MDD (47, 48), this systematic review also found that a therapeutic rTMS course for child and adolescent patients with FEDN MDD may produce modest cognitive enhancing effects. A possible explanation is that cognitive effects were secondary to mood improvement (47). However, the WCST and the HAMD measure used in the included two RCTs (30, 31) do not appear to be suitable for evaluating cognitive performance in MDD. The Assessment of Neuropsychological Status (RBANS) (49) or the MATRICS Consensus Cognitive Battery (MCCB) (50) should be recommended to assess cognitive performance in individuals experiencing MDD in clinical trials. Thus, the cognitive effects of active LF-rTMS compared to sham LF-rTMS should be further examined in FEDN MDD patients among children and adolescents. A recent RCT found that rTMS and tDCS (rTMS-tDCS) than single-tDCS produced greater improvement in neuropsychiatric symptoms (51). As a type of noninvasive cranial electrical stimulation, transcranial alternating current stimulation (tACS) can significantly improve depressive symptoms in adults with FEDN MDD (52). However, there have been no head-to-head studies that compared rTMS either with tACS or tDCS in child and adolescent patients with FEDN MDD.

There are several limitations to this systematic review. First, data were not pooled due to the limited number of studies (3 RCTs) with the heterogeneity of significance between the studies. Second, the sample size ($n = 130$), ranging from 30 to 60, was relatively small. Third, the parameters of LF-rTMS used in the three included studies were varied. For example, the number of total pulses (Table 1) varied from 2,000 to 16,000, which may have resulted in different therapeutic effects and

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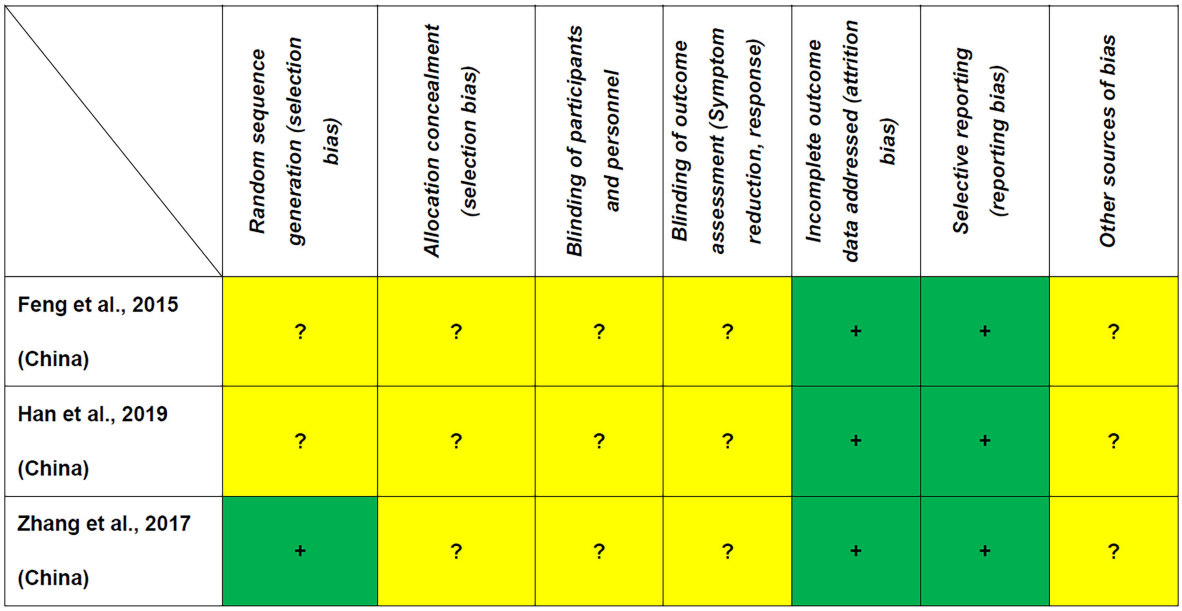

FIGURE 2
Cochrane risk of bias +: Low risk of bias, −: High risk of bias,?: Unclear risk of bias, nd: not determined.

TABLE 2 Active versus sham LF-rTMS for adolescent patients with FEDN depression: study-defined response and remission.

Study	Treatment outcomes	Defination	Active LF-rTMS group	Sham stimulation group	Findings
(29) (China)	Study-defined response	NR	NR	NR	NA
	Study-defined remission	NR	NR	NR	NA
(31) (China)	Study-defined response	Reduction from baseline of ≥ 50% in the HAMD total score	40.0% (12/30)	13.3% (4/30)	$P < 0.05$
	Study-defined remission	Reduction from baseline of ≥ 75% in the HAMD total score	13.3% (4/30)	3.3% (1/30)	$P > 0.05$
(30) (China)	Study-defined response	Reduction from baseline of ≥ 50% in the HAMD total score	46.7% (7/15)	0% (0/15)	$P < 0.05$
	Study-defined remission	Reduction from baseline of ≥ 75% in the HAMD total score	0% (0/15)	0% (0/15)	$P > 0.05$

FEDN = first-episode and drug-naïve; HAMD = Hamilton depression rating scale; NR = not reported; LF-rTMS = low-frequency repetitive transcranial magnetic stimulation.

adverse effects. The optimal parameters of LF-rTMS as a stand-alone treatment for FEDN MDD patients among children and adolescents remain unclear. Interestingly, a recent RCT found a significant superiority of Stanford neuromodulation therapy (SNT), a neuroscience-informed accelerated intermittent theta-burst stimulation protocol (90,000 total pulses), in improving depressive symptoms in adults with TRD when compared to sham stimulation (53). Thus, the efficacy and the safety of SNT for patients with MDD among children and adolescents should be examined. Fourth, all 3 RCTs (29–31) included in this study were conducted in China and involved only Chinese children and adolescents. Thus, the findings of the present study could not be generalizable to children and adolescents in other countries. Finally, this systematic review has not been registered.

Conclusion

These findings preliminarily found that LF-rTMS could benefit children and adolescents with FEDN MDD in a relatively safe manner, although further studies are warranted.

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.

Author contributions

X-JL and Z-JQ selected studies and extracted the data. WZ reviewed all the data and helped mediate disagreements, wrote the first draft. 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.2023.1111754/full#supplementary-material

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Severity related neuroanatomical and spontaneous functional activity alteration in adolescents with major depressive disorder

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Background: Major depressive disorder (MDD) is a disabling and severe psychiatric disorder with a high rate of prevalence, and adolescence is one of the most probable periods for the first onset. The neurobiological mechanism underlying the adolescent MDD remains unexplored.

Methods: In this study, we examined the cortical and subcortical alterations of neuroanatomical structures and spontaneous functional activation in 50 unmedicated adolescents with MDD vs. 39 healthy controls through the combined structural and resting-state functional magnetic resonance imaging.

Results: Significantly altered regional gray matter volume was found at broader frontal-temporal-parietal and subcortical brain areas involved with various forms of information processing in adolescent MDD. Specifically, the increased GM volume at the left paracentral lobule and right supplementary motor cortex was significantly correlated with depression severity in adolescent MDD. Furthermore, lower cortical thickness at brain areas responsible for visual and auditory processing as well as motor movements was found in adolescent MDD. The lower cortical thickness at the superior premotor subdivision was positively correlated with the course of the disease. Moreover, higher spontaneous neuronal activity was found at the anterior cingulum and medial prefrontal cortex, and this hyperactivity was also negatively correlated with the course of the disease. It potentially reflected the rumination, impaired concentration, and physiological arousal in adolescent MDD.

Conclusion: The abnormal structural and functional findings at cortico-subcortical areas implied the dysfunctional cognitive control and emotional regulations in adolescent depression. The findings might help elaborate the underlying neural mechanisms of MDD in adolescents.

KEYWORDS

thalamus, gray matter, premotor cortex, visual cortex, cortical thickness, anterior cingulate, ALFF, adolescent depression

1. Introduction

Major depressive disorder (MDD) is a chronic and debilitating neuropsychiatric disorder affecting populations worldwide and ranking as the leading cause of global disease burden (1). The estimated lifetime risk is from 15% to 18%, and adolescence, specifically mid-adolescence, is one of the most probable periods for the first episode onset. This period is also critically important for adolescent brain development. MDD is fundamentally

characterized by depressed mood and anhedonia with a lack of interest and activity. It also includes the emotional symptoms of persistent and pervasive feelings of worthlessness and guilt, and finally could even generate suicide ideation, plan, or attempt. The neurovegetative symptoms include fatigue or loss of energy, poor sleep quality, and decreased appetite and weight. Moreover, the neurocognitive symptoms include the diminished ability to think or concentrate and psychomotor retardation or agitation (2). The point rate of MDD in Chinese children and adolescents was 1.3%, according to a recent meta-analysis (3). Adolescent depression could generate negative outcomes such as poor educational outcomes, social impairment, insomnia, smoking, and substance use. Thus, the examination of neurobiological features is critical for later preventative measures implementation and appropriate mental health services.

Neuroimaging technique, such as magnetic resonance imaging (MRI), has provided a non-invasive way to gain insight into the brain's anatomical structures and neuronal functional activity. Structural MRI offers an effective way to investigate neuroanatomical structures, and the volumetric analyses of gray matter (GM) and surface calculation of cortical thickness (CT) are two main and reliable measurements used for research. In adolescent studies, neuroanatomical alterations at the frontal–limbic circuit have been implicated in the psychopathology of MDD. Specifically, compared to matched controls, adolescents with MDD were found to have regional cortical reductions in frontal areas, such as medial orbitofrontal and superior frontal gyrus, primary and higher order visual, somatosensory, and motor areas according to the study from ENIGMA working group (4). On the contrary, the thicker middle frontal and anterior cingulate cortex were also observed in MDD adolescents compared to controls, suggesting the developmental trajectory of the frontal lobe in adolescent MDD (5). Alongside the frontal lobe, the thinner cortical area at the left occipital area (precuneus and cuneus) was found in first-episode drug-naive adolescents with MDD (6). The temporal lobe morphology alteration of hippocampal and parahippocampal volumes was also reported in adolescent MDD (7–9). Furthermore, smaller volume at other subcortical nuclei, including the amygdala, thalamus, and nucleus accumbens, was found in depressed adolescents (10).

Resting-state functional MRI (rs-fMRI) is also a branch of technique widely used to evaluate brain neuronal activation. There are several rs-fMRI metrics used to reflect the brain functional activity such as the amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo). ALFF could reflect the intensity of regional spontaneous neuronal activity (11), while ReHo is an indicator of complexity and synchronicity of the neuronal activation (12). Previously, we have successfully applied the ALFF and ReHo analyses to detect the abnormality of neuronal activity in adult depression (13–15). Adolescent studies have suggested that depressive symptoms are associated with aberrant neural processing of reward (16, 17). Moreover, adolescent MDD was reported to have impaired functional activation associated with emotional processing, regulation, and memory (18). Furthermore, the other deficits in developing neural systems, such as visuospatial attention and sustained visual attention, in adolescent MDD patients were also suggested (19, 20).

Considering there is still a lack of consistent findings in adolescent MDD research, which is partly caused by the differences in research sample (i.e., medication) and imaging modality. Therefore, the present study aimed to provide a comprehensive clarification of the neural characteristics of unmedicated adolescent MDD through the application of both structural and functional analyses at the same time. First, we utilized voxel-based morphometry (VBM) to examine the subcortical structure of GM volume in adolescent MDD in comparison with healthy controls (HCs). Second, we used surface-based morphometry (SBM) to examine the CT in MDD patients compared with HC. Third, we also investigated the subcortical ALFF and ReHo as measurements of functional activity in MDD patients compared to HC. Finally, we calculated the surface ALFF and ReHo measurements and compared them between MDD and HC groups. Therefore, we hypothesized that there would be neuroanatomical and functional alterations in cortico-subcortical brain regions in adolescent MDD. Furthermore, we expected those brain morphometry characteristics to be correlated with clinical scores.

2. Materials and methods

2.1. Participants

A total of 66 adolescents with MDD were recruited from the Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University, China. The study was approved by the research Ethics Committee of the university. The experimental procedures were explained, and written informed consent was obtained from the adolescents and their caregivers. Inclusion criteria for MDD and HC groups involved the following: adolescents who are right-handed (determined by patient interview and parents' confirmation), aged between 13 and 18 years, with normal intelligence, and also having normal to corrected vision. The Structured Clinical Interview for Diagnostic and Statistical Manual IV (DSM-IV) Axis I disorder (SCID-I) was administered for the diagnosis of depressive disorder by two qualified psychiatrists. Exclusion criteria included adolescents with a psychiatric axis-I co-morbidity (i.e., anxiety disorder), a history of neurological diseases or seizures, a significant head injury or concussion, standard MRI contraindications, a history of substance/alcohol abuse or dependence, a history of psychiatric disorders or suicide among first-degree relatives, and other clinically relevant abnormalities based on the medical history or the laboratory examination. The severity of depression was measured on the day of MRI scanning using the 17-item Hamilton Depression Rating Scale (HDRS). In addition, 40 right-handed HC matched for gender, age, and education were recruited from the local community through advertisements. The subjects were screened with the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-NP). Subjects with a past or current DSM-IV axis-I diagnosis, neurological illness, a history of head trauma with loss of consciousness, and a history of

psychiatric disorders or suicidal behavior among first-degree relatives were excluded.

2.2. Imaging protocols

All MR images were acquired with a 3.0-T GE Signa HDxt (General Electric Healthcare, Chicago, Illinois, USA) scanner equipped with a standard eight-channel head coil. Contiguous sagittal T1-weighted images across the entire brain were acquired with a fast gradient echo (FGRE) sequence: time of echo (TE) = 3.1 msc, time of repetition (TR) = 8 msc, flip angle = 12°, the field of view (FOV) = 240 mm, voxel size = 0.938 × 0.938 × 1 mm^3, and no gap.

The rs-fMRI data were obtained using an echo-planar image (EPI) pulse sequence with the following parameters: 33 axial slices, TE = 40 msc, TR = 2,000 msc, in-plane resolution = 64 × 64 pixels, flip angle = 90°, FOV = 240 mm, voxel size = 3.75 × 3.75 × 4 mm^3, and no gap. A total of 240 time points were obtained over 8 min.

2.3. Data processing and analysis

2.3.1. Anatomical image processing

Both anatomical and functional image processings were conducted using DPABISurf, a toolbox offering a user-friendly interface for brain imaging data processing and analysis (21). The toolbox was executed in MATLAB (R2021b). For processing and analysis steps, default parameters following standard protocol were used. The images were resampled to the original size (i.e., 0.938 × 0.938 × 1 mm^3 for an anatomical image; 3.75 × 3.75 × 4 mm^3 for a functional image). The T1-weighted (T1w) image was corrected for intensity nonuniformity and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped. Furthermore, brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and GM was performed on the brain-extracted T1w.

Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1) (22), and the brain mask estimated previously was refined with a custom variation of the method to reconcile the derived segmentations of the cortical GM. Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through non-linear registration.

After the anatomical image was preprocessed, the volumetric GM and surface CT were smoothed using a Gaussian filter with a 6-mm full width at half maximum (FWHM).

2.3.2. Functional image processing

For each of the resting-state blood-oxygenation-level dependent (BOLD) signals per subject, the following preprocessing was performed. The first 10 volumes were removed, and then, a reference volume and its skull-stripped version were generated. The BOLD reference was then co-registered with the T1w reference. Head-motion parameters with respect to the BOLD reference are estimated. BOLD runs were slice-time corrected. The BOLD time series were then resampled to surface space (fsaverage5) and original volumetric space. The nuisance covariates of WM, CSF, and global signal as well as head motion were regressed. Principal components are estimated after high-pass filtering the preprocessed BOLD time series for the two component-based noise correction (CompCor) variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask, and the union of CSF and WM masks is calculated in the T1w space, after their projection to the native space of each functional run.

After the functional images were preprocessed, covariates nuisance was further regressed to acquire the subcortical ALFF/ReHo at volumetric space and cortical ALFF/ReHo at surface space. ALFF corresponds to the mean amplitude low-frequency fluctuation bands (0.01–0.1 Hz), and ReHo represents the homogeneity of a time course for a given voxel relative to that of the time courses of the 26 nearest neighboring voxels. Finally, those two metrics were smoothed through a Gaussian filter with a 6-mm FWHM.

2.4. Statistical analysis

Differences in those anatomical and rs-fMRI metrics between MDD patients and HC were assessed using statistical analysis in DPABISurf. To investigate GM volumetric changes in MDD patients, a two-sample *t*-test was used. Age, gender, and total intracranial volume were entered into the general linear model as covariates. An initial voxel-wise threshold was set at a *p*-value of <0.001 with a subsequent family-wise error (FWE) corrected *p*-value of <0.05 at the cluster level. Moreover, differences in the CT between groups were assessed with age and gender entered into the general linear model as covariates. An initial voxel-wise threshold was set at a *p*-value of <0.001. A threshold-free cluster enhancement (TFCE) approach was used to correct for multiple comparisons, and a significance threshold of $q < 0.025$ was used for each hemisphere.

Two-sample *t*-tests were also conducted to investigate the measurements of volumetric and cortical ALFF/ReHo between the MDD and HC groups. Together with the age and gender, the generated mean FD_Jenkinson value was included as covariance to control the head motion effects. An initial voxel-wise threshold was set at a *p*-value of <0.05, and with subsequent FWE corrected *p*-value of <0.05 at the cluster level for volumetric analyses. While for the surface analysis, an initial voxel-wise threshold was set at a *p*-value of <0.05. Still, a TFCE approach was used to correct for multiple comparisons, and a significance threshold of $q < 0.025$ was used for each hemisphere.

Furthermore, we extracted the mean value of GM volume, CT, ALFF, and ReHo of the significant clusters in both MDD and HC. *Post hoc* two-sample *t*-tests were carried out to compare the group differences. Moreover, correlation analyses were carried out to examine the relationship between those structural and functional

TABLE 1 Demographic and clinical characteristics of participants.

Measure (mean, S.D.)	MDD ($n = 50$)	HC ($n = 39$)	Statistics
Gender, *n*			
Female	39	26	[a]$p = 0.232$
Male	11	13	
Age, years	15.80 (1.43)	15.82 (1.89)	$t = 0.058$, $p = 0.95$
Education, years	9.84 (1.75)	9.92 (2.49)	$t = 0.19$, $p = 0.85$
*HDRS[b]	19.94 (5.72)	–	
Age of onset, years	14.77 (2.01)	–	
Course[c], months	14.62 (13.46)	–	
First episode, *n* (%)	48 (96%)	–	
Frequency	1.04 (0.20)	–	

*HDRS, hamilton depression rating scale.
[a]Indicates the chi-square test. [b]This calculation came from 44 MDD subjects.
[c]This calculation came from 46 MDD subjects.

measurements and clinical scores. The xjView toolbox (https://www.alivelearn.net/xjview) and DPABISurf_VIEW were used for later volumetric and surface imaging results visualization.

3. Results

3.1. Participants and clinical characteristics

In total, 66 patients with MDD and 40 HC were initially screened for inclusion in the study. A total of 16 MDD patients and one HC were excluded for missing and invalid imaging or demographics data, as well as taking medication, leaving 50 MDD patients (39 female patients/11 male patients, 15.80 ± 1.43 years old) and 39 HC (26 female/13 male patients, 15.82 ± 1.89 years old) to be included into the analysis. One subject with head motion larger than 3 mm translation and a 3-degree rotation was excluded from functional activity analysis. Among the MDD individuals, 96% of individuals were in the first episode of depression, and the average frequency was 1.04. A total of 46 MDD subjects with records of disease course were available, and the average score was 19.94, corresponding to moderate severity. In total, 46 MDD subjects with records, of course, were available, and the average course of MDD was 14.62 months. The demographic and clinical characteristics of these individuals are shown in Table 1.

3.2. Group comparison of GM volume

3.2.1. Increased GM volume in adolescent MDD

Significant differences were observed in regional GM volume between the MDD and HC groups. Compared to controls, MDD patients showed significantly increased GM volume in the right inferior temporal extending to the right parahippocampus and fusiform gyrus (peak value = 7.92; at [39, −5, −46]; k = 27,758 voxels), the left parahippocampus extending to the left hippocampus and fusiform gyrus (peak value = 7.33; at [−25, 3, −30]; k = 12,230 voxels), right precentral extending to the paracentral lobule (peak value = 7.09; at [41, −13, 65]; k = 13,489 voxels), the right orbital part of the inferior frontal (orbIFG) extending to the right insula and left caudate (peak value = 6.88; at [31, 36, −15]; k = 13,834 voxels), the left inferior temporal extending to middle temporal (mTG, peak value = 6.33; at [−56, −7, −32]; k = 15,996 voxels), the left paracentral lobule extending to precentral (peak value = 6.39; at [−14, −21, 79]; k = 6,487 voxels), the left insula extending to the left orbIFG (peak value = 5.97; at [−35, 21, −1]; k = 7,023 voxels), the left supplementary motor area (SMA, peak value = 5.84; at [−9, 12, 71]; k = 2,013 voxels), and the right SMA (peak value = 5.19; at [8, 10, 71]; k = 1,544 voxels) at a p-value of <0.001 (corrected) at cluster level (see Figure 1 and Table 2).

3.2.2. Decreased GM volume in adolescent MDD

Compared to HC, MDD patients were also found to have significantly decreased GM volume in the right thalamus extending to the left side (peak value = −6.40; at [−1, −22, −23]; k = 35,684 voxels), the right anterior cingulate cortex (ACC) extending to the middle cingulate cortex (MCC) (peak value = −6.83; at [17, 40, 18]; k = 13,965 voxels), the left superior frontal (SFG) extending to the middle frontal gyrus (MFG) (peak value = −6.35; at [−14, 52, 33]; k = 20,335 voxels), right postcentral extending to right supramarginal (peak value = −5.85; at [48, −19, 44]; k = 3,601 voxels), and the left cuneus extending to the left calcarine (peak value = −5.36; at [0, −84, 16]; k = 6,006 voxels) at a p-value of <0.001 (corrected) at the cluster level (see Figure 1 and Table 3).

3.3. Group comparison of CT

3.3.1. Decreased CT in adolescent MDD at the left hemisphere

Significant differences were observed in regional CT between the MDD and HC groups at both the left and right hemispheres. At left side, MDD patients showed a significantly decreased CT in the ***LIPd*** (peak value t = −5.70; at [−5, −53, 42]; k = 852 vertices), ***V3B*** (peak value t = −5.61; at [1, −89, 12]; k = 792 vertices), ***V2*** (peak value t = −6.27; at [23, −102, −4]; k = 644 vertices), ***RI*** (peak value t = −6.25; at [−21, −2, −7]; k = 472 vertices), area ***6a*** (peak value t = −5.39; at [2, 18, 59]; k = 302 vertices), area ***2*** (peak value t = −4.60; at [−1, −31, 61]; k = 272 vertices), area ***6a*** including the area ***6ma*** belonging to the paracentral lobular and mid cingulate cortex (PLMCC), area ***s6–8*** belonging to dorsolateral prefrontal cortex (DLPFC) (peak value t = −5.43; at [6, 39, 53]; k = 236 vertices), ***POS2*** (peak value t = −4.64; at [28, −70, 17]; k = 229 vertices), ***V4*** (peak value t = −5.17; at [−3, −102, −19]; k = 213 vertices), and ***FEF*** (peak value t = −5.05; at [−11, 22, 49]; k = 210 vertices) at a p-value of <0.001 (corrected) at cluster level (see Figure 2A and Table 4). While no significantly increased CT was found in adolescent MDD.

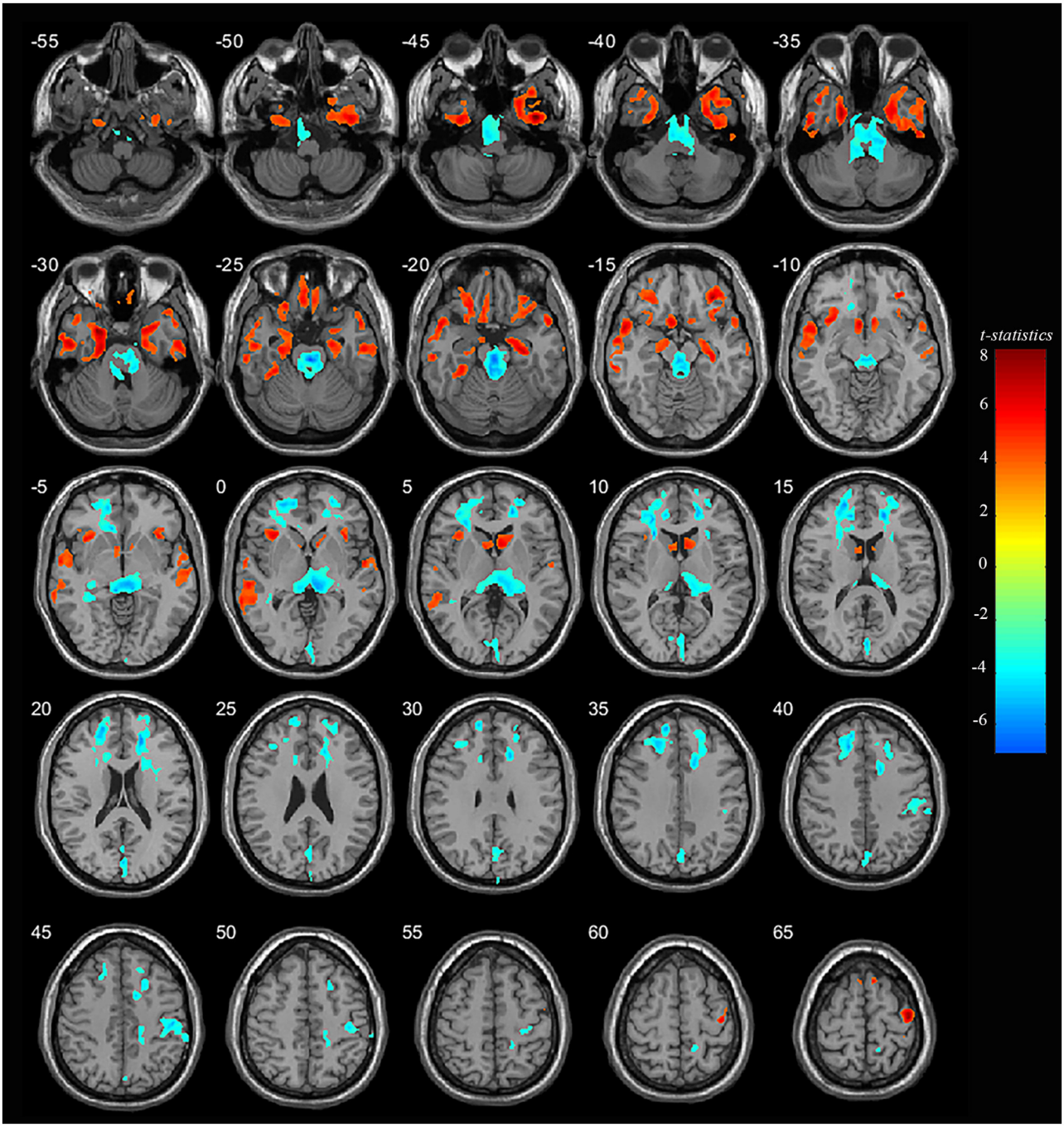

FIGURE 1
Adolescent MDD showed GM volume disturbances at broader frontal–temporal–parietal and subcortical brain areas. Compared to HC, adolescent MDD had significantly increased GM volume at the right inferior temporal including parahippocampal and fusiform gyrus, left parahippocampus extending to inferior temporal, left mTG, left insula extending to orbIFG, right orbIFG extending to the right insula and left caudate, bilateral paracentral lobule and SMA. Meanwhile decreased value was found at the bilateral thalamus, left SFG and MFG, bilateral cuneus, right ACC and MCC, right postcentral and precentral gyrus. The color bar depicts the t-statistics.

3.3.2. Decreased CT in adolescent MDD at the right hemisphere

In the right hemisphere, MDD patients also showed a significantly decreased CT in area ***6a*** including area ***FEF*** (peak value $t = -5.49$; at [0, 20, 56]; $k = 554$ vertices), ***V3B*** (peak value $t = -5.93$; at [−1, −87, 14]; $k = 414$ vertices), ***AIP*** (peak value $t = -4.91$; at [11, −29, 46]; $k = 309$ vertices), area ***6a*** including area ***i6–8*** and ***s6–8*** belonging to DLPFC (peak value $t = -4.53$; at [−5, 46, 49]; $k = 303$ vertices), ***V1*** (peak value $t = -6.17$; at [−22, −59, −15]; $k = 239$ vertices), ***7AL*** (peak value $t = -5.32$; at [−16, −51, 64]; $k = 213$ vertices), and ***V2*** (peak value $t = -4.74$; at [−26, −81, 5]; $k = 145$ vertices, respectively) at $p < 0.001$ (corrected) at the cluster level (see Figure 2B and Table 5). Moreover, no significantly increased CT was found in adolescent MDD.

TABLE 2 Locations of regional increased GM volume in the MDD group.

Region	MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous voxels)
	x	*y*	*z*		
MDD > HC					
R. Inferior temporal	39	−5	−46	7.92	27,758
R. Hippocampus	28	−18	−18	6.30	1,563
L. ParaHippocampus	−25	3	−30	7.33	12,230
R. Precentral	41	−13	65	7.09	13,489
R. Paracentral lobule	12	−25	80	6.81	1,073
R. orbIFG	31	36	−15	6.88	13,834
L. Caudate	−7	11	−12	6.14	1,311
R. Insula	33	22	−3	5.79	1,417
Inferior temporal	−−56	−7	−32	6.33	15,996
L. mTG	−60	−−26	1	5.65	7,077
L. Paracentral lobule	−14	−21	79	6.39	6,487
L. Precentral	−27	−16	75	5.30	1,108
L. Insula	−35	21	−1	5.97	7,023
L. orbIFG	−23	28	−23	5.85	2,735
L. SMA	−9	12	71	5.84	2,013
R. SMA	8	10	71	5.19	1,544

3.4. Group comparison of ALFF/ReHo measurement of functional activity

3.4.1. Increased ALFF in adolescent MDD

When comparing the ALFF measurement of functional activity, only a significant difference was observed in regional ALFF value at the surface space between the MDD and HC groups in the left hemisphere. MDD patients showed a significantly increased ALFF in ***9a*** belonging to the dorsolateral prefrontal cortex (DLPFC) and extending to ***9m*** belonging to the anterior cingulum (ACC) and medial prefrontal cortex (mPFC) (peak value $t = 3.00$; at [−23, 53, 20]; $k = 97$ vertices) at a p-value of <0.05 (corrected) at the cluster level (see Figure 3 and Table 6).

3.4.2. No significant differences in ReHo in adolescent MDD

When comparing the ReHo measurement of functional activity, no significant differences were found between the two groups.

3.5. Group comparison of signal from the region of interests and correlation with clinical scores

The *post hoc* analyses showed significant differences in signal from altered brain regions reported before between the MDD and HC groups (see details in Supplementary material). The altered measurements of the GM volume at several brain regions were found to correlate with HDRS scores. First, the mean GM at the left paracentral lobule was significantly higher in MDD patients (0.263 ± 0.027) compared to HC (0.215 ± 0.041) and positively correlated with HDRS scores ($N = 44$; $r = 0.307$, $p = 0.042$) (see Figure 4A). Second, the mean GM at right SMA was significantly higher in MDD patients (0.268 ± 0.015) compared to HC (0.246 ± 0.018), and it was also found positively correlated with HDRS scores ($N = 44$; $r = 0.362$, $p = 0.016$) (see Figure 4B). Moreover, the altered measurements of CT and ALFF at several brain regions were found to correlate with the course of MDD. The mean CT at ***6a*** was significantly lower in MDD patients (2.490 ± 0.251) compared to HC (2.774 ± 0.213), and it was positively correlated with the MDD course ($N = 46$; $r = 0.334$, $p = 0.023$) (see Figure 4C). Finally, the ALFF at left ACC and mPFC was found significantly higher in MDD patients (0.462 ± 0.412) compared to HC (0.181 ± 0.341), and it was negatively correlated with the course ($N = 46$; $r = -0.573$, $p < 0.0001$) (see Figure 4D).

4. Discussion

The present study examined the neuroanatomical morphometry including regional GM volume and CT and also measured the functional activation through ALFF and ReHo in adolescent MDD. Compared to healthy controls, altered GM volumes were found at frontal–temporal–parietal and subcortical brain areas involved with various information processing in adolescent MDD. Furthermore, thinner CT was observed at

TABLE 3 Locations of regional decreased GM volume in the MDD group.

Region	MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous voxels)
	x	*y*	*z*		
MDD < HC					
R. Thalamus	−1	−22	−23	−6.40	35,684
L. Thalamus	−13	−30	−2	−4.05	1,970
R. ACC	17	40	18	−6.83	13,965
R. MCC	15	22	32	−5.95	1,372
L. SFG	−14	52	33	−6.35	20,335
L. MFG	−22	51	14	−6.22	4,568
R. Postcentral	48	−19	44	−5.85	3,601
R. Supramarginal	60	−32	42	−4.49	685
L. Cuneus	0	−84	16	−5.36	6,006
L. Calcarine	1	−92	1	−4.79	2,471

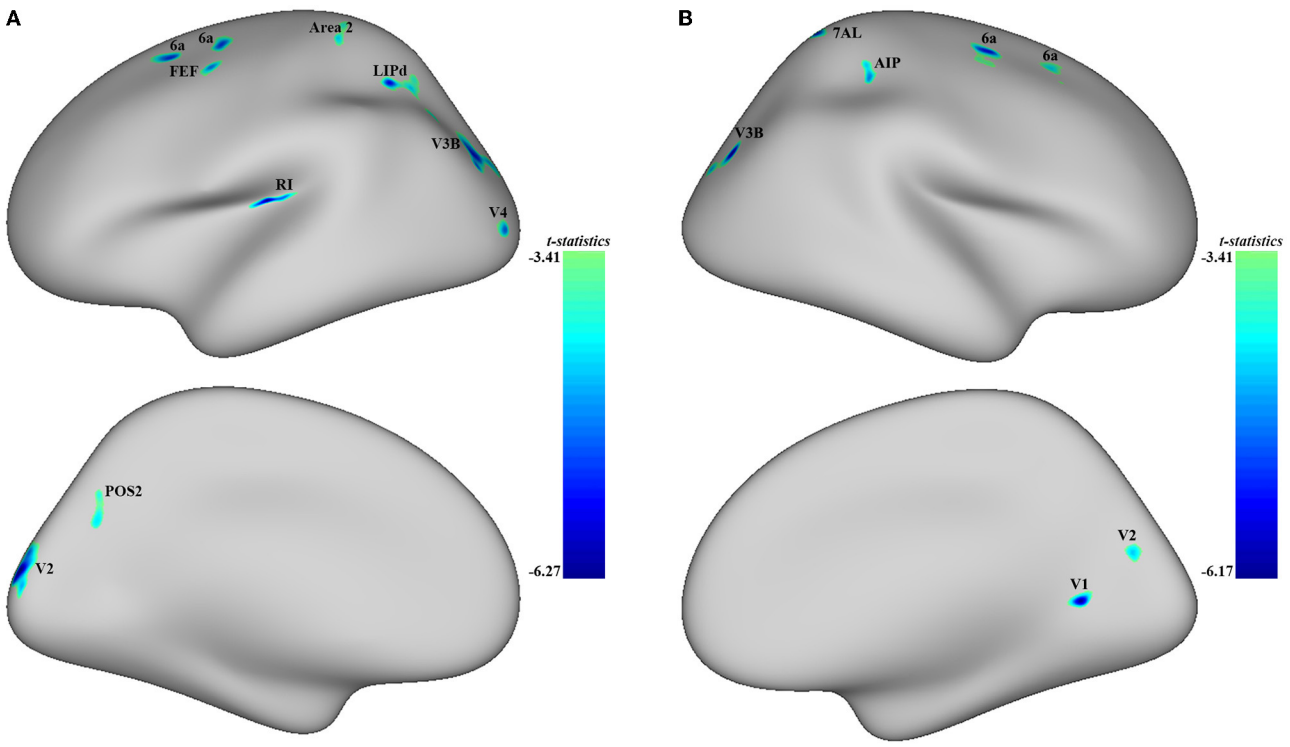

FIGURE 2
Adolescent MDD showed significantly decreased CT at both the left and right hemispheres. **(A)** Adolescent MDD showed significantly decreased CT value at several clusters including the LIPd (superior parietal cortex), V3B (dorsal stream visual cortex), V2 and V4 (early visual cortex), RI (early auditory areas), POS2 (posterior opercular cortex), and 6a and FEF (premotor cortex) at the left hemisphere. The color bar depicts the *t*-statistics; **(B)** Adolescent MDD showed a significantly decreased CT value at several clusters including the 6a (superior premotor subdivision), V3B (dorsal stream visual cortex), AIP and 7AL (superior parietal cortex), V1 (primary visual cortex), and V2 (early visual cortex) at the right hemisphere. The color bar depicts the t-statistics.

cortices responsible for visual and auditory processing and motor movements in adolescent MDD. Moreover, hyperactivity indicated by ALFF was found at ACC and mPFC extending to DLPFC cortices in adolescent MDD. Correlation analyses across those altered structural and functional features showed that increased GM volume at the left paracentral lobule and right SMA was positively correlated with HDRS scores. In the meantime, the thinner CT at the subdivision of the left superior premotor cortex

TABLE 4 Locations of regional decreased CT at the left hemisphere in the MDD group.

Region		MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous vertices)
HCP-MMP1.label	Yeo2011_7Networks	*x*	*y*	*z*		
MDD < HC						
LIPd	**7Networks_3**	−5	−53	42	−5.70	852
V3B	**7Networks_1**	1	−89	12	−5.61	792
V2	**7Networks_3**	23	−102	−4	−6.27	644
RI	**Medial wall**	−21	−2	−7	−6.25	472
6a, 100%	**7Networks_3**	2	18	59	−5.39	302
Area 2	**7Networks_2**	−1	−31	61	−4.60	272
6a, 92.7%	**7Networks_6**	6	39	53	−5.43	236
6ma, 3.4%	PLMCC					
s6–8, 3.4%	DLPFC					
POS2	**7Networks_7**	28	−70	17	−4.64	229
V4	**7Networks_1**	−3	−102	−19	−5.17	213
FEF	**7Networks_3**	−11	22	49	−5.05	210

TABLE 5 Locations of regional decreased CT at the right hemisphere in the MDD group.

Region		MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous vertices)
HCP-MMP1.label	Yeo2011_7Networks	*x*	*y*	*z*		
MDD < HC						
6a, 93.7%	**7Networks_3**	0	20	56	−5.49	554
FEF, 6.3%						
V3B	**7Networks_1**	−1	−87	14	−5.93	414
AIP	**7Networks_3**	11	−29	46	−4.91	309
6a, 53.8%	**7Networks_6**	−5	46	49	−4.53	303
i6–8, 33.3%	DLPFC					
s6–8, 12.2%	DLPFC					
V1	**7Networks_1**	−22	−59	−15	−6.17	239
7AL	**7Networks_3**	−16	−51	64	−5.32	213
V2	**7Networks_1**	−26	−81	5	−4.74	145

was found positively correlated with the course of MDD, while the hyperactivity at left ACC and mPFC was negatively correlated with the course.

4.1. Findings of neuroanatomical alterations and correlates in adolescent MDD

The inferior temporal cortex, the ventral pathway of the two major processing pathways conveying visual information, is crucial for the processing and storage of information about object detection (23, 24). The parahippocampus, located in the medial temporal, has been implicated in navigation and visual memory. A particular area within the parahippocampus named parahippocampal place area was found to represent places by encoding the geometry of the local environment, thus perceiving the local visual environment (25). The fusiform gyrus is a large region in the inferior temporal cortex that plays important roles in object and face recognition. The recognition of facial expressions is located in the fusiform face area, while bodies are selectively in the fusiform body area (26). A recent study has also reported increased functional connectivity between subdivisions of bilateral parahippocampal and right inferior temporal with frontal eye field in adolescent MDD (27). Thus, the increased GM volume found here might be suggestive of abnormal visual information processing that existed in an adolescent with depression.

The left mTG is within the neural pathway in the processing of both concrete and abstract words, underpinning the brain language understanding function (28). A recent meta-analysis regarding the neural correlates of neuroticism, an important factor for the development of MDD, has reported that spontaneous activity in the left mTG was positively correlated with neuroticism. It could reflect the negativity and instability of a highly neurotic individual's emotional experience (29). The orbIFG is closely connected with the lateral orbitofrontal cortex. The left orbIFG was reported higher activation to blend aromatic mixtures components in an odor configural experiment, implying its role as a mediator of configural percepts between temporal and orbitofrontal areas involved in configural memory processes (30). The caudate nucleus, a nucleus of the basal ganglia, is demonstrated to represent action-outcome contingencies sub-serving adaptable goal-directed behavior (31). The altered GM volume might suggest dysfunctional mediation and adaptation in adolescent MDD.

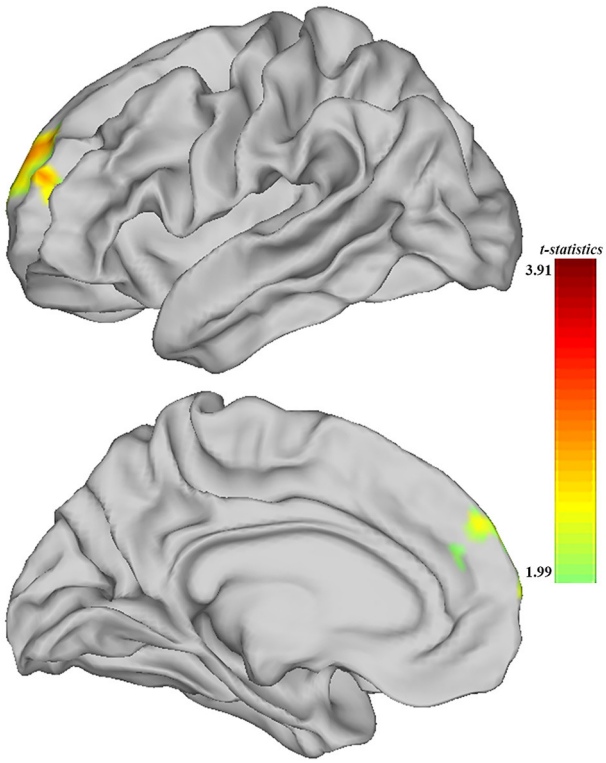

FIGURE 3
Adolescent MDD showed significantly increased ALFF of functional activation at ACC and DLPFC in the left hemisphere. The color bar depicts the *t*-statistics.

Evolved first as a motor–control region aligned with the sensory integration of olfactory-guided group behavior in mammals, the insula evolved later for cortical processing of homeostatic sensory activity in the individual animal. The insula is implicated in a wide range of conditions and behavior such as interoception, recognition, emotional awareness, decisions, cognitive control, and performance monitoring. The primary interoceptive representation of the physiological condition of the body is in the posterior insula, whereas the anterior insula contains interoceptive representations that substantialize all subjective feelings from the body and perhaps emotional awareness (32). In addition, it is part of an extended salience network, which is involved in the bottom–up detection of salient stimuli, interoceptive awareness for positive and negative internal states, and switching between emotional brain areas and more central executive regions. Insula abnormalities may reflect a disproportionate allocation of resources to the internal experience of negative self-focus thinking and emotional experience and a failure to switch to higher-order cognitive processes involved in the reappraisal of negative emotions and in allocating toward the external environment, which may, in turn, contribute to the development of MDD. The altered GM volume found here might reflect such negative self-focus thinking in adolescent MDD.

The paracentral lobule is a U-shaped convolution that loops below the medial part of the central sulcus and includes the motor and sensory areas for the lower limbs. The SMA is a portion of the premotor cortex located on the medial surface of the cortex anterior to the precentral sulcus. Consistent with our findings, a previous study has reported regional cerebral blood flow in the precentral gyrus in unmedicated first-episode MDD adolescents (33). As a key part of the medial premotor system, the SMA is suggested to play an important role in the development of the intention-to-act and the specification and elaboration of action through its mediation between the medial limbic cortex and the primary motor cortex (34). Thus, the positive correlation between the GM volume and depression severity might suggest the potential for paracentral lobule and SMA to serve as neural markers of depression in adolescents.

The thalamus, the largest subdivision of the diencephalon, plays an indispensable role in the modulations of messages involved in corticocortical processing (35). As it relays almost all sensory information except the olfactory, the thalamus is

TABLE 6 Locations of regional altered spontaneous functional activation in the MDD group.

Region		MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous vertices)
HCP-MMP1.label	Yeo2011_7Networks	*x*	*y*	*z*		
ALFF						
MDD > HC						
9a	**7Networks_7**	−23	53	20	3.00	97
9m	**7Networks_7**					

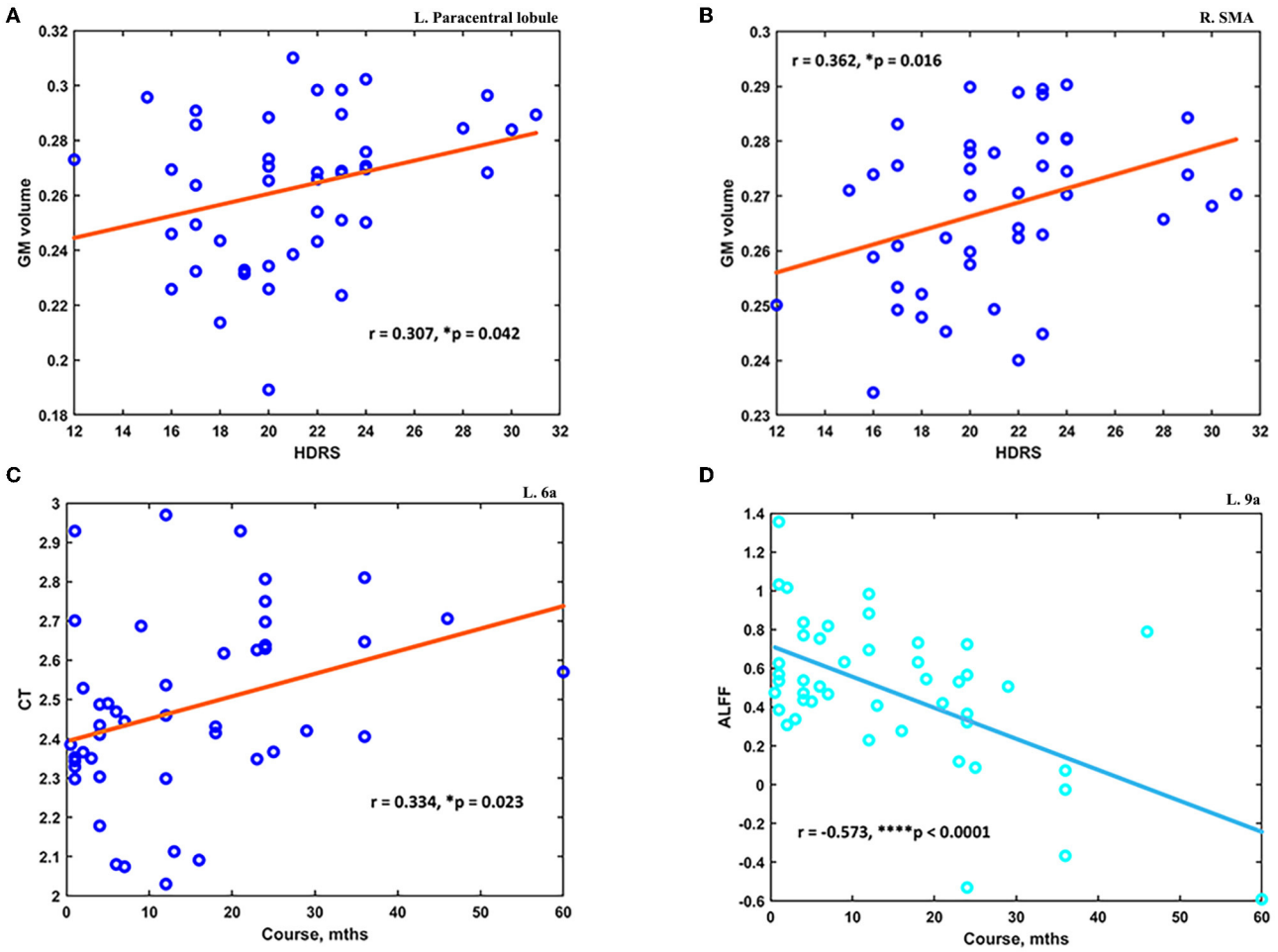

FIGURE 4
The altered measurements in adolescent MDD showed significant correlations with clinical scores. **(A)** The increased GM at the left paracentral lobule was positively correlated with HDRS scores ($N = 44$). **(B)** The increased GM at the right SMA was positively correlated with HDRS scores ($N = 44$). **(C)** The decreased CT value at the subdivision of the left superior premotor cortex was positively correlated with the course of MDD ($N = 46$). **(D)** The increased ALFF at left ACC and mPFC was found negatively correlated with the course of MDD ($N = 46$). $^{*}p < 0.05$; $^{****}p < 0.0001$.

involved in the process of functional activities such as sleep, memory, and motor. Moreover, through the regulation of hormone generation and release, the hypothalamic could regulate the neurovegetative systems. Therefore, the decreased GM volume at the thalamus might be the underlying neural mechanism of impaired information processing and neurovegetative symptoms in adolescent MDD. The decreased GM volume at MFG and SFG has been reported in previous studies on first-episode, medication-naive adult MDD patients (36–38). The volumetric differences of left MFG were found to be predictive of individual differences in cognitive control capacity (39), thus, suggesting its role in cognition processes. In line with the structural alteration, depressive patients were found to have a significantly lower response to reward stimulus in the MFG (40). The deficits of the GM volume in MDD patients implied dysfunctional cognitive and emotional control. Furthermore, the circuit composed of the medial dorsal thalamus and mPFC was identified to control depression-like behavior, and synaptic regulation of this thalamocortical circuit could elicit a decrease in despair-like behavior (41).

Hippocampus, located between the thalamus and medial temporal cortex, belongs to part of the limbic system. Converging evidence showed its role in the pathophysiology of MDD. The elevated glucocorticoid levels associated with MDD may negatively affect neurogenesis, causing excitotoxic damage or further key neurotrophins in the hippocampus (42). The cuneus is the gyrus immediately superior to the calcarine sulcus. It encompasses the primary visual cortex, the region receiving thalamocortical connections from the lateral geniculate nucleus of the thalamus. The left cuneus GM volume was found significantly associated with working memory performance (43). Thus, the decreased GM volume at those two structures might be the neural basis of impaired memory in adolescent MDD.

The ACC forms the anatomical circuit mediating the motivated behavior, and damage to this area would generate apathy (44). Patients are rarely moving, incontinent, drink, and eat only when

fed, and if speech occurs, it is limited to monosyllabic responses to others' questions. Furthermore, as subdivisions of the cingulum, the ACC is argued to be the affective division, and MCC to the cognitive division. The negative affect and cognitive control were reported to activate those anterior midcingulate cortex, and the areas constitute a hub where information can be linked to motor centers responsible for expressing affect and executing goal-directed behavior (45). Thus, decreased GM in those regions might impact the affective and cognitive processing in adolescent MDD. Furthermore, the postcentral and precentral gyrus are the somatosensory and motor cortex, which are responsible for sensorimotor interactions. The reduction of GM in those areas might suggest sensory and motor function deficits in adolescent MDD. Located in the inferior parietal, the supramarginal gyrus, especially the right side, is essential for visuospatial awareness. It was also found to have a negative correlation with neuroticism, and this area could help link the perception of socio-affective stimuli to emotions (29). The decreased GM found might imply the decreased awareness and perception in adolescent MDD.

The broad lower CT was found at the visual, motor, and superior parietal cortex at both hemispheres of the brain in adolescent MDD. V1 is the primary visual cortex, which is proposed to provide a saliency map with V1's output neurons firing rates increasing monotonically with the salience value of the visual input under a given visual scene (46). Furthermore, together with the early visual cortex, the activity in V1, V2, and V3 is demonstrated to sustain during the maintenance of attention in the absence of visual stimulation (47). The dorsal and ventral stream visual cortex commonly contribute to shape perception, and location processing was suggested to be essentially a function of the dorsal visual pathway (48).

Frontal eye fields, located anterior to area 4, are the origination of one of the five parallel neuroanatomical circuits implicated in psychiatric disorders (47). The primary motor cortex was suggested to share the role in the control of libs movement coordination with SMA (49). The premotor cortex was considered to play a role in the perception of speech, providing an internal motor simulation of the perceived phonemes (50). Lower CT was found at two subregions of the *6a* at both the left and right hemispheres. The first cluster peaked at *6a* and contains the areas belonging to the dorsal attention network, which is concerned with the orientation of one's focus to a specific task (51). The second cluster peaked at *6a* and contains subareas supporting cognitive control and decision-making processes (e.g., PLMCC, DLPFC) belonging to the frontoparietal network. Containing the subregions of the same *6a*, the frontoparietal network is anatomically positioned between components of the dorsal attention, and the hippocampal-cortical memory systems for information integration (52). The lower CT found at those two *6a* subregions might suggest the diminished cognitive processes in adolescent MDD. Furthermore, the positive correlation at the subregion belonging to the frontoparietal network could suggest such neurocognitive processing underlying adolescent MDD. Located between the two major sensory modalities of visual and somatosensory domains, the superior parietal cortex forms a bridge between them. The reduced CT found in those regions might suggest decreased visual attention and motor movements in adolescent MDD.

4.2. Findings of functional alterations and characteristics in adolescent MDD

DLPFC and ACC are the central nodes in the circuits mediating motivated behavior and executive control, respectively (44). The previous study reported that greater emotion dysregulation in school-age predicted alterations in connectivity between DLPFC and dorsal ACC in children with a history of depression (53). The higher brain activity in the DLPFC measured by ALFF was also reported in adolescent MDD (54). The reduced DLPFC in response to negative social status explained the positive correlation between self-reported social risk and depressive symptoms in youth, implying the DLPFC underlying the neural substrate of cognitive processing for emotion (55). In the same trend as our findings, adolescents with MDD were found to exhibit a higher connection of DLPFC and ACC with the subcortical insula (18). The increased activity found at ACC and DLPFC, and its negative correlation with MDD course might explain the rumination, impaired concentration, and physiological arousal in adolescent MDD.

The current study examined the neuroanatomical morphometry and functional activation alterations in adolescent MDD through volumetric and surface-based analyses. Broader changes in measurements were observed in cortico-subcortical brain areas. Some limitations existed in the current study. First, the findings were based on a sample size of 50 MDD patients, a large sample size could be carried out in the future to validate and replicate the findings. Furthermore, women were reported to be about two times as likely as men to develop depression and may have different clinical symptoms (56). Therefore, future studies with a large number of samples could be carried out to examine the alterations in women and men, respectively. Moreover, due to the limited records, we could not carry out the examinations of these measurements alterations' correlation with clinical symptoms. Thus, future studies with full-scale assessments of clinical severity or symptoms would benefit the interpretations. Moreover, growing evidence has shown DLPFC as a core brain hub of self-regulation, and it was newly reported to be the neural marker of grit, a psychological trait of perseverance and passion to pursue long-term goals (57). The altered neuronal spontaneous activity at DLPFC in adolescent MDD was found in this study, and it would be interesting to look into how its functional connection with other brain areas in future studies. Finally, MDD patients have a risk of suicide, previous studies have reported differences including decreased nodal efficiency of the GM network in the frontosubcortical circuit, and greater activity at ACC-DLPFC cortical attentional control circuitry in MDD patients with suicidality compared to MDD patients without suicidality (58, 59). Future studies would also examine the differences in adolescent MDD.

5. Conclusion

Combined MRI and fMRI, we demonstrated the morphometric and functional metrics alteration in adolescent MDD. Through whole-brain analyses, we detected GM volume changes in

broader frontal–temporal–parietal and subcortical brain areas. Specifically, the increased GM volume at the left paracentral lobule and right SMA was positively associated with depression severity. Furthermore, we found a lower CT in brain areas for visual and auditory processing as well as motor movements, and the subdivision of the superior premotor area was positively correlated with the MDD course. It suggested decreased visual attention and motor activity in adolescent MDD. Moreover, the functional activity measured by ALFF was found to be increased at ACC and mPFC, and this hyperactivity was negatively correlated with the course of MDD. It might suggest that rumination, impaired concentration, and physiological arousal existed in adolescent MDD. Altogether, our findings provided evidence of neuroanatomical and spontaneous functional activity disturbances in adolescent MDD and might help shed light on the underlying pathophysiology.

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 study was approved by the research Ethics Committee of the Chongqing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XZ: conceptualization, formal analysis, visualization, funding acquisition, writing—original draft, and writing—reviewing and editing. JCa: data curation and funding acquisition. QH: data curation and formal analysis. SH and LD: resources. XC, JCh, MA, YG, and JH: writing—reviewing and editing. LK: project administration, funding acquisition, and writing—reviewing and editing. All authors have 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1157587/full#supplementary-material

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Changes in microstates of first-episode untreated nonsuicidal self-injury adolescents exposed to negative emotional stimuli and after receiving rTMS intervention

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Background: Nonsuicidal self-injury (NSSI) is a common mental health threat in adolescents, peaking in adolescence with a lifetime prevalence of ~17%–60%, making it a high-risk risk factor for suicide. In this study, we compared changes in microstate parameters in depressed adolescents with NSSI, depressed adolescents, and healthy adolescents during exposure to negative emotional stimuli, and further explored the improvement of clinical symptoms and the effect of microstate parameters of repetitive transcranial magnetic stimulation (rTMS) in depressed adolescents with NSSI, and more evidence was provided for potential mechanisms and treatment optimization for the occurrence of NSSI behaviors in adolescents.

Methods: Sixty-six patients with major depressive disorder (MDD) exhibiting NSSI behavior (MDD+NSSI group), 52 patients with MDD (MDD group), and 20 healthy subjects (HC group) were recruited to perform neutral and negative emotional stimulation task. The age range of all subjects was 12–17 years. All participants completed the Hamilton Depression Scale, the Patient Health Questionnaire-9, the Ottawa Self-Injury Scale and a self-administered questionnaire to collect demographic information. We provided two different treatments to 66 MDD adolescents with NSSI; 31 patients received medication and completed post-treatment scale assessments and EEG acquisitions, and 21 patients received medication combined with rTMS and completed post-treatment scale assessments and EEG acquisitions. Multichannel EEG was recorded continuously from 64 scalp electrodes using the Curry 8 system. EEG signal preprocessing and analysis was performed offline, using the EEGLAB toolbox in MATLAB. Use the Microstate Analysis Toolbox in EEGLAB for segmentation and computation of microstates, and calculate a topographic map of the microstate segmentation of the EEG signal for a single subject in each dataset, and four parameters were obtained for each microstate classification: global explained variance (GEV), mean duration (Duration), average number of occurrences per second (Occurrence),

and average percentage of total analysis time occupied (Coverage), which were then statistically analyzed.

Results: Our results indicate that MDD adolescents with NSSI exhibit abnormalities in MS 3, MS 4, and MS 6 parameters when exposed to negative emotional stimuli compared to MDD adolescents and healthy adolescents. The results also showed that medication combined with rTMS treatment improved depressive symptoms and NSSI performance more significantly in MDD adolescents with NSSI compared to medication treatment, and affected MS 1, MS 2, and MS 4 parameters in MDD adolescents with NSSI, providing microstate evidence for the moderating effect of rTMS.

Conclusion: MDD adolescents with NSSI showed abnormal changes in several microstate parameters when receiving negative emotional stimuli, and compared to those not receiving rTMS treatment, MDD adolescents with NSSI treated with rTMS showed more significant improvements in depressive symptoms and NSSI performance, as well as improvements in EEG microstate abnormalities.

KEYWORDS

nonsuicidal self-injury, adolescents, repetitive transcranial magnetic stimulation, EEG microstates, emotional stimulation tasks

Introduction

Nonsuicidal self-injury (NSSI) is a common mental health problem in adolescents that peaks during adolescence (1). Studies have found that NSSI has a high lifetime prevalence ranging from ~17%–60% and a multifactorial etiology, including social factors, interpersonal stress, neurobiological background, emotional dysregulation, and traumatic childhood experiences (2). Notably, NSSI behaviors are associated with a large number of negative states, including high levels of negative emotions, interpersonal tension, and academic stress (3). NSSI behaviors, although not usually fatal, have been shown in both large cross-sectional and longitudinal studies to be at significantly increased risk for suicidal ideation and suicide attempts, particularly in recurrent NSSI (4–6). Repeated self-injury implies that adolescents with NSSI lack control over inappropriate or unwanted behavior, and this ability to control inappropriate or unwanted behaviors is inhibitory control. Previous research has demonstrated that inhibitory control is impaired in the context of negative emotions (7). Thus, exposure to negative emotional stimuli may lead to the occurrence of impulsive behaviors in adolescents, which include NSSI behaviors (8, 9). Therefore, a better understanding of NSSI in adolescents, early identification for prevention as well as timely intervention is crucial for current and future prediction of suicide risk (10).

However, there is a lack of research on the treatment of adolescents with NSSI, or those with other psychiatric disorders that frequently co-occur with NSSI (11). One study found the odds of co-existing depression in adolescents with NSSI of ~41.6% (12). In general, treatment for NSSI should always include interventions for other comorbid psychiatric disorders, if present. Much of the previous research has focused on psychotherapy and psychopharmacological treatment. However, because of the small number of published studies, no specific treatment has been established as superior or the treatment of choice at this stage (13). Because of the long duration of psychotherapy and the potential adverse effects of medication, treatment adherence is low among adolescents with NSSI. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulation technique, has shown good clinical efficacy in depression (14). A longitudinal study of rTMS for depressive disorders in adolescents and adults found higher rates of symptom improvement and remission in adolescent patients than in adults and no safety or tolerability issues (15). However, existing studies of rTMS for depression have focused more broadly on its effects on overall clinical outcomes, including changes in mood symptoms, rather than on its effects on impulsivity and self-injury (16). Notably, a recent consensus statement by a European expert group on rTMS did not even include self-injury as a short-term or long-term goal (17). Therefore, there is a need and an opportunity to correct this gap and translate cognitive neuroscience activities into treatment options. In a recent study involving 377 in patients treated with a 3-day intensive 10 Hz rTMS in the left dorsolateral prefrontal cortex (DLPFC), patients showed rapid improvement on the Beck Scale of Suicidal Ideation (BSSI) (18). Thus, it is reasonable to speculate that rTMS may be an effective treatment for nonsuicidal self-injury in adolescent depression.

Multichannel EEG is a powerful tool for exploring the spatiotemporal activity of the human brain and has been applied to study neural activity in the brain because of its advantage of displaying neurodynamic at high temporal resolution. Unlike traditional ERP analysis, microstate (MS) analysis (19) allows exploration and comparison of the activation of brain activity by precisely quantifying temporal features such as onset time or duration. Microstate analysis, a technique first proposed by Lehmann (20), utilizes the high temporal resolution of the EEG to segment the EEG signal into short continuous time segments characterized by a sub-steady state scalp topology corresponding to a consistent synchronous activation period of a large-scale neuronal network (21). Lehmann et al. propose the concept of microstates, as "thought atoms," which suggests that they are basic components of

information processing, whether generated spontaneously generated or in response to a stimulus (20). This view is consistent with the suggestion that neurocognitive networks evolve through a series of coordinated quasi-stable states rather than continuous neuronal activity (22). For stimulus-induced task microstates, each microstate represents a specific information processing step from perception to action (23). Based on this view, different methods have been used to objectively and automatically define different microstates using modules of the EEGLAB's Microstate Analysis Toolkit such as "Microstate Segmentation" and "Map Fitting" (24). These modules can also be used to statistically assess the specificity of certain microstates under given experimental conditions. Microstates can be measured quantitatively using metrics such as global explained variance, mean duration, frequency of occurrence per unit time, and temporal coverage. We anticipate that microstate analysis may provide new perspectives or evidence for identifying biomarkers in adolescents with NSSI or to understand the potential mechanisms of rTMS in treating the adolescent population with NSSI.

Therefore, this study aimed to address the following questions: (1) how do the microstate characteristics of adolescents with NSSI change after exposure to negative emotional stimuli? and (2) how does rTMS treatment affect the microstate characteristics of adolescents with NSSI? Addressing these questions will provide new insights into the neural basis of NSSI behavior in adolescence and potential markers for development of effective treatment modalities.

Methods

Participants

This study included 20 healthy subjects (HC group, 8 males, 12 females, mean age: 15.45 years), 52 adolescents with depression (MDD group, also as a patient control group, 20 males, 32 females, mean age: 15.31 years), and 66 MDD adolescents with NSSI (MDD + NSSI group, 12 males, 54 females, mean age: 14.33 years). These patients were recruited from the outpatient and inpatient wards of the First Affiliated Hospital of Chongqing Medical University and the University City Hospital of Chongqing Medical University. All patients were diagnosed with major depressive disorder according to the ICD-10 diagnostic criteria. NSSI was determined based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (25) diagnostic criteria for nonsuicidal self-injury and the Ottawa Self-Injury Scale (26). Healthy subjects were recruited from secondary schools and matched as closely as possible to the patient group in terms of sex and age. All participants were fully informed of the procedures and purpose of the study and provided written consent before the start of the study. All procedures met ethical standards and were approved by the Ethics Committee of Chongqing Medical University. All subjects were right-handed, with normal or corrected vision and normal hearing. Exclusion criteria included history of neurological or other psychiatric disorders other than depression, history of chronic substance use, learning disabilities, and head injury resulting in loss of consciousness. Before conducting the experiment, all subjects were interviewed using the MINI-International Neuropsychiatric Interview (M.I.N.I. KID 5.0) (27), followed by a scale assessment by two trained psychiatrists.

Questionnaires

All participants completed the Hamilton Depression Scale (HAMD-17) (28) and the Patient Health Questionnaire-9 (PHQ-9) (29) to determine participants' levels of depressive symptoms, and the Ottawa Self-Injury Scale to determine details of the severity of self-injury behaviors. In addition, all participants completed a self-administered questionnaire to collect demographic information.

Negative emotional stimuli task

Stimuli

The stimuli selected in this study were emotional face pictures, including one neutral emotional picture and eight different negative emotional pictures. The different negative emotional pictures were used to avoid the confounding repetitive effects of the stimuli. Both the neutral and negative emotional pictures were selected from the Chinese Facial Affective Picture System (CFAPS) (30), which controls the arousal, luminance, color, and other relevant attributes of the emotional pictures using standardized set of stimuli. All images were identical in size and resolution.

Procedure

Participants, seated at ~60 cm from a computer screen, were presented with a stimulus task with E-Prime 3.0. Both neutral and negative emotional stimuli task were used in our study. The task is shown in Figure 1A.

Briefly, all emotional pictures were presented on a black background. By randomly disrupting the presentation of the stimuli, all emotional pictures appeared a total of 200 times, including 150 times for neutral emotional picture 50 times for negative emotional picture. To control the effect of onset, at the beginning of each stimulus presentation, a fixed intersection of randomly selected durations of 500–1000 ms was initially presented on the computer screen, followed by a blank screen for 300 ms. Subsequently, a randomly presented emotion pictures were randomly presented for a duration of 1000 ms before disappearing or ending early based on the participant's response. Finally, a blank screen was presented again for 1000 ms on the computer screen. Participants were asked to press either "1" button when presented with a neutral emotion picture or the "2" button when presented with a negative emotion as quickly and accurately as possible. Participants were required to achieve at least 80% accuracy in the exercise before the start of the formal trial.

EEG acquisition, preprocessing, and EEG segmentation

Multichannel EEG was recorded continuously from 64 scalp electrodes using the Curry 8 system. For accurate measurement, these electrodes were placed according to the international 10/20 system. One vertical EEG electrode was placed above and below the left eye and one horizontal EEG electrode was placed at the orbital canthus of the left and right eyes to allow for monitoring of eye movements and subsequent removal of eye movement artifacts from the recordings. All channels were digitally sampled at 1000 Hz and the reference electrode between Cz and Cpz was chosen as an online reference. Bandpass filtering was set to 0.5–80 Hz. Data acquisition did not start until all impedance values were below 5 kΩ.

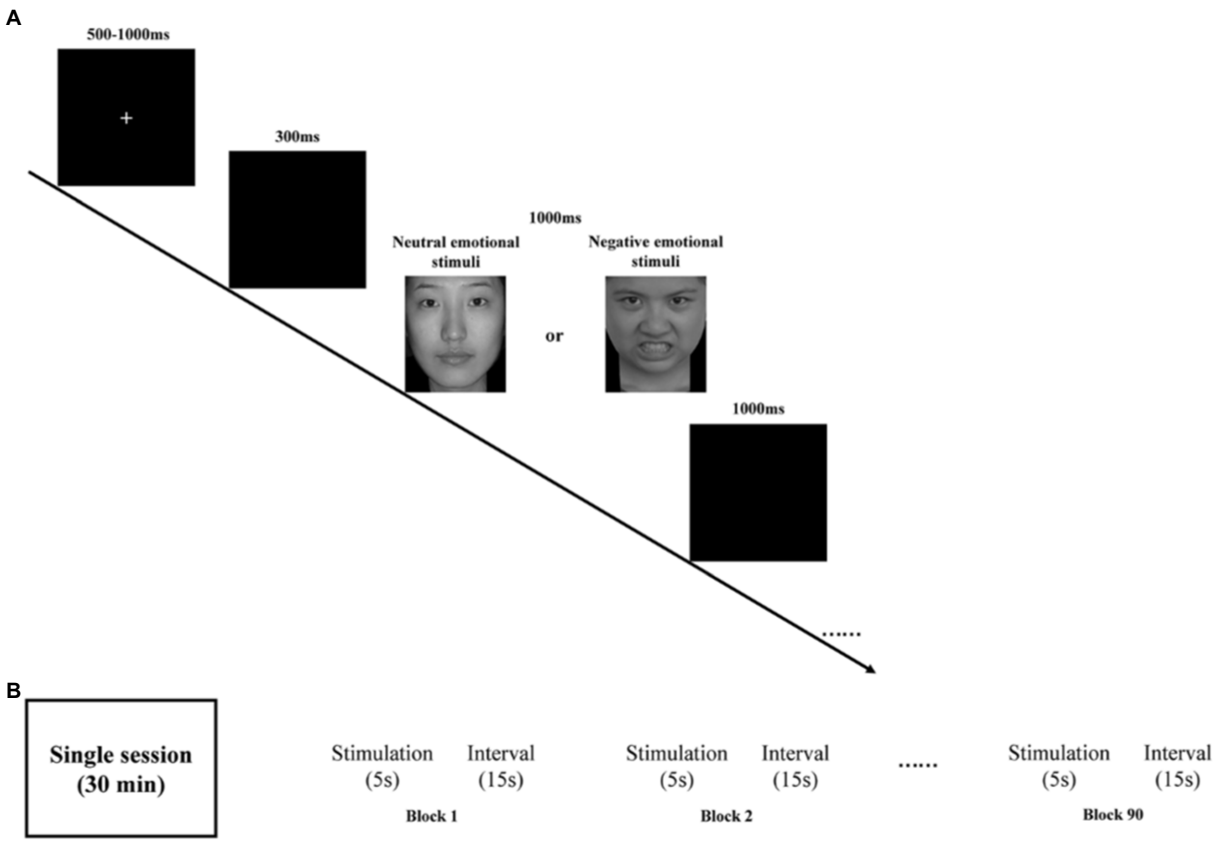

FIGURE 1
(A) Schematic illustration of the experimental procedure and examples of stimuli. **(B)** *r*TMS program: each session is 30min and consists of 90 blocks. Each block has 5s stimulation and 15s stimulus intervals.

EEG signals were preprocessed and analyzed offline using the EEGLAB toolbox in MATLAB (31). First, to obtain cleaner and accurate data, we resampled all EEG data with the sampling rate set to 500 Hz and performed secondary filtering with the frequency range set to 0.1–30 Hz. Useless electrodes such as EKG, EMG, CB1, and CB2 were also removed. The data were reviewed to remove incorrect responses as well as non-responsive time segments, retaining only those with correct responses. Subsequently, the EEG data were re-segmented to generate segments, each comprising 200 ms before and 1000 ms after stimulation. Segments with large artifacts were rejected and poor channels were interpolated. Independent component analysis (ICA) was used to remove artifact components, mainly including blinks, horizontal eye movements, and muscle artifacts (32). To identify individual responses to emotional stimuli, EEG data segments were selected for all correct responses to negative emotional stimuli and the EEG data for this condition were averaged to obtain the mean EEG signal for each subject. The average difference waveforms on the midline electrodes were also plotted for comparison with the EEG microstate classification (Figure 2).

EEG microstate segmentation and computation

Microstate analysis was performed using the Microstate analysis toolbox (33) in EEGLAB. First, we used the toolbox to load the pre-processed EEG data into EEGLAB and examined the data structure bodies. The average EEG signal was obtained by averaging all channel EEG data for each subject across periods and then normalizing the data. Subsequently, the mean EEG signal was segmented for microstates. A prototype topographic map of the EEG signal was determined using the k-means clustering algorithm. The k-means clustering analysis is a classical pattern recognition method, involving an iterative process that starts with an initial guess of the map and terminates when the differences are negligible in successive iterations (34). Because of differences in the number of iterations, the results of k-means clustering analysis may differ slightly from one run to another. It is not recommended to set the number of iterations too low. Therefore, the number of iterations of k-means in this study was set to 1000. The optimal number of topographic maps calculated, i.e., the microstate classification, was also determined using the cross-validation method (CV) and the global explained variance (GEV). The larger the GEV and the smaller the CV, the better the microstate classification (33). The number of microstate classifications was plotted (Figure 3). The determined microstate classification topographies were fitted to each subject's EEG signal to calculate a topographic map of the microstate segmentation of the EEG signal for a single subject in each dataset. In addition, global explained variance ("GEV"), mean duration ("Duration"), average number of occurrences per second ("Occurrence"), and average percentage of total analysis time occupied ("Coverage") for the four microstate parameters were determined as follows:

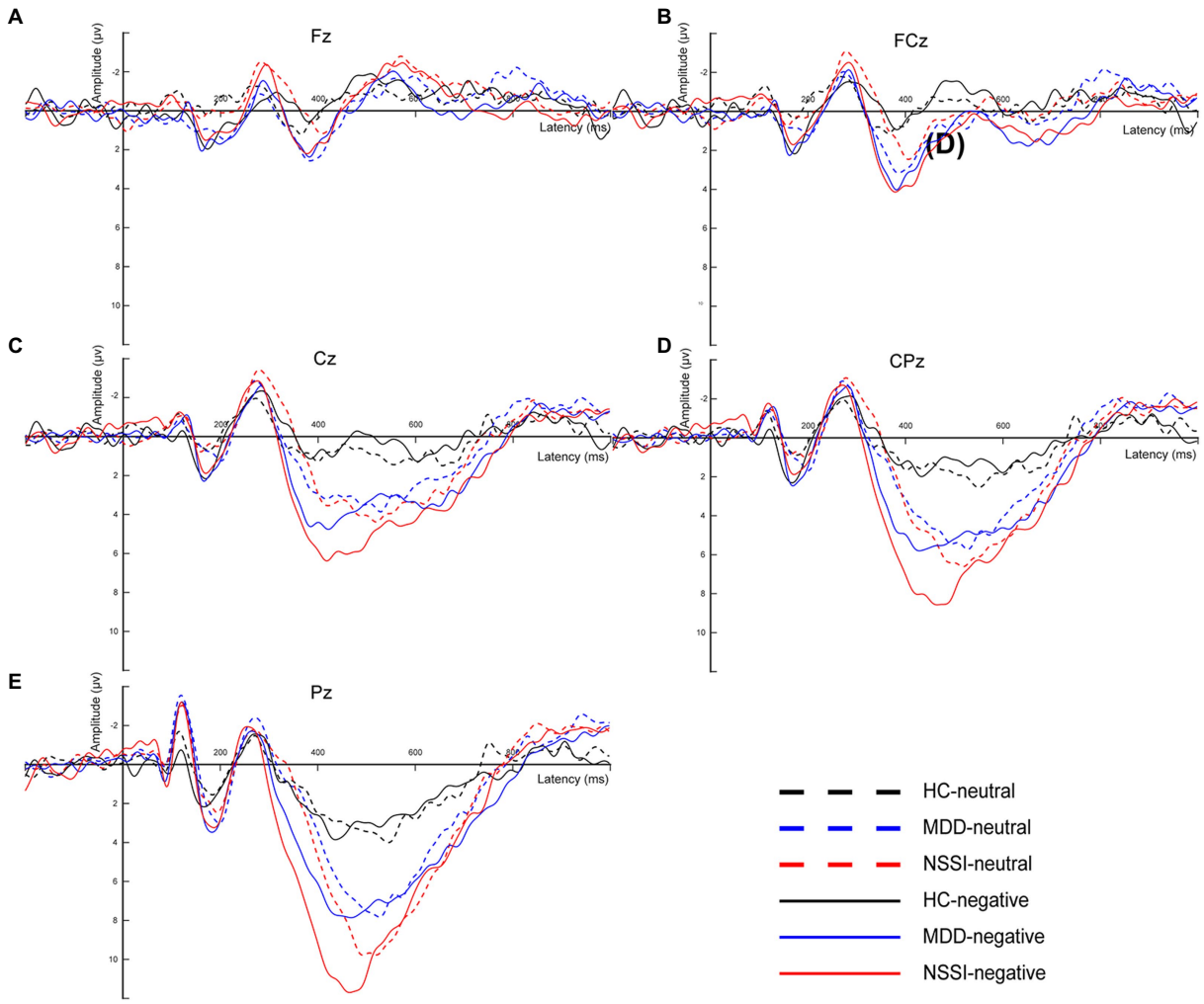

FIGURE 2
(A) The average difference waveforms at Fz electrode under neutral and negative emotional cues in the HC, MDD and MDD+NSSI groups. **(B)** The average difference waveforms at FCz electrode under neutral and negative emotional cues in the HC, MDD and MDD+NSSI groups. **(C)** The average difference waveforms at Cz electrode under neutral and negative emotional cues in the HC, MDD and MDD+NSSI groups. **(D)** The average difference waveforms at CPz electrode under neutral and negative emotional cues in the HC, MDD and MDD+NSSI groups. **(E)** The average difference waveforms at Pz electrode under neutral and negative emotional cues in the HC, MDD and MDD+NSSI groups. HC, healthy control; MDD, major depressive disorder; MDD+NSSI, MDD with nonsuicidal self-injury.

(1) GEV: the sum of the explained variance, weighted by the global field power at each moment.
(2) Duration: the average time a single microstate was classified as present.
(3) Coverage: the percentage of time covered by a single microstate classification.
(4) Occurrence: the number of occurrences of a single microstate classification per unit time.

Treatment

We treated 66 MDD adolescents with NSSI for 8 weeks. Among them, 41 patients received medication only and 25 patients received medication combined with rTMS. Scale assessments and EEG data collection were repeated for these participants at the end of treatment. However, 14 treated adolescents were unable to complete the post-treatment scale assessment and EEG collection and were therefore excluded from the data set. Ultimately, 31 patients completed medication follow-up and 21 patients completed medication combined with rTMS treatment follow-up.

The medication of choice was selective serotonin reuptake inhibitors (SSRIs), such as sertraline, at a therapeutic dose of 150 mg/day. The widely recognized figure-of-eight coil was used for rTMS treatment targeting the left dorsolateral prefrontal cortex region. The following simulation parameters (Figure 1B) were used: location (left DLPFC, EEG International 10–20 system, F3 electrode), intensity (100% of individual resting motor threshold), stimulation frequency (10 Hz), 4500 stimulations per session (90 blocks, 50 trains), single train duration (5 s), inter-train interval (15 s), and stimulation period (once per day, 5 days per week for 4 weeks). These parameters are consistent with published safety guidelines for rTMS (35, 36).

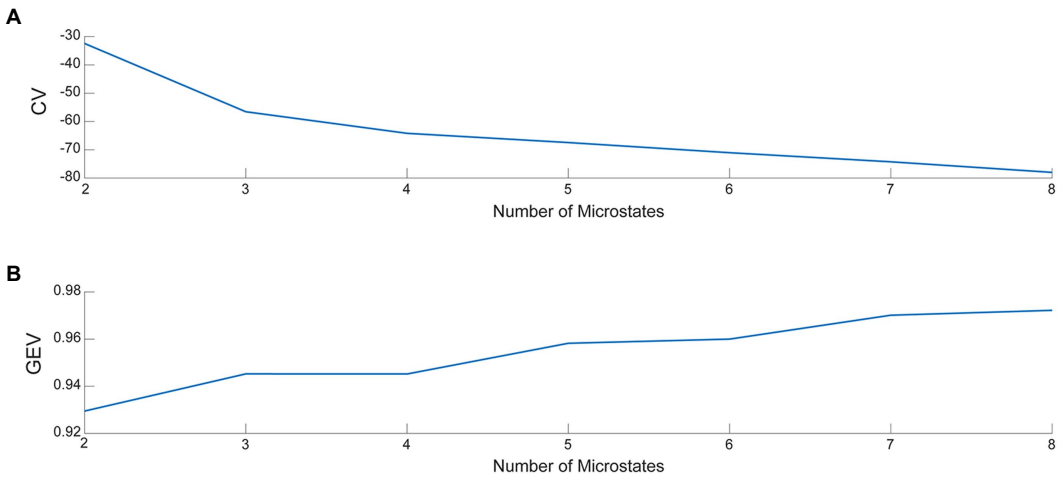

FIGURE 3
(A) The value of CV for various microstate classifications. **(B)** The value of GEV for various microstate classifications.

Data analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. We first conducted cross-sectional analyses using ANOVA or Chi-square tests for demographic data of participants in each group, one-way ANOVA for scale data of participants in each group, and 2×3 repeated-measures ANOVA for microstate parameters, where emotional cues were used as within-group factors (two levels: neutral emotional cues, negative emotional cues) and group as between-group factors (three levels: HC group, MDD group, MDD+NSSI group). Then, we performed a 2×2 repeated-measures ANOVA on the scale data of participants in the MDD+NSSI group who received medication treatment or medication combined with rTMS treatment where treatment time was used as a within-group factor (two levels: before treatment, after treatment) and treatment method as a between-group factor (two levels: medication treatment, medication combined with rTMS treatment); a 2×2×2 repeated-measures ANOVA was performed on microstate parameters, where emotional cues were used as within-group factor 1 (two levels: neutral emotional cues, negative emotional cues), treatment time was used as a within-group factor 2 (two levels: before treatment, after treatment), and treatment method as a between-group factor (two levels: medication treatment, medication combined with rTMS treatment). All significant interaction effects were further analyzed using simple effects analysis. Post-hoc comparison was performed for significant main or between-group effects using the Bonferroni–Holm method. In cases where sphericity could not be assumed, statistical values were reported using the Greenhouse–Geisser correction. The alpha level of significance was set at $p<0.05$.

Results

Cross-sectional analysis

Demographic and baseline clinical characteristic

The demographic and clinical characteristics of the three groups at the baseline are shown in Table 1. Age and sex were significantly different in the three groups ($p=0.002$, $p=0.025$). Subsequently, to control for the effects of age and sex, age and sex were used as covariates in the follow-up microstate analysis. There were significant group differences in the HAMD and PHQ-9 scores (all $p<0.001$). Compared with HCs, participants with MDD and MDD+NSSI had significantly higher levels of depression (all $p<0.001$). The NSSI characteristics, including NSSI numbers, NSSI first onset age and NSSI types, of the participants in the MDD+NSSI group are shown in Table 1.

Microstate parameters

When age and gender were included as covariates, the ANOVA results (see Table 2; Figure 4) showed that GEVs of all three groups were above 79%, which was highly explainable. There was a significant between-group main effect ($F(2, 133)=6.742$, $p=0.002$, $\eta_p^2=0.092$) for MS 3 duration, a significant cue × group interaction effect ($F(2, 133)=5.246$, $p=0.006$, $\eta_p^2=0.073$) and a significant between-group main effect ($F(2, 133)=9.746$, $p<0.001$, $\eta_p^2=0.128$) for MS 3 coverage; and there was a significant cue×group interaction effect ($F(2, 133)=3.369$, $p=0.037$, $\eta_p^2=0.048$) and a borderline significant between-group main effect ($F(2, 133)=2.935$, $p=0.057$, $\eta_p^2=0.042$) for MS 4 coverage, and a significant cue×group interaction effect ($F(2, 133)=5.669$, $p=0.004$, $\eta_p^2=0.079$) and a significant between-group main effect ($F(2, 133)=6.640$, $p=0.002$, $\eta_p^2=0.091$) for MS 4 occurrence; and there was a significant between-group main effect ($F(2, 133)=5.263$, $p=0.006$, $\eta_p^2=0.073$) for MS 6 duration, a significant cue×group interaction effect ($F(2, 133)=4.547$, $p=0.012$, $\eta_p^2=0.064$) and a significant between-group main effect ($F(2, 133)=10.191$, $p<0.001$, $\eta_p^2=0.133$) for MS 6 coverage, and a borderline significant between-group main effect ($F(2, 133)=2.901$, $p=0.058$, $\eta_p^2=0.042$) for MS 6 occurrence. No cue main effect, between-group main effect, or cue×group interaction effect was found for any of the other microstates.

The results of further simple effects analysis showed that the MS 3 duration and coverage in the MDD+NSSI group under negative emotional cues were significantly greater than those in the HC group (224.472±64.911 vs. 152.192±75.408, 0.448±0.094 vs. 0.307±0.124, all $p<0.05$), and greater than in the MDD group, but the latter difference was not significant. And the MS 3 duration and coverage under negative emotional cues in the MDD+NSSI group were significantly greater than those under neutral emotional cues

TABLE 1 Demographic and clinical characteristics of participants in the three groups at the baseline.

	HC group (n=20) $M\pm SD$	MDD group (n=52) $M\pm SD$	MDD+NSSI group (n=66) $M\pm SD$	F/χ^2	p value
Age (years)	15.45 ± 2.282	15.31 ± 1.449	14.33 ± 1.601	6.464	**0.002**
Sex (male/female)	8/12	20/32	12/54	7.190	**0.025**
HAMD scores	1.30 ± 1.809	22.62 ± 3.448	23.14 ± 4.220	295.378	**<0.001**
PHQ-9 scores	1.50 ± 2.115	19.60 ± 3.610	20.14 ± 3.586	246.842	**<0.001**
NSSI number	/	/	10.26 ± 3.763		
NSSI first onset age	/	/	12.77 ± 1.644		
NSSI type					
Cutting			66/66		
Pinching			13/66		
Biting			4/66		
Knocking			10/66		
Burning			1/66		

HC, healthy controls; MDD, major depressive disorder; MDD + NSSI, MDD with nonsuicidal self-injury; HAMD, Hamilton Depression Scale; PHQ-9, Patient Healthcare Questionnaire. The bolded p values indicate statistical significance. We bolded for greater visibility.

TABLE 2 Microstate parameters of HC group, MDD group, and MDD+NSSI group exposed to neutral emotional cues and negative emotional cues.

Microstate parameters			HC group (n=20) $M\pm SD$	MDD group (n=52) $M\pm SD$	MDD+NSSI group (n=66) $M\pm SD$	Cue main effect $F(p)$	Between-group main effect $F(p)$	Cue×Group interaction effect $F(p)$
GEV		Neutral	0.824 ± 0.071	0.802 ± 0.121	0.819 ± 0.068	1.028 (0.312)	0.798 (0.452)	0.135 (0.874)
		Negative	0.821 ± 0.073	0.793 ± 0.123	0.814 ± 0.068			
Duration	MS3	Neutral	154.558 ± 63.305	191.082 ± 88.582	205.392 ± 76.819	0.126 (0.723)	6.742 (**0.002**)	0.596 (0.553)
		Negative	152.192 ± 75.408	212.864 ± 80.701	224.472 ± 64.911			
	MS6	Neutral	102.350 ± 73.351	96.531 ± 74.048	75.273 ± 49.292	0.015 (0.903)	5.263 (**0.006**)	1.494 (0.228)
		Negative	136.625 ± 82.443	95.571 ± 67.874	85.697 ± 64.675			
Coverage	MS3	Neutral	0.346 ± 0.109	0.372 ± 0.125	0.413 ± 0.093	0.132 (0.717)	9.746 (**<0.001**)	5.246 (**0.006**)
		Negative	0.307 ± 0.124	0.426 ± 0.094	0.448 ± 0.094			
	MS4	Neutral	0.082 ± 0.073	0.091 ± 0.051	0.107 ± 0.055	2.404 (0.123)	2.935 (**0.057**)	3.369 (**0.037**)
		Negative	0.081 ± 0.051	0.064 ± 0.050	0.098 ± 0.055			
	MS6	Neutral	0.145 ± 0.107	0.144 ± 0.114	0.103 ± 0.076	0.090 (0.765)	10.191 (**<0.001**)	4.547 (**0.012**)
		Negative	0.202 ± 0.122	0.122 ± 0.081	0.091 ± 0.070			
Occurrence	MS4	Neutral	0.875 ± 0.504	1.058 ± 0.574	1.212 ± 0.550	0.126 (0.723)	6.640 (**0.002**)	5.669 (**0.004**)
		Negative	1.125 ± 0.677	0.769 ± 0.518	1.174 ± 0.506			
	MS6	Neutral	1.417 ± 0.979	1.314 ± 0.953	1.212 ± 0.803	0.001 (0.973)	2.901 (**0.058**)	1.298 (0.277)
		Negative	1.542 ± 0.867	1.330 ± 0.966	0.960 ± 0.571			

The bolded p values indicate statistical significance. We bolded for greater visibility.

(224.472 ± 64.911 vs. 205.392 ± 76.819, 0.448 ± 0.094 vs. 0.413 ± 0.093, all $p < 0.05$). The MS 4 coverage and occurrence in the MDD + NSSI group under negative emotional cues were significantly greater than those in the MDD group (0.098 ± 0.055 vs. 0.064 ± 0.050, $p = 0.002$; 1.174 ± 0.506 vs. 0.769 ± 0.518, $p < 0.001$) and greater than those in the HC group, but the differences compared with the HC group were not statistically significant. In addition, the MS 6 duration, coverage, and occurrence in the MDD + NSSI group under negative emotional cues were significantly lower than those in the HC group (85.697 ± 64.675 vs. 136.625 ± 82.443, $p = 0.005$; 0.091 ± 0.070 vs. 0.202 ± 0.122, $p < 0.001$; 0.960 ± 0.571 vs. 1.542 ± 0.867, $p = 0.007$), and the MS 6 coverage and occurrence in the MDD + NSSI group were significantly lower than those in the MDD group (0.091 ± 0.070 vs. 0.122 ± 0.081, $p = 0.032$; 0.960 ± 0.571 vs. 1.330 ± 0.966, $p = 0.022$), and the MS 6 occurrence under negative emotional cues in the MDD + NSSI group was significantly lower than those under neutral emotional cues (0.960 ± 0.571 vs. 1.212 ± 0.803, $p = 0.038$).

Longitudinal analysis

Changes in HAMD scores, PHQ-9 scores, and NSSI scores after receiving different interventions in the MDD+NSSI group

A repeated-measures ANOVA (see Table 3) on depression scores and NSSI scores in the MDD + NSSI group, using treatment method

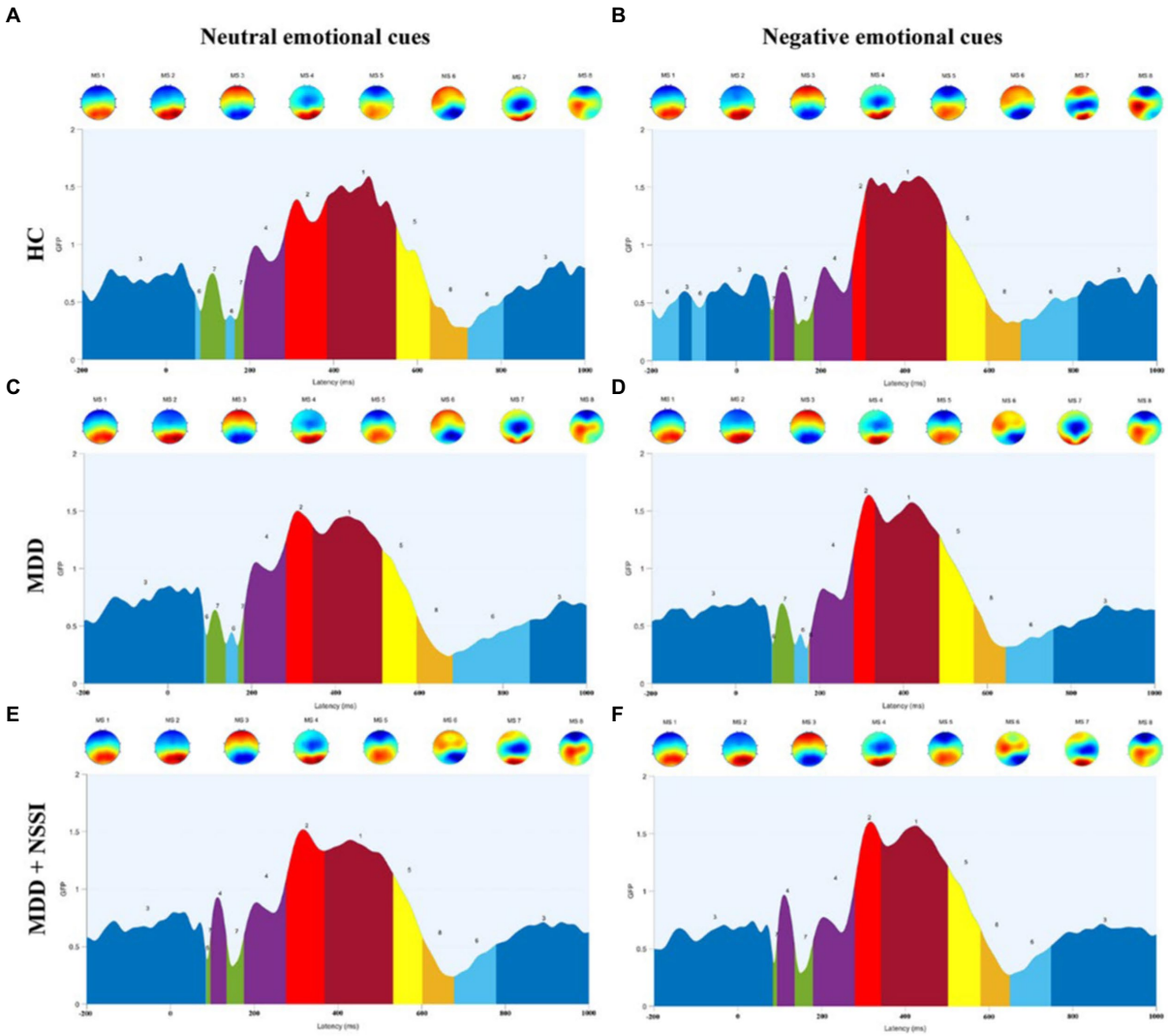

FIGURE 4
(A) Microstate categories of the HC group under neutral emotional cues. **(B)** Microstate categories of the HC group under negative emotional cues. **(C)** Microstate categories of the MDD group under neutral emotional cues. **(D)** Microstate categories of the MDD group under negative emotional cues. **(E)** Microstate categories of the MDD+NSSI group under neutral emotional cues. **(F)** Microstate categories of the MDD+NSSI group under negative emotional cues. HC, healthy control; MDD, major depressive disorder; MDD+NSSI, MDD with nonsuicidal self-injury.

TABLE 3 Changes in depression scores and NSSI scores before and after treatment in the MDD+NSSI group after receiving different treatment.

Clinical scales		Medication treatment (n=31) $M\pm SD$	Medication+rTMS treatment (n=21) $M\pm SD$	Time main effect $F(p)$	Between-group main effect $F(p)$	Time×Group interaction effect $F(p)$
HAMD	Before	23.612 ± 4.248	23.000 ± 4.336	223.063 (**<0.001**)	8.560 (**0.005**)	5.416 (**0.024**)
	After	12.936 ± 3.829	8.381 ± 5.084			
PHQ-9	Before	20.290 ± 3.175	19.905 ± 3.780	178.727 (**<0.001**)	6.730 (**0.012**)	6.482 (**0.014**)
	After	11.968 ± 4.167	7.667 ± 5.713			
NSSI	Before	2.065 ± 0.250	2.143 ± 0.359	225.491 (**<0.001**)	7.754 (**0.008**)	11.882 (**0.001**)
	After	0.871 ± 0.718	0.238 ± 0.539			

The bolded p values indicate statistical significance. We bolded for greater visibility.

as a between-group factor and treatment time as a within-group factor, showed that there was a significant time × group effect for HAMD scores [$F(1, 50) = 5.416$, $p = 0.024$, $\eta_p^2 = 0.098$], PHQ-9 scores [$F(1, 50) = 6.482$, $p = 0.014$, $\eta_p^2 = 0.115$], and NSSI scores [$F(1, 50) = 11.882$, $p = 0.001$, $\eta_p^2 = 0.192$]; and a significant time main effect for HAMD scores [$F(1, 50) = 223.063$, $p < 0.001$, $\eta_p^2 = 0.817$], PHQ-9

TABLE 4 Changes in microstate parameters before and after treatment in the MDD+NSSI group after receiving different treatment.

Microstate parameters		Time main effect $F(p)$	Time × Group interaction effect $F(p)$	Cue main effect $F(p)$	Cue×Group interaction effect $F(p)$	Time×Cue interaction effect $F(p)$	Time×Cue×Group interaction effect $F(p)$	Between-group main effect $F(p)$
GEV		0.048 (0.827)	0.011 (0.916)	1.121 (0.295)	0.127 (0.723)	0.599 (0.443)	1.620 (0.209)	1.820 (0.183)
Duration	MS1	1.171 (0.284)	2.438 (0.125)	15.483 (**<0.001**)	4.334 (**0.042**)	3.903 (**0.054**)	2.962 (0.091)	0.052 (0.820)
	MS2	1.408 (0.241)	1.791 (0.187)	6.553 (**0.014**)	6.883 (**0.012**)	15.515 (**<0.001**)	4.778 (**0.034**)	0.354 (0.554)
	MS3	46.361 (**<0.001**)	0.028 (0.869)	0.718 (0.401)	3.811 (**0.057**)	4.362 (**0.042**)	3.576 (0.064)	6.340 (**0.015**)
	MS6	13.077 (**0.001**)	1.571 (0.216)	0.049 (0.826)	0.739 (0.394)	2.092 (0.154)	5.439 (**0.024**)	1.201 (0.278)
Coverage	MS1	0.002 (0.962)	0.426 (0.517)	14.114 (**<0.001**)	2.628 (0.111)	1.814 (0.184)	0.717 (0.401)	0.058 (0.810)
	MS2	1.493 (0.227)	3.298 (0.075)	2.314 (0.134)	12.737 (**0.001**)	10.257 (**0.002**)	2.568 (0.115)	0.022 (0.883)
	MS3	70.214 (**<0.001**)	0.163 (0.688)	5.127 (**0.028**)	1.176 (0.283)	14.069 (**<0.001**)	13.525 (**0.001**)	7.237 (**0.010**)
	MS4	2.133 (0.150)	4.566 (**0.038**)	6.237 (**0.016**)	7.853 (**0.007**)	8.784 (**0.005**)	3.884 (**0.054**)	0.409 (0.525)
	MS6	56.794 (**<0.001**)	0.882 (0.352)	2.177 (0.146)	0.990 (0.325)	6.529 (**0.014**)	13.050 (**0.001**)	7.631 (**0.008**)
Occurrence	MS4	0.931 (0.339)	3.394 (0.071)	2.984 (0.090)	9.646 (**0.003**)	13.098 (**0.001**)	15.791 (**<0.001**)	0.038 (0.846)
	MS6	41.832 (**<0.001**)	0.272 (0.604)	9.005 (**0.004**)	2.359 (0.131)	2.604 (0.113)	4.721 (**0.035**)	10.456 (**0.002**)

The bolded p values indicate statistical significance. We bolded for greater visibility.

scores [$F(1, 50) = 178.727$, $p < 0.001$, $\eta_p^2 = 0.781$], and NSSI scores [$F(1, 50) = 225.491$, $p < 0.001$, $\eta_p^2 = 0.819$]; and a significant between-group main effect for HAMD scores [$F(1, 50) = 8.560$, $p = 0.005$, $\eta_p^2 = 0.146$], PHQ-9 scores [$F(1, 50) = 6.730$, $p = 0.012$, $\eta_p^2 = 0.119$], and NSSI scores [$F(1, 50) = 7.754$, $p = 0.008$, $\eta_p^2 = 0.134$]. Further simple effects analysis revealed that participants who received medication combined with rTMS exhibited lower HAMD scores (8.381 ± 5.084 vs. 12.936 ± 3.829, $p = 0.001$), PHQ-9 scores (7.667 ± 5.713 vs. 11.968 ± 4.167, $p = 0.001$), and NSSI scores (0.238 ± 0.53 vs. 0.871 ± 0.718, $p < 0.001$) compared with those who received medication treatment.

Changes in microstate parameters after receiving different interventions in the MDD+NSSI group

A repeated-measures ANOVA (see Table 4; Figure 5) was performed on microstate parameters in the MDD + NSSI group using treatment method as a between-group factor, treatment time as a within-group factor1, and emotional cues as a within-group factor2, showed that GEVs in the MDD + NSSI group receiving the two different treatment methods was above 80% for both neutral and negative emotional cues before and after treatment, which was highly explainable. There was a significant cue × group interaction effect ($F(1, 50) = 4.334$, $p = 0.042$, $\eta_p^2 = 0.080$) for MS 1 duration, a significant cue × group interaction effect ($F(1, 50) = 6.883$, $p = 0.012$, $\eta_p^2 = 0.121$) and a significant time × cue × group interaction effect ($F(1, 50) = 4.778$, $p = 0.034$, $\eta_p^2 = 0.087$) for MS 2 duration, and a significant cue × group interaction effect ($F(1, 50) = 12.737$, $p = 0.001$, $\eta_p^2 = 0.203$) for MS 2 coverage; there was a significant time main effect ($F(1, 50) = 46.361$, $p < 0.001$, $\eta_p^2 = 0.481$), a borderline significant cue × group interaction effect ($F(1, 50) = 3.811$, $p = 0.057$, $\eta_p^2 = 0.071$) and a significant between-group main effect ($F(1, 50) = 6.340$, $p = 0.015$, $\eta_p^2 = 0.113$ for MS 3 duration; and a significant time main effect ($F(1, 50) = 70.214$, $p < 0.001$, $\eta_p^2 = 0.584$), a significant time × cue × group interaction effect ($F(1, 50) = 13.525$, $p = 0.001$, $\eta_p^2 = 0.213$) and a significant between-group main effect ($F(1, 50) = 7.237$, $p = 0.010$, $\eta_p^2 = 0.126$) for MS 3 coverage; there was a significant time × group interaction effect ($F(1, 50) = 4.566$, $p = 0.038$, $\eta_p^2 = 0.084$), a significant cue × group interaction effect ($F(1, 50) = 7.853$, $p = 0.007$, $\eta_p^2 = 0.136$) and a marginal significant time × cue × group interaction effect ($F(1, 50) = 3.884$, $p = 0.054$, $\eta_p^2 = 0.072$) for MS 4 coverage, a significant cue × group interaction effect ($F(1, 50) = 9.646$, $p = 0.003$, $\eta_p^2 = 0.162$) and a significant time × cue × group interaction effect ($F(1, 50) = 15.791$, $p < 0.001$, $\eta_p^2 = 0.240$) for MS 4 occurrence. There was a significant time main effect ($F(1, 50) = 13.077$, $p = 0.001$, $\eta_p^2 = 0.207$) and a significant time × cue × group interaction effect ($F(1, 50) = 5.439$, $p = 0.024$, $\eta_p^2 = 0.098$) for MS 6 duration; a significant time main effect ($F(1, 50) = 56.794$, $p < 0.001$, $\eta_p^2 = 0.532$) and a significant time × cue × group interaction effect ($F(1, 50) = 13.050$, $p = 0.001$, $\eta_p^2 = 0.207$) and a significant between-group main effect ($F(1, 50) = 7.631$, $p = 0.008$, $\eta_p^2 = 0.132$) for MS 6 coverage; a significant time main effect ($F(1, 50) = 41.832$, $p < 0.001$, $\eta_p^2 = 0.456$) and a time × cue × group interaction effect ($F(1, 50) = 4.721$, $p = 0.035$, $\eta_p^2 = 0.086$) and a significant between-group main effect ($F(1, 50) = 10.456$, $p = 0.002$, $\eta_p^2 = 0.173$) for MS 6 occurrence.

Further simple effects analysis revealed that MS 1 duration under negative emotional cues was significantly different before and after the medication combined with rTMS treatment (104.191 ± 54.232 vs. 47.635 ± 35.020, $p = 0.002$), and MS 1 duration under negative emotional cues in medication combined with rTMS treatment group (47.635 ± 35.020 vs. 97.774 ± 82.159, $p = 0.011$) was significantly different compared to the medication treatment group. MS 2 duration and coverage under negative emotional cues were significantly different before and after medication combined with rTMS treatment (77.318 ± 40.961 vs. 154.095 ± 82.002, $p = 0.001$; 0.095 ± 0.072 vs. 0.166 ± 0.077, $p = 0.003$), MS 2 duration and coverage under negative emotional cues in medication combined with rTMS treatment group (154.095 ± 82.002 vs. 107.484 ± 86.773, $p = 0.011$; 0.166 ± 0.077 vs. 0.105 ± 0.086, $p = 0.012$) were significantly different compared to the medication treatment group. MS 4 coverage and occurrence under negative emotional cues were significantly different before and after medication combined with rTMS treatment (0.106 ± 0.068 vs. 0.041 ± 0.444, $p = 0.001$; 1.349 ± 0.557 vs. 0.516 ± 0.491, $p < 0.001$), and MS 4 coverage and occurrence under negative emotional cues in medication combined with rTMS treatment group (0.041 ± 0.444 vs. 0.100 ± 0.073, $p = 0.002$; 0.516 ± 0.491 vs. 1.210 ± 0.675, $p < 0.001$) were significantly different compared to the medication treatment group. MS 3 duration and coverage under negative emotional cues were significantly different before and after medication treatment (232.608 ± 64.021 vs.

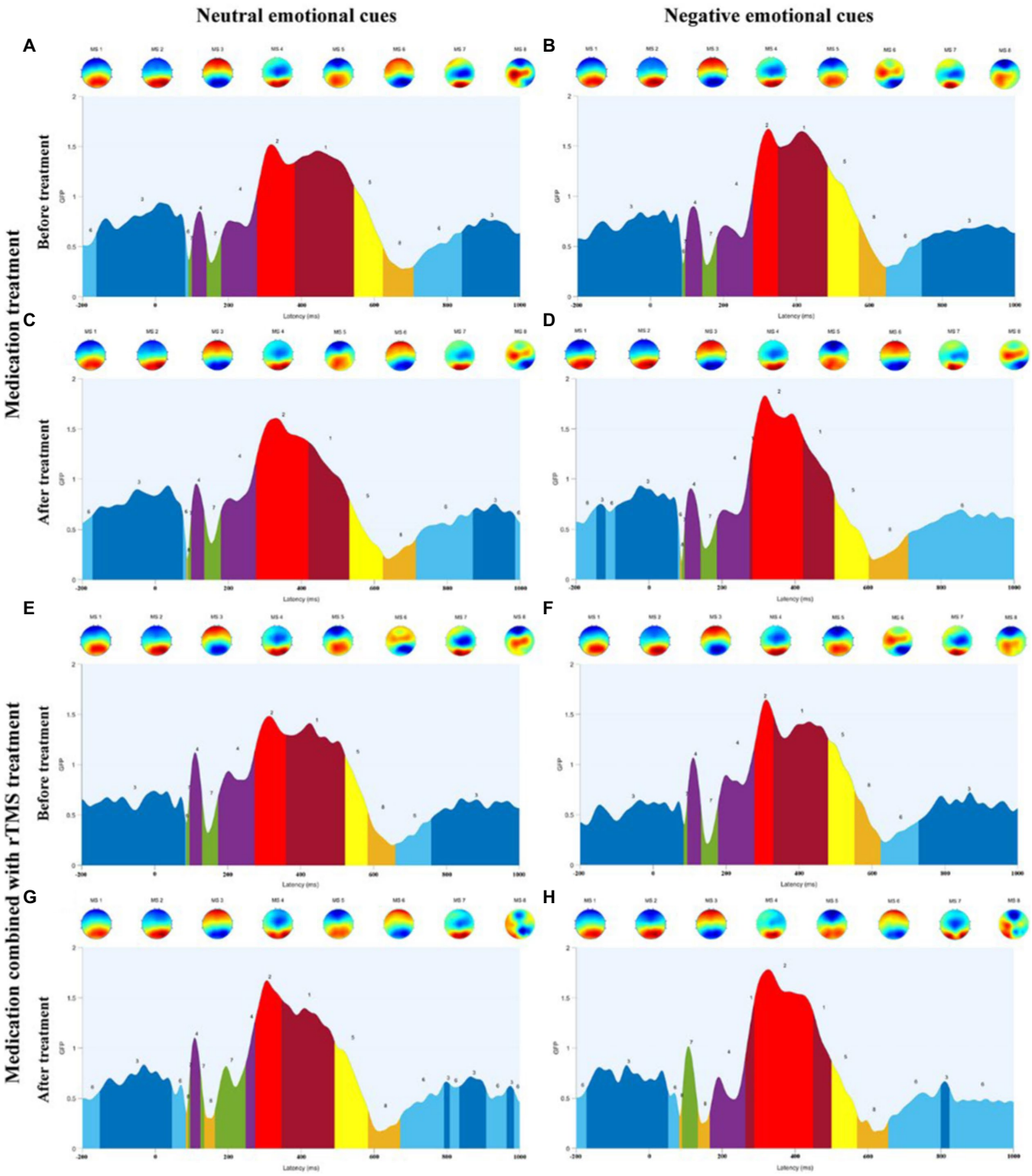

FIGURE 5
(A) Microstate categories of MDD adolescents with NSSI under neutral emotional cues before medication treatment. **(B)** Microstate categories of MDD adolescents with NSSI under negative emotional cues before medication treatment. **(C)** Microstate categories of MDD adolescents with NSSI under neutral emotional cues after medication treatment. **(D)** Microstate categories of MDD adolescents with NSSI under negative emotional cues after medication treatment. **(E)** Microstate categories of MDD adolescents with NSSI under neutral emotional cues before medication combined with rTMS treatment. **(F)** Microstate categories of MDD adolescents with NSSI under negative emotional cues before medication combined with rTMS treatment. **(G)** Microstate categories of MDD adolescents with NSSI under neutral emotional cues after medication combined with rTMS treatment. **(H)** Microstate categories of MDD adolescents with NSSI under negative emotional cues after medication combined with rTMS treatment.

123.589 ± 74.201, $p < 0.001$; 0.466 ± 0.062 vs. 0.233 ± 0.132, $p < 0.001$), and significantly different before and after medication combined with rTMS treatment (232.608 ± 64.021 vs. 123.589 ± 74.201, $p < 0.001$; 0.449 ± 0.125 vs. 0.321 ± 0.101, $p < 0.001$). MS 3 duration and coverage under negative emotional cues in medication combined with rTMS treatment group (150.124 ± 61.809 vs. 123.589 ± 74.201, $p < 0.001$; 0.321 ± 0.101 vs. 0.232 ± 0.132, $p = 0.012$) were significantly different compared to the medication treatment group. MS 6 duration, coverage, and occurrence under negative emotional cues were significantly different before and after medication treatment (75.172 ± 41.462 vs. 134.685 ± 78.014, $p = 0.001$; 0.083 ± 0.055 vs. 0.270 ± 0.125, $p < 0.001$; 0.995 ± 0.545 vs. 2.124 ± 0.982, $p < 0.001$) and

significantly different before and after medication combined rTMS treatment (80.976 ± 80.843 vs. 126.873 ± 80.213, $p = 0.032$; 0.085 ± 0.085 vs. 0.207 ± 0.114, $p < 0.001$; 0.873 ± 0.721 vs. 1.667 ± 0.697, $p < 0.001$) were significantly different.

Correlation analysis

We performed a correlation analysis of the differences in scale scores and microstate parameters before and after treatment between the medication combined with rTMS treatment group and the medication treatment group and did not find a correlation.

Discussion

In this study, we first investigated the performance of depression, NSSI, and microstate parameters in MDD adolescents with NSSI, MDD adolescents, and healthy adolescents exposed to neutral emotional cues and negative emotional cues. We found that MDD adolescents with NSSI had significant depressive symptoms and NSSI symptoms. In terms of microstates, we found that MDD adolescents with NSSI under negative emotional cues had significantly greater duration and coverage of MS 3 than those of healthy adolescents, significantly greater coverage and occurrence of MS 4 than those of MDD adolescents and healthy adolescents, and significantly smaller duration, coverage, and occurrence of MS 6 than those of MDD adolescents and healthy adolescents. Moreover, compared with neutral emotional cues, MDD adolescents with NSSI showed significantly greater duration and coverage of MS 3 and significantly less occurrence of MS 6 with negative emotional cues. This suggests that negative emotional stimuli induce more pronounced changes in microstate parameters in MDD adolescents with NSSI compared to neutral emotional stimuli than adolescents in the other two groups.

We then treated MDD adolescents with NSSI in two different methods and found that both two treatment methods significantly improved depression scores and NSSI scores, with medication combined with rTMS showing lower depression scores and NSSI scores compared to medication. In terms of microstates, we found that both two treatment methods showed significant pre- and post-treatment changes in duration and coverage of MS 3, and duration, coverage, and occurrence of MS 6 under negative emotional cues, with a significant decrease in MS 3 indicators and a significant increase in MS 6 indicators after treatment compared to pre-treatment. Furthermore, there was also a significant change in MS 3 indicators in the medication combined with rTMS treatment group compared to the medication treatment. This suggests that both treatment methods were effective in influencing MS 3 and MS 6 in MDD adolescents with NSSI. In addition to this, the medication combined with rTMS treatment group also showed a significant decrease in duration of MS 1, a significant increase in duration and coverage of MS 2, and a significant decrease in coverage and occurrence of MS 4 before and after treatment. Compared to medication treatment, medication combined with rTMS treatment showed a significant decrease in MS 1 duration, a significant increase in MS 2 duration and coverage, and a significant decrease in MS 4 coverage and occurrence. This suggests that medication combined with rTMS treatment can lead to unique alterations in microstate parameters compared to medication alone, which may be the specific neurophysiological mechanism by which rTMS affects MDD adolescents with NSSI.

Microstate analysis is an important tool for studying the functional brain activity of depressed adolescents with NSSI. Compared with traditional ERP analysis, microstate analysis can present quasi-stable periods of scalp topography over a short window (60–120 ms), reflecting global functional brain activity (37). However, there is no consensus on the classification of microstates. Notably, EEG microstates have been studied in depth both during task performance and in the resting state (i.e., in the absence of a task) (38). Unlike resting-state EEG microstates, task-state EEG microstates have more than four classifications, which are associated with the task, and the polarity of the topographic map and the time course of the EEG (23, 24). In this study, the ERP time course was partitioned into several time-stable topographies, identified as microstates specific to different time processes of the brain during the execution of the task, and corroborated with the average ERP waveforms of the midline electrodes in terms of time course. MS 3 and MS 6 occur mostly from 200 ms before stimulation to 100 ms after stimulation and after 700 ms after stimulation, reflecting a transition from resting brain activity to specific task activity, or a gradual convergence from an active state to a resting state. This is an important stage of functional transition in the brain, as shown in the topographic map showing activation of prefrontal regions of the brain. In the cross-sectional analysis of this study, we found that MDD adolescents with NSSI had altered MS 3 and MS 6 parameters compared to MDD adolescents and healthy adolescents, and that both medication and medication combined rTMS treatments were able to modulate impaired MS 3 and MS 6 indicators, but MS 3 and MS 6 were not specific in the comparison of the two treatment methods, so MS 3 and MS 6 were considered to be indicators with generalized neurophysiological indicators. MS 4 appeared mainly between 100 ms and 300 ms after stimulation, and the topography showed activation in the occipitotemporal region of the brain. The ERP component that appears during this time period is the N250 component, which reflects the early attention and monitoring process of the brain to the received stimulation. In our previous study (39), we found that MDD adolescents with NSSI exhibited an increase in N250 amplitude (absolute value), indicating the presence of impaired early attention and monitoring function in MDD adolescents with NSSI. In this study, we found an increase in MS 4 coverage and occurrence in MDD adolescents with NSSI compared to the other two groups, reconfirming this view from a microstate perspective. In the time period from 300 ms to 500 ms after stimulation, the microstates were mainly reflected in MS 1 and MS 2, which were shown on the topographic map as activation in the parieto-occipital region of the brain, and the topographic map of MS 2 showed more pronounced activation. The ERP component during this time period is the P300 component, which reflects the brain's cognitive executive processes in response to stimuli. Our previous study (39) found that MDD adolescents with NSSI showed an increase in P300 amplitude, but in the present study, we did not find significant changes in MS 1 and MS 2 parameters in the cross-sectional analysis. For this result, we tried to explain that although the main ERP component present during this time period is P300, there may be other ERPs, and therefore, MS 1 and MS 2 cannot be directly equated to P300 and need to be considered synergistically.

Repetitive transcranial magnetic stimulation was approved by the FDA in 2008 for the treatment of major depression and has been

well-documented in numerous studies as a promising treatment for adolescents with MDD (17). However, there is a paucity of research using rTMS intervention with adolescents with NSSI, and its neuromodulatory mechanisms are still not clearly elucidated. A recent study on rTMS-targeted therapy showed that high-frequency stimulation of the left dorsolateral prefrontal region can reduce depressive symptoms (40). Therefore, in the present study, we chose the left dorsolateral prefrontal region as the target site for the rTMS intervention. We conducted two different treatment regimens for MDD adolescents with NSSI, medication alone and medication combined with rTMS. We found that the improvement in clinical symptoms differed between treatments, with patients receiving medication combined with rTMS showing more significant improvement in depressive symptoms and a significant reduction in the occurrence of NSSI. In addition, the changes in microstate parameters exhibited by MDD adolescents with NSSI differed between treatments, with the changes in MS 3 and MS 6 common to both treatment methods, and medication combined with rTMS treatment also had an effect on MS 1, MS 2, and MS 4. We found that medication combined with rTMS treatment downregulated MS 4 parameters more significantly than medication treatment, and that medication combined with rTMS treatment significantly decreased MS 1 parameters and significantly increased MS 2 parameters compared with medication treatment. MS 1 and MS 2 were unchanged in the cross-sectional analysis, but in the longitudinal analysis, we found that medication combined with rTMS treatment was able to harmonize the parameters of MS 1 and MS 2 for better effects in addition to down-regulating the originally increased MS 4 parameters, which may be a potential neural mechanism for the more pronounced effect of medication combined with rTMS treatment than medication treatment. In a recent study (41) of rTMS in schizophrenia microstates, changes in EEG microstate parameters following rTMS were associated with improved symptoms in schizophrenia patients, suggesting that changes in EEG microstates may be a potentially effective indicator of symptom improvement with rTMS. Therefore, we suggest that changes in microstate indicators can be a key neuromodulatory target for the improvement effect of rTMS.

In this study, we compared changes in microstate parameters in MDD adolescents with NSSI, MDD adolescents, and healthy adolescents when exposed to neutral and negative emotional cues, and found differences in microstate parameters that provide a new neurophysiological perspective on the occurrence of NSSI behaviors in MDD adolescents. We also evaluated the improvement effects and changes in microstate parameters in MDD adolescents with NSSI with two different treatments, in which medication combined with rTMS treatment showed more significant improvement in depressive symptoms and NSSI symptoms compared to medication treatment, providing reliable evidence for optimization of treatment in MDD adolescents with NSSI and neurophysiological evidence for the neuromodulatory effect of rTMS treatment.

Although we attempted to optimize the study design as much as possible, there are several limitations that should be noted: First, although NSSI behaviors not only occur in depressed patients, given the impact of patient population heterogeneity on the study, we only chose MDD was as the primary diagnosis and therefore, our results are not applicable to those who do not meet the primary diagnosis of MDD despite having NSSI behaviors. Second, the analysis of baseline demographic data in this study found that the age and sex of subjects in the MDD + NSSI group did not match the other two groups, mainly due to the fact that NSSI behaviors were more common among younger adolescents and were more prevalent in females, which is consistent with the epidemiological characteristics of NSSI. In the cross-sectional microstate analysis of this study, we included age and sex as covariates in the ANOVA to exclude the effect caused by age and sex mismatch, but a study with a large sample matched for age and sex is still needed in the follow-up study has confirmed the results. Third, due to the COVID-19 epidemic, we were somewhat affected in collecting subjects, and some patients were unable to undergo post-intervention EEG acquisition for reasons such as traffic control under the epidemic, so the sample size of MDD adolescents with NSSI receiving both two treatments was insufficient, and future longitudinal studies with larger sample sizes are needed. Fourth, we conducted a correlation analysis between the difference in clinical symptoms and the difference in microstate parameters before and after treatment for MDD adolescents with NSSI receiving different treatment methods, and found no correlation, suggesting that although we found significant changes in microstate characteristics, there was no significant correlation with clinical scales, which may be due to the small sample size of the longitudinal analysis, and correlations may exist when the sample size is increased in the future. Fifth, there are still some shortcomings in the choice of the intervention area for rTMS, our current choice of intervention area is the left dorsolateral prefrontal region, but it may ignore the variability caused by head size, the best option is to use functional MRI to guide the implementation of this area, but the high cost of functional MRI does not allow it to be widely used in clinical practice. For this reason, we used the EEG International 10/20 system to try to avoid the effects of head size differences.

Conclusion

The results of our study indicate that MDD adolescents with NSSI show abnormal MS 3, MS 4, and MS 6 parameters when exposed to negative emotional stimuli compared to MDD adolescents and healthy adolescents, suggesting a potential neurophysiological mechanism for the occurrence of NSSI behavior in MDD adolescents with NSSI. We further explored the optimization of treatment for MDD adolescents with NSSI, and found the effects of rTMS treatment on MS 1, MS 2, and MS 4 parameters in MDD adolescents with NSSI, providing microstate evidence for the moderating effect of rTMS.

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 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. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

LZ conceived the structure of the manuscript and wrote the manuscript. LZ, XH, XP, LM, JH, RC, and ZJ did EEG. CZ, JL, JX, QZe, LD, QZh, and SH prepared the samples. LZ and DZ wrote the code, analyzed the data, and discussed to solve the problem. WW and LK critically reviewed the manuscript. 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.

Publisher's note

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The prevalence of underweight and obesity in Chinese children and adolescents with major depressive disorder and relationship with suicidal ideation and attempted suicide

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Background: The high rates of obesity and suicide have become serious public health problems worldwide, especially in children and adolescents with major depressive disorder (MDD). This research aimed to explore the rates of underweight, overweight or obesity, suicidal ideation and attempted suicide in hospitalized children and adolescents with MDD. Then, we analyzed the correlation between underweight or obesity and suicidal ideation and attempted suicide, and finally obtained the independent influencing factors of underweight or obesity.

Methods: A total of 757 subjects in the Third People's Hospital of Fuyang from January 2020 to December 2021 were enrolled in this study. According to the underweight, overweight and obesity screening table for school-age children and adolescents published and implemented by the health industry standard of China, all subjects were divided into different body mass index (BMI) categories. We measured fasting blood glucose (FBG) and lipid levels in all subjects and assessed suicidal ideation, attempted suicide, and the severity of depressive symptoms. The socio-demographic and clinical data were collected and analyzed by SPSS 22.0.

Results: The rates of underweight, overweight, obesity, suicidal ideation and attempted suicide were 8.2% (62/757), 15.5% (117/757), 10.4% (79/757), 17.2% (130/757), and 9.9% (75/757), respectively. Correlation analysis indicated that BMIs level was positively correlated with age, age of first hospitalization, total duration of disease, number of hospitalizations, FBG, TG (triglyceride), TC (total cholesterol), LDL (low density lipoprotein), and negatively correlated with HDL (high density lipoprotein). Binary logistic regression analysis showed that male and high level of HDL were risk factors for MDD inpatients with underweight, while high level of TG was a protective factor. Meanwhile, higher levels of FBG, TG and CGI-S were risk factors and suicidal ideation and high dose of antidepressant drugs were protective factors for obesity in children and adolescents with MDD.

Conclusion: The prevalence of underweight, obesity, suicidal ideation and attempted suicide were high in children and adolescents with MDD, and severe depressive symptoms are independent risk factors for obesity, while suicidal ideation and high dose of antidepressants may be protective factors for obesity.

KEYWORDS

underweight, obesity, suicidal ideation, attempted suicide, children, adolescents, major depressive disorder

Introduction

Major depressive disorder (MDD) is a kind of mental illness with high incidence in adolescence. The Chinese national surveys found that the prevalence of MDD in adolescents was about 3.0–23.2% (1, 2). During the COVID-19 pandemic, due to the impact of isolation, school suspension, disrupted pace of life, frequent use of social electronic media and other factors, children and adolescents have significantly increased psychological problems such as depression (3), with a comprehensive prevalence as high as 29% (4). Moreover, the incidence of adolescent obesity increased rapidly during the pandemic (5). It has been reported that the prevalence of underweight, overweight and obesity among Chinese adolescents were 5.9, 10.1 and 5.3%, respectively, and rising continually (6). By 2030, China will rank first among 42 countries with more than one million obese children, followed by India, the United States and Indonesia, according to projections by the World Obesity Federation (7). While the rates of obesity among adolescents have stabilized in developed countries, it continued increasing in low - and middle-income countries (8). Studies have revealed the significant U-shaped association between body mass index (BMI) categories (underweight, normal, overweight and obese) and depressive symptoms (9), suggesting that both underweight and obesity were closely related to severe depressive symptoms (10). Meta-analysis showed that the rates of overweight and obesity in adolescence with depressive disorder were about 9.0–16.9% and 10.1–26.7%, respectively, which were higher than those of healthy people in the same age group (11). Underweight or obesity was closely related to poorer mental health in adolescents (12), and adolescents with weight stigma suffered from heavier depressive symptoms (13). Historical literature has shown a bidirectional association between depressive symptoms and underweight or obesity (14), and depressive symptoms in adolescence could predict underweight or obesity in early or later adulthood (15), and vice versa (16).

Suicide is now the second leading cause of death in adolescents among 10–19 years old, and MDD significantly increases the risk of suicidal ideation, attempted suicide and other self-injury behaviors (17). It has been documented that nearly one in ten high school students reported at least one previous suicide attempt, yet more than 80% of suicide attempts were never recognized by pediatricians (18). Foreign studies have shown that the incidence of suicidal ideation in adolescence population was 13.1% (19). During the COVID-19 epidemic, the rate of suicidal ideation in the general population was 17%, while that in psychiatric patients was 36% (20), and the risk of suicide in the overall population was significantly higher than that before the epidemic (21). According to the Chinese national epidemiological survey, the prevalence of suicidal ideation in adolescents was 15.7%, and both underweight and obesity were associated with a higher risk of suicidal ideation (6). Furthermore, attempted suicide was also significantly associated with depressive symptoms and being underweight or overweight (22). Other studies have shown that BMI level was strongly inversely associated with suicide, and with BMI increasing, the risk of suicide might decrease (23). Attempted suicide was negatively associated with BMI in males. However, in female patients with MDD, there was a U-shaped correlation between attempted suicide and BMI levels (24), suggesting that the risk of attempted suicide was increased in both underweight and obese women. In summary, MDD and suicide-related behaviors are both major global public health issues due to their severe consequences.

To our best knowledge, although there are many studies on different BMI categories or suicidal behaviors in children and adolescents, few studies have discussed the association between underweight or obesity and suicidal ideation and attempted suicide in children and adolescents with MDD. This study aims to explore the prevalence of underweight, overweight or obesity, suicidal ideation and attempted suicide in hospitalized children and adolescents with MDD, and to analyze the correlation between underweight or obesity and suicidal ideation and attempted suicide, and finally to obtain the independent influencing factors of underweight or obesity.

Methods

Subjects

The subjects of this study were hospitalized children and adolescents with MDD in the Third People's Hospital of Fuyang from January 2020 to December 2021. Inclusion criteria: (1) 8–18 years old; and (2) meeting the diagnostic criteria of MDD in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Exclusion criteria: (1) Patients with other severe mental disorders in accordance with DSM-V (such as schizophrenia, obsessive–compulsive disorder, etc.); (2) complicated with intellectual disability or severe neurological diseases; and (3) complicated with serious physical diseases (such as cardiovascular disease, digestive system disease, respiratory system disease, etc.). The enrolled patients and their guardians agreed to participate in the study after knowing the purpose, process, and related advantages and disadvantages, and signed an informed consent form. This study was approved by the Medical Ethics Committee of the Third People's Hospital of Fuyang (granted number: [2018]2018-340-10).

General information and biochemical indicators

Height, weight and BMI

The height and weight of the subjects were measured accurately, keeping one decimal place. BMI was calculated as weight (kg)/height (m)^2. According to the "Malnutrition Screening of School-age Children and Adolescents" issued and implemented by the health industry standard of the People's Republic of China (25), the BMI levels of children at different ages, such as 8 years old (boys <14.0, girls <13.6), 9 years old (boys <14.1, girls <13.8), 10 years old (boys <14.4, girls <14.0), 11 years old (boys <14.9, girls <14.3), 12 years (boys <15.4, girls <14.7), 13 years old (boys <15.9, girls <15.3), 14 years old (boys <16.4, girls <16.0), 15 years old (boys <16.9, girls <16.6), 16 years old (boys <17.3, girls <17.0), 17 years old (boys <17.7, girls <17.2), 18 years old (boys <17.9, girls <17.3), and the overall patients were divided into underweight group and non-underweight group. According to the "Overweight and Obesity Screening Table for School-age Children and Adolescents" published and implemented by the health industry standard of the People's Republic of China (26), according to the BMI levels of children at different ages, such as 8 years old (boys ≥19.7, girls ≥19.4), 9 years old (boys ≥20.8, girls ≥20.4), 10 years old (boys ≥21.9, girls ≥21.5), 11 years old (boys ≥23.0, girls ≥22.7), 12 years old (boys ≥24.1, girls ≥23.9), 13 years old (boys ≥25.2, girls ≥25.0), 14 years old (boys ≥26.1, girls ≥25.9), 15 years old boys/girls ≥26.6, 16 years old boys/girls ≥27.1, 17 years old boys/girls ≥27.6, 18 years old boys/girls ≥28.0. All patients were divided into obesity group and non-obesity group, and also see (26) for criteria of normal-weight group or overweight group.

Clinical data collection

Clinical electronic medical records and questionnaires were used to collect the general information of the subjects, such as gender, age, and education level. The age of previous onset, age of first hospitalization, number of hospitalizations, total course of disease, whether accompanied by physical diseases, current medication category and therapeutic dose were recorded. The antidepressant dose of each subject was converted to fluoxetine equivalent, and the conversion formula was: fluoxetine 20 mg = citalopram 20 mg = escitalopram 9 mg = paroxetine 17 mg = sertraline 49.3 mg = venlafaxine 74.7 mg = mirtazapine 25.5 mg = fluvoxamine 71.7 mg (27, 28).

Biochemical criterion

On the second day after enrollment, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and other hematological indicators were detected in enrolled patients.

Suicidal ideation and attempted suicide

Three simple questions were used to assess whether the patient had suicidal ideation, attempt or behavior in the past 3 months (29), which were: (1) "Have you ever seriously considered suicide or killing yourself?"; (2) "Have you ever made detailed plans to kill yourself?"; (3) "Do you really try to kill yourself in your life?." A "yes" or "no" answer was given to each question.

Clinical global impression

Clinical Global Impression of Severity Scale (CGI-S) was used to assess the severity of the disease. Using an 8-point scoring method from 0 to 7 points (30), according to the disease severity of the specific patient compared with other similar patients in the same study, the score corresponds to the disease severity: 0 – no disease; 1 – essentially no disease; 2 – very light; 3 – mild; 4 – moderate; 5 – heavier; 6 – severe; 7 – extremely heavy.

Statistical analysis

IBM SPSS 22.0 statistical software was used for data analysis. Measurement data conformed to normal distribution and were expressed as ($\bar{x} \pm s$), and One-Way ANOVA was used for comparison between groups. If not, the results were expressed as median M (P25, P75), and Kruskal Wallis Test was used for comparison between groups. Count data were expressed as constituent ratio [n (%)] and compared by Chi-Square Tests. Spearman rank correlation was used to analyze the correlation between overall patients' BMI, suicidal ideation, attempted suicide and multiple study variables. Socio-demographic and clinical variables with a value of $p < 0.05$ in univariate analysis were included in binary logistic regression analysis to determine the independent influencing factors of underweight or obesity in children and adolescents with MDD, and to obtain the correlation between underweight or obesity and suicidal ideation and attempted suicide. The test level $\alpha = 0.05$.

Results

Comparison between different BMI groups of the patients with MDD

A total of 757 children and adolescents with depressive disorder were enrolled in this study, including 28.4% (215/757) males and 71.6% (542/757) females. The average age was 15 (14, 16) years old, the age of first onset was 14 (12, 15) years old, and the duration of illness was 12 (4, 24) months. The prevalence of underweight, normal weight, overweight and obesity in MDD patients was 8.2% (62/757), 65.9% (499/757), 15.5% (117/757), and 10.4% (79/757), respectively. As shown in Table 1, comparison between different BMI groups showed statistically significant differences in age, gender, age of onset, age of first hospitalization, total duration of disease, number of hospitalizations, FBG, TG, TC, HDL, LDL, types of antidepressant medications, and dosage of antidepressants ($p < 0.05$).

Prevalence of suicidal ideation and attempted suicide in overall patients and different BMI groups

The prevalence of suicidal ideation and attempted suicide was 17.2% (130/757) and 9.9% (75/757) in all subjects, respectively. The prevalence of suicidal ideation in underweight, overweight and obese patients were 22.6% (14/62), 20.5% (24/117), and 19.0% (15/79), respectively. The prevalence of attempted suicide in underweight, overweight and obese patients were 8.1% (5/62), 12.0% (14/117), and 13.9% (11/79), respectively. See Table 1.

TABLE 1 Comparison of general data and biological indexes of underweight group, normal weight group, overweight group and obesity group.

Variable	Underweight (*n*=62)	Normal weight (*n*=499)	Overweight (*n*=117)	Obese (*n*=79)	F/X²/H	*P*
Age (years)	15.27 ± 1.80	15 (14, 16)	15 (14, 16)	14 (13, 16)	11.206	0.011[c]
Gender (%)					22.741	<0.001[b]
Male	33 (53.2)	135 (27.1)	32 (27.4)	15 (19.0)		
Female	29 (46.8)	364 (72.9)	85 (72.6)	64 (81.0)		
Education (%)					9.359	0.154[b]
Primary school	2 (3.2)	37 (7.4)	11 (9.4)	11 (13.9)		
Junior middle school	35 (56.5)	298 (59.7)	64 (54.6)	49 (62.0)		
High school or above	25 (40.3)	164 (21.9)	41 (35.0)	19 (24.1)		
Age of onset (years)	14.11 ± 2.07	14 (13, 15)	13 (12, 14)	12.85 ± 1.96	22.565	<0.001[c]
Age of first admission (years)	14.89 ± 1.92	15 (13, 16)	14 (13, 16)	14 (13, 15)	10.185	0.017[c]
Total course of disease (months)	6 (2.75, 24)	12 (3, 24)	12 (6, 24)	12 (6, 24)	16.564	0.001[c]
Number of hospitalizations (times)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	12.362	0.006[c]
BMI	15.83 ± 0.94	19.58 ± 1.89	24.31 ± 1.44	29.48 ± 3.37	814.932	<0.001[a]
Hematological index						
FBG (mmol/L)	4.93 ± 0.72	4.98 ± 0.48	5.06 ± 0.42	5.18 ± 0.62	4.168	0.006[a]
TG (mmol/L)	0.76 (0.62, 0.87)	0.79 (0.61, 1.09)	1.06 (0.73, 1.46)	1.55 ± 0.82	84.734	<0.001[c]
TC (mmol/L)	3.60 ± 0.80	3.66 (3.24, 4.18)	3.90 ± 0.73	4.42 ± 1.02	46.888	<0.001[c]
HDL (mmol/L)	1.57 ± 0.40	1.41 (1.22, 1.65)	1.42 (1.17, 1.61)	1.30 (1.02, 1.53)	20.248	<0.001[c]
LDL (mmol/L)	2.12 ± 0.59	2.09 (1.73, 2.43)	2.25 (1.95, 2.65)	2.31 (1.59, 3.00)	14.914	0.002[c]
Suicidal ideation (%)					3.440	0.329[b]
Yes	14 (22.6)	77 (15.4)	24 (20.5)	15 (19.0)		
No	48 (77.4)	422 (84.6)	93 (79.5)	64 (81.0)		
Suicidal behavior (%)					2.661	0.447[b]
Yes	5 (8.1)	45 (9.0)	14 (12.0)	11 (13.9)		
No	57 (91.9)	454 (91.0)	103 (88.0)	68 (86.1)		
CGI-S	4 (4, 5)	4 (4, 5)	4 (4, 5)	4 (4, 5)	3.559	0.313[c]
Antidepressant medications (%)					17.064	0.009[b]
No	5 (8.1)	59 (11.8)	16 (13.7)	19 (24.1)		
Monotherapy	51 (82.3)	413 (82.8)	97 (82.9)	60 (75.9)		
Polypharmacy	6 (9.7)	27 (5.4)	4 (3.4)	0		
Antidepressant dosage (mg/d)	20.3 (20, 40)	20.3 (20, 40.15)	20.3 (20, 40.6)	20 (6.23, 32.8)	12.370	0.006[c]
Antipsychotic medications (%)					1.266	0.974[b]
No	36 (58.1)	302 (60.5)	72 (61.5)	51 (64.6)		
Monotherapy	25 (40.3)	185 (37.1)	43 (36.8)	27 (34.2)		
Polypharmacy	1 (1.6)	12 (2.4)	2 (1.7)	1 (1.3)		
Chlorpromazine equivalent (mg/d)	185.55 ± 167.05	150 (75, 200)	150 (75, 181.88)	117.90 ± 135.33	5.765	0.124[c]

[a]One-way ANOVA; [b]Chi-Square Tests; [c]Kruskal Wallis Test. NSSI, Non-suicidal self-injury; BMI, body mass index; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Monotherapy, Taking one kind of antidepressant or antipsychotic medication; Polypharmacy, Taking two kinds of antidepressant or antipsychotic medication.

Association of demographic data and clinical variables with BMI, suicidal ideation, and attempted suicide

The Spearman correlation coefficient showed that BMIs were positively correlated with age, age of first hospitalization, total duration of disease, number of hospitalizations, FBG, TG, TC, and LDL, and negatively correlated with HDL ($p < 0.05$). Suicidal ideation was positively correlated with gender, total duration of disease, number of hospitalizations, TC, LDL, attempted suicide, CGI-S, antidepressant dosage, antipsychotic medications and chlorpromazine equivalent ($p < 0.05$). Attempted suicide was positively correlated with

gender, total duration of disease, number of hospitalizations, TC, LDL, suicidal ideation, CGI-S, antidepressant dosage, and antipsychotic medications, and negatively correlated with education and age of onset ($p < 0.05$). As shown in Table 2.

Influencing factors of underweight and obesity in patients with MDD

Using binary logistic regression analysis with underweight (non-underweight = 0, underweight = 1) as the dependent variable, age, gender (assignment: male = 1, female = 2), age of onset, age of first hospitalization, total duration of disease, number of hospitalizations, FBG, TG, TC, HDL, LDL, suicidal ideation (assignment: no = 0, yes = 1), attempted suicide (assignment: no = 0, yes = 1), CGI-S, several types of antidepressants (assignment: none = 0, one type = 1, two types = 2), dosage of antidepressants as independent variable, the results showed that male ($OR = 4.04$, 95%CI: 2.19–7.44, $p < 0.001$), higher levels of HDL ($OR = 2.68$, 95%CI: 1.24–5.76, $p = 0.012$) were risk factors for MDD adolescents with underweight, and higher levels of TG ($OR = 0.40$, 95%CI: 0.17–0.93, $p = 0.033$) was a protective factor. The R^2 of the overall model was 0.158. As shown in Table 3.

Similarly, binary logistic regression analysis showed that higher levels of FBG ($OR = 1.83$, 95%CI: 1.13–2.96, $p = 0.013$), TG ($OR = 1.96$, 95%CI: 1.30–2.97, $p = 0.001$) and CGI-S ($OR = 2.00$, 95%CI: 1.16–3.44, $p = 0.013$) were risk factors and suicidal ideation ($OR = 0.17$, 95%CI: 0.04–0.76, $p = 0.021$) and higher dosage of antidepressant drugs ($OR = 0.97$, 95%CI: 0.95–0.99, $p = 0.015$) were protective factors for obesity in children with MDD. The R^2 of the overall model was 0.224. As shown in Table 4.

Discussion

This study aimed to explore the prevalence of underweight, overweight and obesity in children and adolescents' inpatients with MDD, and analyze the correlation between suicidal ideation, attempted suicide and underweight and obesity. The main results are as follows: (1) The prevalence of underweight, overweight, obesity, suicidal ideation and attempted suicide were 8.2% (62/757), 15.5% (117/757), 10.4% (79/757), 17.2% (130/757), and 9.9% (75/757), respectively. (2) Correlation analysis indicated that BMIs were positively correlated with age, age of first hospitalization, total duration of disease, number of hospitalizations, FBG, TG, TC, LDL, and negatively correlated with HDL. (3) Binary logistic regression analysis revealed that male and higher HDL level were risk factors for MDD inpatients with underweight, while higher TG level was a protective factor. Meanwhile, higher levels of FBG, TG and CGI-S were risk factors and suicidal ideation and higher dosage of antidepressant drugs were protective factors for obesity.

Previous study reported the rates of underweight, overweight and obesity of adolescents in China were 5.9, 10.1, and 5.3%, respectively, and the rates of boys in each weight category were higher than that of girls (6). Clinical studies suggested the higher incidence of overweight and obesity in Chinese adolescents with MDD than that of adolescents without MDD (13.15% vs. 9.88, 11.95% vs. 6.75%) (2). A meta-analysis of 11 studies also found that the prevalence of overweight and obesity in children and adolescents with depressive disorder was approximately 9.0–16.9% and 10.1–26.7%, respectively (11). This study indicated that the rates of underweight, overweight and obesity in children and adolescents with MDD were 8.2, 15.5, and 10.4%,

TABLE 2 Association of demographic data and clinical variables with BMI, suicidal ideation, and attempted suicide.

Variable	BMI		Suicidal ideation		Attempted suicide	
	r	*P*	*r*	*P*	*r*	*P*
Age (years)	0.129	<0.001	0.029	0.432	−0.008	0.817
Gender	0.063	0.084	0.085	0.020	0.111	0.002
Education	0.044	0.223	−0.049	0.178	−0.104	0.004
Age of onset (years)	0.028	0.436	−0.037	0.308	−0.085	0.019
Age of first admission (years)	0.106	0.003	0.046	0.202	−0.007	0.845
Total duration of disease (months)	0.173	<0.001	0.146	<0.001	0.132	<0.001
Number of hospitalizations (times)	0.082	0.024	0.149	<0.001	0.197	<0.001
FBG (mmol/L)	0.102	0.005	−0.040	0.276	0.008	0.816
TG (mmol/L)	0.278	<0.001	0.050	0.173	0.060	0.099
TC (mmol/L)	0.193	<0.001	0.098	0.007	0.075	0.038
HDL (mmol/L)	−0.137	<0.001	−0.038	0.295	−0.034	0.347
LDL (mmol/L)	0.136	<0.001	0.146	<0.001	0.091	0.013
Suicidal ideation	0.017	0.650	1		0.728	<0.001
Attempted suicide	0.057	0.114	0.728	<0.001	1	
CGI-S	0.061	0.094	0.702	<0.001	0.560	<0.001
Antidepressant medications	−0.060	0.098	−0.011	0.769	−0.061	0.091
Antidepressant dosage (mg/d)	−0.020	0.588	0.161	<0.001	0.128	0.001
Antipsychotic medications	−0.014	0.700	0.153	<0.001	0.136	<0.001
Chlorpromazine equivalent (mg/d)	0.010	0.850	0.144	0.007	0.078	0.141

TABLE 3 Influencing factors for underweight in patients with MDD.

Variables	Unstandardized coefficients		*P*	*OR*	95.0% CI	
	B	*S.E.*			Lower	Upper
Age (years)	−0.346	0.386	0.371	0.71	0.33	1.51
Male (ref. Female)	1.396	0.311	<0.001	4.04	2.19	7.44
Age of onset (years)	0.441	0.380	0.246	1.55	0.74	3.27
Age of first admission (years)	−0.074	0.117	0.528	0.93	0.74	1.17
Total course of disease (months)	0.034	0.033	0.298	1.04	0.97	1.10
Number of hospitalizations (times)	0.371	0.287	0.196	1.45	0.83	2.55
FBG (mmol/L)	−0.361	0.321	0.260	0.70	0.37	1.31
TG (mmol/L)	−0.916	0.430	0.033	0.40	0.17	0.93
TC (mmol/L)	−0.297	0.294	0.312	0.74	0.42	1.32
HDL (mmol/L)	0.984	0.391	0.012	2.68	1.24	5.76
LDL (mmol/L)	0.212	0.484	0.661	1.24	0.48	3.19
Suicidal ideation (ref. No)	−1.122	0.685	0.101	0.33	0.09	1.25
Suicidal behavior (ref. No)	−0.517	0.744	0.487	0.60	0.14	2.56
CGI-S	−0.127	0.289	0.662	0.88	0.50	1.55
Antidepressant medications (ref. No)						
Monotherapy	−1.058	1.541	0.492	0.35	0.02	7.11
Polypharmacy	−0.278	1.641	0.866	0.76	0.03	18.88
Antidepressant dosage	−0.003	0.010	0.768	1.00	0.98	1.02

TABLE 4 Influencing factors for obesity in patients with MDD.

Variables	Unstandardized coefficients		*P*	*OR*	95.0% CI	
	B	*S.E.*			Lower	Upper
Age (years)	−0.243	0.416	0.560	0.78	0.35	1.77
Male (ref. Female)	−0.509	0.384	0.186	0.60	0.28	1.28
Age of onset (years)	0.085	0.399	0.830	1.09	0.50	2.38
Age of first admission (years)	0.042	0.172	0.809	1.04	0.74	1.46
Total course of disease (months)	0.024	0.035	0.480	1.03	0.96	1.10
Number of hospitalizations (times)	0.320	0.319	0.316	1.3	0.74	2.58
FBG (mmol/L)	0.605	0.244	0.013	1.83	1.13	2.96
TG (mmol/L)	0.674	0.211	0.001	1.96	1.30	2.97
TC (mmol/L)	0.394	0.268	0.141	1.48	0.88	2.51
HDL (mmol/L)	−0.552	0.508	0.277	0.57	0.21	1.56
LDL (mmol/L)	0.598	0.409	0.144	1.82	0.82	4.05
Suicidal ideation (ref. No)	−1.802	0.781	0.021	0.17	0.04	0.76
Suicidal behavior (ref. No)	0.194	0.833	0.816	1.21	0.24	6.22
CSI-S	0.692	0.277	0.013	2.00	1.16	3.44
Antidepressant medications (ref. No)						
Monotherapy	−0.930	1.191	0.435	0.40	0.04	4.07
Polypharmacy	−19.163	6.265E3	0.998	0.00	0.00	
Antidepressant dosage	−0.030	0.012	0.015	0.97	0.95	0.99

respectively, which were roughly the same as previous studies and significantly higher than that of normal adolescents. Literature indicated that underweight adolescents were more likely comorbid depression (31, 32), and underweight was closely associated with more severe depressive symptoms (9, 12) or more internalization problems (33). In addition, a study of comorbid mental disorders in people of different BMI categories found that underweight boys had higher risk comorbid with depressive disorders (34). In addition to the actual

measured BMI, perceived underweight was also strongly associated with higher depressive symptoms in adolescents (35, 36). Moreover, the risk of depression was more than two times higher in people who thought they were underweight than in people perceived normal weight (37), and in fact there was a positive correlation between perceived body weight and actual body weight (35, 38). Besides, large cohort studies have revealed that underweight in adolescence significantly could predict depressive symptoms in adulthood, and depressive symptoms in early life also predicted underweight in men in adulthood, suggesting a bidirectional relationship between underweight and depressive symptoms (16).

Historical literature suggested a bidirectional association between depressive symptoms and obesity (14), and the relation between depressive symptoms and obesity seemed to be stronger than that between obesity and depressive symptoms (39). In previous studies, mental health of obese adolescents was significantly lower than that of normal-weight adolescents (40), and obese adolescents may have higher stress levels, depressive symptoms, and lower psychological resilience (41), which were related to stronger inferiority complex, body dissatisfaction, and impaired self-esteem (42, 43). A systematic review of 17,894 participants found that obese adolescents had an obviously higher incidence of depressive symptoms than non-obese adolescents (21.73% vs. 17.96%) (44). Secondly, studies have shown that women who were heavier in adolescence and gained weight significantly in early adulthood had a significantly higher risk of new onset depression (45). Obesity was a significant predictor of depressive symptoms in children and adolescents aged 7–18 years old (46, 47). In addition, compared to healthy weight adolescents, the level of depression in obese adolescents was significantly higher (48), and the risk of developing depressive disorder in the latter group was increased by 1.85 times or more (11, 49). On the other hand, the risk of obesity in children and adolescents with MDD was increased by 2 times (50), and depressive symptoms were closely related to adolescence obesity (51). Furthermore, depressive symptoms could significantly predict adult overweight or obesity (15), while early identification and reduction of depressive symptoms could effectively prevent the occurrence of obesity (52).

In addition to the relationship between measured body weight and depressive symptoms, adolescents who perceived themselves as overweight had a significantly increased risk of depressive symptoms (36). Compared to adolescents with normal weight perception, adolescents who considered themselves overweight had a higher incidence of depression and significantly poorer mental health (53). In addition, a follow-up study showed that self-perceived overweight in early adolescence predicted symptoms of depression and anxiety one year later (54). At present, the causality of the bidirectional relationship between depressive symptoms and obesity is not clear, but both of them do have negative effects on each other.

We found the rates of suicidal ideation and attempted suicide in children and adolescents with MDD were 17.2 and 9.9%, respectively. A study involving five countries in Southeast Asia showed that the prevalence of suicidal ideation and attempted suicide among middle school students were 11.7 and 2.4%, respectively, (22), while the prevalence of suicidal ideation among Chinese adolescents was 15.7% (6), and suicidal ideation or attempted suicide was significantly related to adolescent depressive symptoms and underweight or overweight (6, 22). Previous study has shown that male BMI level was negatively correlated with suicide attempts, and with every 5 kg/m^2 increase in BMI, the risk of suicide might decrease 15% (23). The U-shaped correlation between BMI level and attempted suicide in depressed women indicates that underweight or obese was related to the higher risk of attempted suicide (24). Other studies have pointed to attempted suicide as an independent risk factor for overweight in adolescents (55). In addition, suicidal ideation and attempted suicide were significantly correlated with self-perception of being overweight or underweight. People who thought they were underweight or overweight had an elevated risk of suicidal ideation or attempted suicide compared to people who thought they were normal weight (38). However, the results of this study showed that suicidal ideation is a protective factor for obesity in children and adolescents with MDD, which is similar to the results of related studies, and may be related to the severe depressive symptoms, long course of disease, and low daily food intake of the subjects (23, 24).

The results of this study suggested that higher dosage of antidepressants was a protective factor for obesity in children and adolescents with MDD. A meta-analysis of 42 studies showed that (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) may improve patients' body weight in the short term, while the long-term effect remains unclear (56). Moreover, former study has pointed out that the higher body mass index was correlated to selective serotonin reuptake inhibitors (SSRIs) treatment in adolescents (57), and the widespread use of antidepressants may lead to a significantly higher long-term risk of weight gain (58). The latest review indicated that weight change induced by antidepressants involves central and peripheral mechanisms, including histamine, cholinergic, 5-serotonin (5-HT), norepinephrine, dopamine, and peripheral effects (59). However, strong evidence demonstrated that fluoxetine was an antidepressant with the low risk of weight gain, and short-term use usually had no significant effect on body weight, or might reduce body weight in obese patients (60, 61). Because the subjects in this study were adolescents, most of the patients took fluoxetine, which might have no effect on weight gain in the short term or improve the body weight index of the patients. Although the prevalence of overweight or obesity in children and adolescents with MDD is significantly increased and is associated with clinical drug use, there are still few clinical trials evaluating antidepressant drug-induced obesity in children and adolescents with MDD.

Our study has several limitations. First, the cross-sectional nature of this study makes it difficult to determine the causal relationship between being underweight or obese and suicidal ideation or attempted suicide. And it seems that the causal relationship between suicidal ideation, high dose of antidepressants and obesity could not be determined. Second, the questionnaire in this study was mostly subjective, and there was no objective scale to assess the psychiatric symptoms of each subject other than depressive symptoms. Subsequent studies can introduce a variety of clinical assessment scales to track the changes of patients' disease outcome and psychiatric symptoms, so as to clarify the clear correlation between depressive symptoms, weight change, suicidal ideation and attempted suicide in children and adolescents' inpatients with MDD.

Conclusion

The high rates of obesity and suicide in children and adolescents have become serious public health problems worldwide, especially in children and adolescents with MDD. The prevalence of underweight, obesity, suicidal ideation and attempted suicide were high in children and adolescents with MDD, and severe depressive symptoms are

independent risk factors for obesity, while suicidal ideation and high dose of antidepressants may be protective factors for obesity. In clinical treatment, the weight changes of patients should be closely detected, and the drugs with less influence on weight should be selected as far as possible. The clinical psychiatric symptoms of patients should be evaluated regularly, and the occurrence of suicidal ideation and attempted suicide should be closely monitored to reduce the occurrence of related adverse events.

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 Medical Ethics Committee of the Third People's Hospital of Fuyang. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ZL, LiS, YZ, JW, and RY collected and statistically analyzed the data, and wrote the first draft. 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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A cross-sectional study of non-suicidal self-injury in a Chinese adolescent inpatient cohort

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Background: Non-suicidal self-injury (NSSI) is a significant predictor of completed suicide and is increasingly recognized as a serious public health concern. Multiple factors, including social, familial, mental, and genetic factors could influence the occurrence of this behavior. Identifying the early risk factors is important for screening and preventing this behavior.

Methods: Here, we recruited a total of 742 adolescent inpatient participants from a mental health center and conducted a series of diagnostic interviews and questionnaires to assess NSSI behavior and other events. Bivariate analysis was used to detect differences between groups in NSSI and non-NSSI. Then, binary logistic regression was fitted to identify predictors of NSSI as a function of these questionnaire scores.

Results: Of the 742 adolescents examined, a total of 382 (51.5%) participants engaged in NSSI. Bivariate analysis showed that age, gender, depression, anxiety, insomnia, and childhood trauma was significantly associated with NSSI. Logistic regression results suggested that females had 2.43 higher odds of engaging in NSSI when compared to their male counterparts (OR=3.43, 95%CI=2.09–5.74, $p=1.70\times10^{-6}$). Depression was a primary risk predictor for NSSI with each additional increase in symptoms of depression increasing the odds of engaging in NSSI by 18% (OR=1.18, 95%CI=1.12–1.25, $p=2.25\times10^{-8}$).

Conclusion: More than half of the adolescent inpatients with psychiatric disorders have NSSI experience. Depression and gender were the risk factors for NSSI. Age at a specific range had a high prevalence of NSSI.

KEYWORDS

non-suicidal self-injury, inpatient, adolescent, depression, gender

Introduction

Non-suicidal self-injury (NSSI) is defined as the direct and deliberate destruction of one's own bodily tissue, in the absence of any suicidal intent. This behavior typically involved cutting or carving the skin and has a consistent presentation cross-nationally (1). According to a 30 years epidemiology investigation study estimated in 2019, the aggregate lifetime prevalence of NSSI

was 22.1% in children and adolescents (2). In particular, in inpatient cohorts with psychiatric disorders, the one-year prevalence of NSSI was as high as 62.2% (3). Moreover, the prevalence of NSSI had increased substantially in recent years (4). It was one of the strongest predictors of completed suicide (5, 6) and more attention should be paid to NSSI individuals from family and society.

So far, many risk factors have been identified to be associated with NSSI. First, a number of investigations suggested that childhood maltreatment (including sexual abuse, physical abuse, physical neglect, and emotional abuse), particularly childhood emotional abuse, was associated with NSSI (7, 8). However, other studies also found a non-significant relationship between childhood emotional abuse and NSSI, and sexual abuse featured prominently in NSSI (9, 10). Second, gender could have an influence on NSSI behavior, in which several studies showed girls were more likely to engage in NSSI than their male counterparts (9, 11, 12), though other studies failed to find any significant association between gender and NSSI (13–15). Third, depression and mood disorders were known predictors of NSSI and this association was found in almost all NSSI risk factor studies (9, 16, 17). Additionally, although studied less, genetics was also reported to be associated with NSSI, and the single nucleotide polymorphism (SNP) heritability of NSSI was estimated to be 13% (18). Adolescents who carried a mutation in the serotonin transporter gene *SLC6A4* showed an elevated likelihood of engaging in NSSI when exposed to severe interpersonal stress (19). Other factors, like maternal criticism (20), school bullying, peer rejection (21), cigarette smoking (22, 23), etc. were also the risk factors for NSSI.

Despite the increasing number of studies on NSSI, some results were inconsistent and most of these studies were conducted on people of European ancestry. Due to the large amount of NSSI behavior among Chinese children and adolescents (13, 24, 25), there is a need for studies of risk factors for NSSI in Chinese populations. Therefore, the aim of the current study is to investigate the risk factors for NSSI in a Chinese cohort. We collected a total of 742 inpatients aged from 11 to 19 in a mental health hospital in China. The self-rating scales and face-to-face interviews, including Self-Rating Depression Scale (SDS), Childhood Trauma Questionnaire-Short Form (CTQ-SF), and the Life Event Scale (LES), etc., were used to measure the depression state, childhood maltreatment, and negative life events, and so on. Then, the chi-square test and one-way analysis of variance (ANOVA) were conducted to compare the categorical variables and continuous variables between different genders, suicidal attitude, depression degree, etc. among children and adolescents who engaged in NSSI versus children and adolescents who did not engage in NSSI. Furthermore, binary logistic regression was chosen to establish the relationship between early childhood events, depression state, and NSSI behavior.

Methods

Sample collection

All the samples used in this study were collected from the child and adolescent inpatient ward of Wuhan Mental Health Center from October 2018 to December 2019. The basic population information, including gender, age, and grade was recorded. Individuals with other organic diseases or a history of smoking and drinking were excluded from this study. A total of 742 Han Chinese adolescents aged 11–19 years old (Mean = 14.69; SD = 1.69) were analyzed in this study. All participants wrote the informed consent, and for those participants aged under 18 years old, written informed consent of all legal guardians was gathered. The study protocol has been accepted by the ethics committee of the Wuhan Mental Health Center, China.

Scale description

NSSI behavior

The dependent variable in this study was a single question about NSSI; "Have you, in the recent past 12 months, had an episode of self-injury without any intention of committing suicide?" The participants were asked to answer yes or no (1 = No, 2 = Yes).

PHQ-9 depression scale

The Patient Health Questionnaire-9 (PHQ-9) depression scale, which is based on 9 core symptoms of depression diagnosis described in DSM-IV, was used to measure depression state (26). Generally, this scale has 9 questions about "Over the last 2 weeks, how often have you been bothered by any of the following problems," such as "Little interest or pleasure in doing things," "Feeling down, depressed, or hopeless." Each question has four choices (0 = Not at all, 1 = Several days, 2 = More than half the days, 3 = Nearly every day). Participants need to answer all 9 questions and the total score of the 9 items is the final depression score. The higher score indicates the more severe depression.

Generalized anxiety disorder 7-item scale

The GAD-7 scale, which is based on 7 core symptoms of anxiety described in DSM-IV, was used to measure the anxiety state (27). This scale had 7 questions about "Over the last 2 weeks, how often have you been bothered by any of the following problems," like "Feeling nervous, anxious, or on edge," "Not being able to stop or control worrying." Like PHQ-9, each question had four choices (0 = Not at all, 1 = Several days, 2 = More than half the days, 3 = Nearly every day). Participants need to answer all 7 questions and the total score of the 7 items is the final anxiety score. Higher scores represent more severe anxiety symptoms.

Childhood trauma questionnaire-short form scale

The CTQ-SF scale was used to assess the childhood negative experiences. The CTQ-SF was a widely used self-report assessment that measures exposure to five types of trauma - physical, sexual, and emotional abuse, and physical and emotional neglect (28). The CTQ-SF consisted of 25 trauma evaluation items and three validity items. Each type of maltreatment was represented by five items, like when I was growing up "I thought that my parents wished I had never been born" for emotional abuse, "Someone tried to touch me in a sexual way or tried to make me touch them" for sexual abuse, to provide adequate reliability and content coverage, while the three-item Minimization/Denial validity scale, like "I had the perfect childhood," was used to detect the underreporting of maltreatment (28). Each of the abuse and neglect subscales items was rated on a 5-point Likert

scale (1 = Never true, 2 = Rarely true, 3 = Sometimes true, 4 = Often true, 5 = Very often true) and a special maltreatment score was the total score of 5 relative items. Higher scores indicate more severe childhood maltreatment.

Perceived devaluation and discrimination scale

The PDD scale was one of the most widely-applied measurements, which consisted of 12 questions, like "People would accept someone who had mental illness as a friend" (question 1) and "People think that seeking psychiatric services is a mark of personal failure" (question 5), that measure individual's perceptions of social attitudes toward mental illness on stigma and discrimination (29). Each question had a five-point scale answer which ranged from "strongly agree (score 1)" to "strongly disagree (score 5)." Half of the questions of the scale (questions 5, 6, 7, 9, 11, 12) need to be reverse scored. The sum score of the 12 items was the total score of the PDD scale. Higher scores indicate greater severity of the perceived devaluation and discrimination.

Pittsburgh sleep quality index scale

The PSQI was one of the most widely used sleep questionnaires, which consisted of 19 self-rating questions and 5 observer-rating questions that assess a number of aspects of sleep quality (30). Respondents were asked to indicate how frequently they have experienced certain sleep difficulties over the past month and to rate their overall sleep quality. Scores for each question ranged from 0 to 3, with higher scores indicating more acute sleep disturbances. Details about the question setting, reliability, and validity of this questionnaire could be found in the original publication (30).

Suicide attitude questionnaire scale

Suicidal ideation was defined as seriously thinking of killing oneself and was measured by the QSA scale (31). This self-report questionnaire consisted of 29 questions rating on 4 sub-scale (a 5-point Likert scale each, to rate suicide attitudes from 1 = "strongly agree" to 5 = "strongly disagree"): attitude to suicide behavior (questions 1, 7, 12, 17, 19, 22, 23, 26, 29), attitude to suicide (question 2, 3, 8, 9, 13, 14, 18, 20, 24, 25), attitude to family members of suicide (question 4, 6, 10, 15, 28), and attitude to euthanasia (question 5, 11, 16, 21, 27). Thirteen items (questions 1, 3, 7, 8, 10, 11, 12, 14, 15, 18, 20, 22, 28) need reverse scoring. The sum score of a sub-scale is the total score with a higher score indicating less tolerance to suicide. A score less than 2.5 (code as 1) indicated an approbatory attitude to suicide; a score of 2.5–3.5 (code as 2) indicated a neutral attitude; scores more than 3.5 (code as 3) indicated an opposing attitude.

Adolescent self-rating life events check list

The ASLEC was used to assess whether the negative events occurred, and if any, how serious the impact is on the participant in the past year (32). It listed 26 negative life events, like "beaten by parents" and "failure in an exam," covering 5 aspects: interpersonal stress, study pressure, adaption, loss, and being punished. Participants were asked to answer whether each negative event occurred in the last year. Each question had a five-point scale answer which ranges from 0 (Not happen) to 1 (if occurred, but no effect) and 5 (if occurred, strong impact).

Social support rating scale

The SSRS was a widely used 10-item questionnaire for measuring social support in the Chinese adolescent population from 3 dimensions: objective social support (3 items), subjective social support (4 items), and utilization of social support (3 items) (33, 34). Objective social support refers to material and tangible support; subjective social support refers to emotional support, which was the feelings of respect, support, and being understood. A higher score indicated more social support.

The multidimensional scale of perceived social support scale

MSPSS was a 12-item questionnaire, which measured perceived social support in 3 dimensions: family (questions 3, 4, 8, 11), friends (questions 6, 7, 9, 12), and significant others (questions 1, 2, 5, 10) (35, 36). Each dimension had 4 questions, such as "There is a special person who is around when I am in need," scored on a seven-point Likert scale, ranging from 1 (very strongly disagree) to 7 (very strongly agree). The sum score of 4 questions of a subscale was the total subscale score and a higher score represented higher perceived social support.

Statistical analysis

Descriptive statistics for all the variables were first conducted using percentages for the categorical variables. For continuous variables (like age, depression, anxiety, etc.), mean, standard deviation (SD), and range were computed. Then Pearson chi-square test of association was used to test the bivariate association between NSSI and the categorical variables and one-way analysis of variance (ANOVA) was used to compare the mean value of continuous variables in adolescents who engaged in NSSI versus adolescents who did not engage in NSSI. Furtherly, the Binary logistic regression was fitted to identify risk factors for NSSI as a function of gender, age, depression, anxiety, sleep quality, etc. A series of model fitness indexes were leveraged to evaluate the general fit of the model, including the Hosmer-Lemeshow test, Omnibus Tests of model Coefficients, and Nagelkerke pseudo-R square. The Hosmer-Lemeshow test and Nagelkerke pseudo-R square, which is used frequently in risk prediction models, were employed to test for goodness of fit for logistic regression models (37, 38). The Omnibus Tests of model Coefficients were used to evaluate the statistical significance of the logistic regression model. Predictors were considered significant if the value of p was less than 0.05. Odd ratios (OR) and 95% confidence interval (CI) were recorded. All statistical analyses were conducted with R (version 4.0.2). HosmerLemeshowTest and PseudoR2 function

in DescTools package (version 0.99.42) were used to conduct the Hosmer-Lemeshow test and compute the Nagelkerke pseudo-R square, respectively (39). All the data analysis R code could be found at https://github.com/wuyong0103/NSSI.

Results

Descriptive statistics

The demographical and clinical characteristics of the master sample were summarized in Table 1. In all, we collected 742 Chinese adolescent inpatients aged 11–19 years old. Of these participants, 51.5% (382 individuals) self-reported being engaged in NSSI. Approximately three out of four (71.3%) female adolescents had NSSI behavior. More than half of the inpatient respondents agreed with suicide (54%) and euthanasia (58.4). The mean and SD for traumatic symptoms are for depression: 14.64 (7.36), anxiety: 10.87 (5.87), stigma: 38 (9.86), insomnia: 8.81 (4.34). Childhood trauma, adolescent life events, social support, and perceived social support results were listed in Table 1.

Bivariate analysis

We then conducted a series of chi-square (Table 2) and one-way ANOVA (Table 3) analyses between adolescents who engaged in NSSI and who did not engage in NSSI on categorical variables and continuous variables, respectively. As shown in Table 2, we found the frequency of NSSI was significantly higher in girls (58.8%) than in boys (23.0%, $\chi^2 = 76.43$, $p < 2.2 \times 10^{-16}$). The attitude toward suicidal behavior was also significantly different between individuals engaged in NSSI and individuals not engaged in NSSI, with the former showing more tolerance toward suicidal behavior (74.6% NSSI individuals answered "Yes" versus 8.6% no NSSI individuals answered "Yes" to suicide behavior, $\chi^2 = 249.07$, $p < 2.2 \times 10^{-16}$). Compared to individuals engaged in NSSI, individuals without NSSI behaviors were more cautious about euthanasia (60.7% NSSI individuals answered "Yes" versus 16.4% no NSSI individuals answered "Yes" to euthanasia, $\chi^2 = 69.02$, $p = 1.03 \times 10^{-15}$).

Most of the continuous variables examined in this study were significantly associated with NSSI as shown in Table 3. In terms of age, the younger individuals seemed to be more inclined to NSSI ($Mean_{noNSSI} = 15.01$ versus $Mean_{NSSI} = 14.36$, $p = 1.12 \times 10^{-7}$). Consistent with other studies (40, 41), depression ($Mean_{noNSSI} = 10.46$ versus $Mean_{NSSI} = 19.09$, $p < 2 \times 10^{-16}$) and anxiety ($Mean_{noNSSI} = 8.27$ versus $Mean_{NSSI} = 13.63$, $p < 2 \times 10^{-16}$) were also significantly associated with NSSI in our study. Adolescents were more likely engaged in NSSI if they: had a low level of self-stigma ($Mean_{noNSSI} = 40.72$ versus $Mean_{NSSI} = 35.13$, $p = 3.29 \times 10^{-15}$), were disturbed by insomnia ($Mean_{noNSSI} = 6.91$ versus $Mean_{NSSI} = 10.82$, $p < 2 \times 10^{-16}$), were more emotionally abused ($Mean_{noNSSI} = 9.07$ versus $Mean_{NSSI} = 11.91$, $p < 2.23 \times 10^{-16}$), were more emotionally neglected ($Mean_{noNSSI} = 13.45$ versus $Mean_{NSSI} = 16.14$, $p = 1.73 \times 10^{-11}$), experienced more negative events or were more affected by negative events (Table 3, interpersonal stress, study pressure, adaption, loss and punish score were significantly higher in NSSI group compared with non-NSSI group), gained less support from society (SumSocial: $Mean_{noNSSI} = 53.10$ versus

TABLE 1 Sample characteristics (N=742).

Variables	Frequency (%)	Mean	SD
Age at assessment		14.69	1.69
Engaged in NSSI			
Yes	382 (51.5)		
No	360 (48.5)		
Gender			
Male	213 (28.7)		
Female	529 (71.3)		
Depress		14.64	7.36
Anxiety		10.87	5.87
Stigma		38.00	9.86
Insomnia		8.81	4.34
Emotional abuse		10.45	4.81
Body abuse		7.49	3.74
Sex abuse		5.88	2.27
Emotional neglect		14.75	5.54
Body neglect		9.50	3.43
Attitude to suicide behavior			
Approbatory	406 (54.7)		
Neutral	231 (31.1)		
Opposed	105 (14.2)		
Attitude to suicide			
Approbatory	570 (76.8)		
Neutral	162 (21.8)		
Opposed	10 (1.3)		
Attitude to suicide dependent			
Approbatory	417 (56.2)		
Neutral	311 (42.0)		
Opposed	14 (1.9)		
Attitude to euthanasia			
Approbatory	433 (58.4)		
Neutral	248 (33.4)		
Opposed	61 (8.2)		
Interpersonal stress		9.67	6.21
Study pressure		9.84	4.88
Adaptation		9.18	4.73
Lose		7.56	5.30
be punished		8.92	6.50
Support from family		15.92	6.71
Support outside of family		32.08	12.36
Sum perceived support		47.82	17.59
Objective support		8.03	2.84
Subjective support		15.48	3.92
Utilization support		6.27	2.20
Sum social support		29.87	7.40

TABLE 2 Bivariate association between NSSI and predictors (N=742).

Variables	History of NSSI		Chi-square	*p*-value
	No	Yes		
Gender				
Male	164	49	76.43	$< 2.20 \times 10^{-16}$
Female	218	311		
Attitude to suicide behavior				
Approbatory	103	303	249.07	$< 2.20 \times 10^{-16}$
Neutral	183	48		
Opposed	96	9		
Attitude to suicide				
Approbatory	260	310	34.25	3.65×10^{-8}
Neutral	114	48		
Opposed	8	2		
Attitude to suicide dependent				
Approbatory	210	207	0.58	0.75
Neutral	164	147		
Opposed	8	6		
Attitude to euthanasia				
Approbatory	170	263	69.02	1.03×10^{-15}
Neutral	161	87		
Opposed	51	10		

TABLE 3 ANOVA result between NSSI and predictors (N=742).

Variables	NO NSSI	NSSI	*p*-value
	Mean (SD)	Mean (SD)	
Age	15.01 (1.74)	14.36 (1.56)	1.12×10^{-7}
Depress	10.46 (6.52)	19.09 (5.30)	$<2.00 \times 10^{-16}$
Anxiety	8.27 (5.56)	13.63 (4.86)	$<2.00 \times 10^{-16}$
Stigma	40.72 (9.19)	35.13 (9.73)	3.29×10^{-15}
Insomnia	6.91 (3.87)	10.82 (3.89)	$<2.00 \times 10^{-16}$
Emotional abuse	9.07 (4.16)	11.91 (5.02)	$<2.23 \times 10^{-16}$
Body abuse	7.16 (3.47)	7.83 (3.99)	0.02
Sex abuse	5.73 (1.86)	6.03 (2.63)	0.08
Emotional neglect	13.45 (5.40)	16.14 (5.35)	1.73×10^{-11}
Body neglect	8.85 (3.11)	10.19 (3.62)	7.99×10^{-8}
Interpersonal stress	7.92 (4.29)	11.54 (7.30)	5.35×10^{-16}
Study pressure	8.62 (4.54)	11.14 (4.91)	8.12×10^{-13}
Adaptation	7.69 (4.37)	10.77 (4.59)	$<2.00 \times 10^{-16}$
Lose	6.79 (5.00)	8.37 (5.50)	4.51×10^{-5}
be punished	7.65 (5.75)	10.27 (6.99)	3.26×10^{-8}
Support from family	17.76 (6.50)	13.98 (6.39)	5.17×10^{-15}
Support outside of family	35.42 (12.24)	28.53 (11.48)	1.05×10^{-14}
Sum perceived support	53.10 (17.22)	42.23 (16.21)	$<2.00 \times 10^{-16}$
Objective support	8.43 (2.91)	7.61 (2.70)	7.24×10^{-5}
Subjective support	16.20 (4.06)	14.72 (3.62)	2.11×10^{-7}
Utilization support	6.78 (2.33)	5.73 (1.91)	4.48×10^{-11}
Sum social support	31.49 (7.56)	28.16 (6.84)	5.28×10^{-10}

$Mean_{NSSI} = 43.23$, $p < 2 \times 10^{-16}$), had lower levels of perceived social support (SumPerceived: $Mean_{noNSSI} = 31.49$ versus $Mean_{NSSI} = 28.16$, $p < 5.28 \times 10^{-10}$). However, unlike some previous studies (7, 11, 42, 43), we did not observe differences in childhood sexual abuse between adolescents engaged in NSSI and adolescents not engaged in NSSI. In fact, this might be partly due to, the sexual abuse score was relatively low among all participants (Table 1, Mean = 5.88, SD = 2.27).

Multivariate analysis

Although most of the variables in our study were significantly different between the NSSI group and the non-NSSI group, we could not confirm the net effect of each variable on NSSI. Because when we analyzed a specific variable, we could not exclude the influence of other factors on this variable. We then conducted binary Logistic regression analysis on NSSI using age, depression, anxiety, insomnia, and other variables as predictors. As results shown in Table 4, we observed gender, depression, and attitude toward suicidal behavior were the risk factors for NSSI. Females were 3.4 times more likely to be engaged in NSSI compared with their male counterparts (OR = 3.43, 95%CI = 2.08–5.74, $p = 1.70 \times 10^{-6}$). Each additional increase in symptoms of depression increases the odds of engaging in NSSI by 18%, net the effect of all the other predictors (OR = 1.18, 95% CI = 1.12–1.25, $p = 2.25 \times 10^{-8}$). Compared to adolescents with approbatory attitude to suicide behavior, adolescents, who were neutral (OR = 0.163, 95% CI = 0.10–0.27, $p = 4.05 \times 10^{-12}$) or opposed (OR = 0.13, 95% CI = 0.05–0.32, $p = 1.24 \times 10^{-5}$) to suicide behavior, were less likely being engaged in NSSI. Other factors were not significant in multivariate analysis.

The Hosmer-Lemeshow Goodness of Fit test result showed the overall fit of the model was good and the variables made a significant contribution to the model ($\chi^2 = 4.56$, $p = 0.80$). The chi-square value of the Omnibus Tests of Model Coefficients was 441.97 with a statisticaly significant $p < 0.001$. The Nagelkerker pseudo-R square was 0.599 which indicated that 59.9% variances of NSSI could be explained by all the predictors in the Logistic regression model. In all, 82.6% of adolescents could be correctly classified into the NSSI group and non-NSSI group according to the regression model.

Discussion

Here, we observed a total of 51.5% prevalence of NSSI in mental clinical adolescent inpatients. This prevalence was almost equal to that of prevalence in inpatients with psychiatric disorders (40–60%) from other reports (1, 9). Evidence from genetic (44) and epidemiological (41) studies also support that NSSI had a high comorbidity with mental illness. In this study, we also found depression, anxiety, insomnia, and childhood trauma (except for sexual abuse) were significantly associated with NSSI (Table 3).

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TABLE 4 Binary Logistic regression analysis of NSSI (N=742).

Variables	Estimate	SE	OR	95%CI	*p*-value
Intercept	−0.40	1.46	0.67	0.04–11.70	0.79
Gender - female	1.23	0.26	3.43	2.09–5.74	1.70×10^{-6}
Age	−0.09	0.07	0.91	0.80–1.04	0.18
Depress	0.17	0.03	1.18	1.12–1.25	2.25×10^{-8}
Anxiety	−0.02	0.03	0.98	0.92–1.05	0.59
Stigma	−0.01	0.01	0.99	0.97–1.02	0.57
Insomnia	0.00	0.04	1.00	0.94–1.07	0.99
Emotional abuse	−0.01	0.03	0.99	0.92–1.06	0.72
Body abuse	−0.02	0.04	0.98	0.91–1.05	0.56
Sexual abuse	0.03	0.05	1.03	0.93–1.14	0.60
Emotional neglect	−0.02	0.03	0.98	0.93–1.04	0.51
Body neglect	0.04	0.04	1.04	0.96–1.13	0.38
Attitude to suicide behavior					
Neutral	−1.81	0.26	0.16	0.10–0.27	4.05×10^{-12}
Opposed	−2.01	0.46	0.13	0.05–0.32	1.24×10^{-5}
Attitude to suicide					
Neutral	−0.13	0.29	0.88	0.50–1.56	0.66
Opposed	−0.67	1.26	0.51	0.04–4.90	0.60
Attitude to suicide dependent					
Neutral	−0.36	0.24	0.70	0.44–1.12	0.13
Opposed	−1.23	0.73	0.29	0.07–1.21	0.09
Attitude to euthanasia					
Neutral	0.37	0.27	1.45	0.87–2.47	0.16
Opposed	−0.17	0.55	0.85	0.28–2.44	0.76
Interpersonal stress	0.05	0.03	1.05	0.99–1.12	0.12
Study pressure	−0.04	0.03	0.96	0.91–1.02	0.17
Adaptation	0.04	0.03	1.04	0.98–1.11	0.22
Lose	−0.04	0.03	0.96	0.92–1.01	0.16
be punished	0.01	0.03	1.01	0.96–1.06	0.84
Support from family	0.07	0.07	1.08	0.96–1.28	0.30
Support outside of family	0.12	0.07	1.13	1.00–1.34	0.09
Sum perceived support	−0.12	0.07	0.89	0.75–1.00	0.09
Objective support	0.13	0.07	1.14	0.98–1.32	0.08
Subjective support	0.04	0.06	1.04	0.91–1.17	0.58
Utilization support	0.07	0.08	1.08	0.92–1.26	0.35
Sum social support	−0.07	0.05	0.94	0.84–1.05	0.22

Omnibus chi-square = 414.80 ($p < 0.001$).
Hosmer-Lemeshow G.O.F. test statistic = 9.34 ($p = 0.32$).
Nagelkerke pseudo-*R* square = 0.60.
Overall percent correctly classified = 82.6%.

The finding that NSSI was more common in younger adolescents than in older adolescents both corroborates and contradicts previous research on NSSI. Consistent with some previous studies (23, 45, 46), age was found significantly associated with NSSI in our investigation. However, different from some of the other studies (9, 47), which reported older adolescents were more likely to engage in NSSI, we observed a totally opposite trend that younger adolescents were more likely to engage in NSSI. Muehlenkamp and Gutierrez found that by age 13, 15% of their respondents had engaged in NSSI, and 26% had engaged in NSSI as the age increased to 14, then fell to 17% when the age went to 15 (14). This trend was also found in our study with the prevalence of NSSI in ages 11–13, 13–15, 15–17, and 17–19 were 55.8, 58.5, 48.6, and 29.1%, respectively. The parabolic prevalence of NSSI with age further suggested that age was indeed a risk factor

for NSSI and partially explained why age was not a significant predictor in the Logistic regression analysis. Why was the prevalence of NSSI high in ages between 12 and 15? A cross-sectional survey that used a measure of pubertal stage in individuals aged 12–15 years in schools showed that the onset of NSSI was related to the pubertal phase, especially late or completed puberty, rather than chronological age (45, 48). Another investigation also suggested that earlier-developing adolescents had a higher risk of NSSI and this increased risk attenuated as adolescents transition into adulthood (49). In addition, due to the liberalization of China's second-child policy, parents of these adolescents at this age range were distracted by the increase in family members, so they used this behavior to attract the attention of their parents. Inherently, this pathological behavior in puberty might be related to neurodevelopmental vulnerability around this time and changes hormonally, physically, psychologically, and socially (50, 51).

Results from some investigations showed that female adolescents were more likely to be engaged in NSSI (9, 52), whereas other scholars did not find any significance between different genders (15, 53, 54). Anyhow, in our survey, we did observe more girls engaged in NSSI. This gender difference might be due to the closer relationship between puberty and the onset of NSSI in girls than in boys (48) or the different manner in which males and females responded to stress or regulate emotions (9). Moreover, some scholars believed that female patients are exposed to greater childhood maltreatment, at least in the case of sexual abuse, could explain the gender differences (55, 56). However, in our research, we failed to find a relationship between childhood sexual abuse and NSSI.

Consistent with previous studies (23, 57, 58), we found depression, anxiety, and insomnia were significantly associated with NSSI. However, in the binary Logistic regression model, anxiety and insomnia were not predictors for NSSI. This might be due to the strong correlation between anxiety, insomnia, and depression (59). In fact, we indeed observed a significant correlation between anxiety (OR = 2.16, 95% CI = 2.03–2.30, $p < 2 \times 10^{-16}$), insomnia (OR = 1.72, 95% CI = 1.58–1.86, $p < 2 \times 10^{-16}$) and depression using linear regression model in our data. In addition, evidence from genetics correlation and Mendelian randomization also suggested depression and other psychiatric disorders, like attention-deficit/hyperactivity disorder and schizophrenia were the most plausible causal risk factors for NSSI (44).

Childhood trauma and negative adolescent life events were significantly associated with NSSI (60, 61), and have also been found in this study. However, sexual abuse, which was controversial in previous studies (7, 10), was not significant in our study. We found the total childhood sexual abuse score was relatively low compared to other forms of childhood trauma. A meta-analysis of child sexual abuse in China from 27 studies suggested the total child sexual abuse for Chinese girls was lower than the international composites, which might be attributed to Chinese Confucian culture, collectivist values, or the one-child policy (62). It was also possible that Chinese people were more reserved about sex, and adolescents were generally reluctant to disclose their experiences of sexual abuse to people they did not fully trust. Regardless, other forms of childhood trauma and youth negative events were indeed related to NSSI, although they were not significant in the Logistic regression analysis. Like anxiety and insomnia, these negative events might also be correlated with depression as reported by some other studies (63, 64).

Although the attitude to suicide behavior was significantly associated with NSSI and also significant in the Logistic regression model, this was probably due to the fact that the participants in our study were inpatients. The mental and psychological state of these adolescents during the questionnaire investigation might affect their judgment on some problems. Unfortunately, we did not collect the suicide attitude data when they were discharged from the hospital. Future studies might take this factor into their consideration.

We also summarize several limitations of this study. Firstly, we only collected samples from one hospital, which might lead to sample-collection bias in our result. Since China is a multi-ethnic country with a vast territory, sampling from one place may not be representative. As more attention is paid to NSSI, future multi-center studies could solve this problem well. Secondly, also about the sample collection, we only included samples from inpatient cohorts. Samples from outpatient or community, or remote areas, were not included in this study. Since inpatients were more severe than outpatients, this might lead to a winner's curse, in which we overestimated the effects of risk factors on NSSI. Lastly, the current study is a cross-sectional study, which only assessed the associations between depression, anxiety, insomnia, and negative life events with NSSI. Strictly, the cross-sectional study is not a type of cause-and-effect study. We need to use other methods, such as Mendelian randomization (65), animal experiments, etc., to confirm the causal relationship between these factors and NSSI.

In all, we found gender, depression, and attitude to suicidal behavior (at least during the hospital stay) were the risk factors for NSSI. Other factors like anxiety, insomnia, childhood trauma (except for sexual abuse), negative life events, and support from family and society might affect NSSI through depression. Age had a particular effect on NSSI, which might be the proxy of puberty. This reminds us that parents, schools, and society should pay more attention to the mental and physical health of children and adolescents, especially girls in puberty.

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 Ethics Committee of Wuhan Mental Health Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YW and JM designed the study. KS, AL, YL, JX, and YT recruited participants and collected the data. YW performed the statistical analysis and wrote the first draft of the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. 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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Gender difference in the associations of childhood maltreatment and non-suicidal self-injury among adolescents with mood disorders

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Background: Non-suicidal self-injury (NSSI) is a common feature among adolescents with mood disorders. Although childhood maltreatment has shown to be associated with non-suicidal self-injury (NSSI), previous studies have yielded mixed results in terms of different subtypes of childhood maltreatment and only few studies have investigated the effects of gender. The present cross-sectional study investigated effects of different types of childhood maltreatment on NSSI, as well as the role of gender in these effects.

Methods: In this cross-sectional study, a total of 142 Chinese adolescent inpatients with mood disorders (37 males and 105 females) were consecutively recruited within a psychiatric hospital. Demographic and clinical characteristics were collected. Participants were administered the Childhood Trauma Questionnaire (CTQ), the Functional Assessment of Self-Mutilation (FASM).

Results: 76.8% of the sample reported engaging NSSI in the previous 12 months. Female participants were more likely to engage in NSSI than males ($p<0.001$). Participants in the NSSI group reported significantly more experiences of emotional abuse ($p<0.001$) and emotional neglect ($p=0.005$). With regards to gender differences, female participants who have experienced emotional abuse were more likely to engage in NSSI ($p=0.03$).

Conclusion: As a whole, NSSI represents a frequent phenomenon among adolescent clinical populations and females were more likely to engage in NSSI than males. NSSI was significantly related to experiences of childhood maltreatment and specifically related to emotional abuse and emotional neglect over and above other types of childhood maltreatment. Females were more sensitive to emotional abuse than males. Our study highlights the importance of screening for subtypes of childhood maltreatment as well as considering the effects of gender.

KEYWORDS

non-suicidal self-injury, adolescent, childhood maltreatment, mood disorder, gender difference

1. Introduction

Non-suicidal self-injury (NSSI) is defined as the deliberate and direct destruction of one's body tissue without suicidal intent and for purposes not socially or culturally sanctioned (1). Common forms of NSSI include cutting, biting, hitting, burning, and scratching (2). NSSI is most present among adolescents, with an estimated lifetime prevalence to be 17.2% for adolescents compared to 5.5% for adults in community samples (3). NSSI is even more prevalent in clinical samples and usually co-occurs with mood disorders (4, 5). It has been identified as a strong predictor of subsequent suicide behavior for adolescents and people who engage in NSSI are more likely to die by suicide (6–9).

Previous research has shown the link between childhood maltreatment and NSSI (10, 11). Across the globe, the overall estimated prevalence of common types of child maltreatment were 12.7% for sexual abuse, 22.6% for physical abuse, 36.3% for emotional abuse, 16.3% for physical neglect, and 18.4% for emotional neglect (12). There is substantial evidence that experiencing childhood maltreatment increases the risk of NSSI in adolescence. Previous research from both community and clinical adolescent samples has shown strong associations between childhood maltreatment and NSSI (13–16). However, there are differences in the relationships between specific types of childhood maltreatment and NSSI. On the one hand, sexual abuse has received considerable research attention and there is some evidence that sexual abuse is associated with an increased risk of NSSI relationship (17–19). On the other hand, previous studies have yielded mixed results for other types of childhood maltreatment (10, 11). Further research is needed in this field.

In terms of gender difference, not enough studies have investigated the moderating role of gender in the relationship between childhood maltreatment and NSSI. One study found that physical abuse and physical neglect increased the odds of NSSI among females, but for males, only physical abuse was associated with more NSSI behavior (20). Yet another study found no impact of physical abuse on NSSI for both genders (13). The discrepancy might be explained by the heterogeneity of the study cohorts. As a whole, the role of gender remained unclear due to a lack of studies.

Patients with mood disorders were more likely to have experiences of childhood maltreatment and more susceptible to NSSI. In a study of patients with major depressive disorder and bipolar disorder, Janiri et al. found that childhood emotional abuse, the severity of depression and female gender were associated with lifetime suicide attempts (21). Another study has shown that there was a significant association between emotional abuse score and the age of onset in drug-free bipolar depression patients (22). These studies have suggested the specific role of childhood maltreatment in the occurrence and progression of mood disorder.

In China, a recent study found that 62.2% of patients with depression or bipolar disorder reported NSSI in the past year (5). In addition, a systematic review estimated that 8.7% of Chinese children have suffered sexual abuse, 26.6% physical abuse, 19.6% emotional abuse and 26.0% neglect (23). Considering the high prevalence of both NSSI and childhood maltreatment in China and their potential clinical consequences, it is of great importance to explore their relationship in people with mood disorders.

To better understand the risk factors related to NSSI as well as informing clinical implications for prevention and intervention, the current study aimed to investigate the association between specific types of childhood maltreatment and NSSI. We examined this relationship in a clinical adolescent sample, including an exploration of gender differences. It was hypothesized that individuals with experiences of childhood maltreatment would be more likely to engage in NSSI and this relationship would be different for specific types of maltreatment. In addition, gender would moderate the relationship between childhood maltreatment and NSSI.

2. Methods

2.1. Participants

The participants for this study were consecutively admitted adolescents to a psychiatric inpatient unit in Suzhou GuangJi Hospital between Jan 2021 and Dec 2021. The sample consisted of 142 subjects, including 37 males and 105 females. All participants recruited in this study met the following inclusion criteria: (1) aged between 12 and 18 years; (2) diagnosed with major depressive disorder or bipolar disorder currently with a depressive episode by two independent experienced psychiatrists, according to the International Statistical Classification of Disease and Related Health Problems, 10th Edition (ICD-10); (3) able to understand and participate in the clinical assessment. Exclusion criteria included intellectual disability, autism spectrum disorder, organic brain syndrome and any psychotic disorders such as schizophrenia. Patients diagnosed with two or more mental disorders were also excluded.

After a full explanation of the study, written consent was obtained from all participants. This study was approved by the ethical committees of Suzhou GuangJi Hospital. All study procedures were carried out in Suzhou GuangJi Hospital.

2.2. Measures

2.2.1. Demographic data

Basic demographic data included age, gender, years of education and residence. Clinical characteristics included age of onset, history of NSSI (yes, no).

2.2.2. Clinical symptoms measures

2.2.2.1. Non-suicidal self-injury

The Functional Assessment of Self-Mutilation (FASM) measures the methods and functions of NSSI. It is a self-report questionnaire to assess frequency of 11 NSSI behaviors and 22 function domains within the last 12 months (24). In the current study, we used the Chinese Version of FASM (C-FASM) (25). It includes a 10-item method checklist (e.g., cutting, scratching) and 15-item NSSI function checklist (e.g., to stop bad feelings; to punish yourself). Responses were rated on a scale of 1 (never) to 4 (very often). In the current study, we mainly used the method checklist and the Cronbach α coefficient of the method list was 0.78.

To avoid misunderstanding, researchers explained definition of NSSI to participants beforehand. Participants were told that: "self-injury means deliberately hurting yourself without the intent of killing yourself." Participants were then asked if they had self-injured in the last 12 months. Data regarding methods, frequency, severity, and age

at onset of NSSI behaviors was collected to ensure that they met the criteria of NSSI. In the current study, we used NSSI as a binary outcome for logistic regression analysis.

2.2.2.2. Childhood maltreatment

Childhood maltreatment was assessed by the Child Trauma Questionnaire (26). It is a 28-item self-report questionnaire assessing the severity of five types of childhood maltreatment: emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Responses were rated on a scale of 1 (never true)- 5 (very often true). A higher score indicates more experiences of childhood maltreatment. The CTQ has demonstrated good reliability and validity among Chinese adolescents (27). With the present study, the Cronbach α coefficient as a whole was 0.73.

2.3. Data analysis

To compare demographic data and clinical characteristics, Chi-square test and student t test were applied for categorical variables and continuous data, respectively. A binary logistic regression analysis, with the "enter" method, was conducted to examine the relationship between specific types of childhood maltreatment and NSSI. The computation of separate models for male and female participants allowed for the examination of gender differences. To control for the confounding variables, age and psychiatric diagnosis were specified as covariates. The magnitudes of association between NSSI behavior and specific types of child maltreatment were based on odds ratio with 95% confidence intervals. These OR can be interpreted as a measurement of increase or decrease of NSSI in the presence of different types of child maltreatment. All tests were performed with the Statistical Package for the Social Science (SPSS) version 23.0. The p-values were set as two-tailed with the significance level $\alpha = 0.05$.

3. Results

3.1. Social demographic and clinical characteristics of the sample

As shown in Table 1, with regards to demographic data, male participants were significantly older than female participants ($t = 3.15$, $p = 0.002$). There was no significant gender difference in any other social demographic characteristics including years of education and residence (both $p > 0.05$).

With regards to clinical characteristics, a total of 109 (76.8%) participants reported 12-month engagement in NSSI. Twenty male participants (54.1%) and 89 female participants (84.8%) reported engagement in NSSI within the last 12 months. The proportion of female participants in the NSSI group was higher than that of males compared with the non-NSSI group ($\chi^2 = 14.462$, $p < 0.001$). In terms of types of childhood maltreatment, male participants were more likely to experience physical neglect than female participants ($t = 2.486$, $p = 0.014$). There was no significant gender difference in any other types of childhood maltreatment (all $p > 0.05$). In addition, no significant gender difference was identified in terms of age at onset ($p > 0.05$).

TABLE 1 Social demographic and clinical characteristics of the sample.

	Male (n=37)	Female (n=105)	t/χ^2	p
Age	15.27 ± 1.67	14.32 ± 1.54	3.148	0.002**
Diagnosis				
Major depressive disorder	30(81.1)	89(84.8)	0.273	0.609
Bipolar disorder	7(18.9)	16(15.2)		
Age at onset				
	13.15 ± 2.83	12.82 ± 1.66	0.501	0.621
Years of education				
	9.05 ± 1.76	8.54 ± 1.58	1.64	0.104
Residence				
Rural	6	26	1.15	0.363
Urban	31	79		
NSSI				
Yes	20(54.1)	89(84.8)	14.462	<0.001***
No	17(45.9)	16(15.2)		
NSSI frequency				
	86.1 ± 22.8	121.7 ± 14.6	−1.27	0.206
CTQ subscale				
CTQ emotional abuse	10.8 ± 5.3	10.8 ± 4.6	0.041	0.967
CTQ physical abuse	7.8 ± 5.3	6.8 ± 3.2	1.471	0.143
CTQ sexual abuse	6.2 ± 3.3	6.5 ± 4.0	0.804	0.423
CTQ emotional neglect	13.1 ± 5.2	13.7 ± 4.6	−0.66	0.511
CTQ physical neglect	10.5 ± 3.8	9.0 ± 3.0	2.486	0.014*

Bold values meet significance at *P<0.05; **P<0.01; ***P<0.001.

3.2. Gender differences of childhood maltreatment experience between participants with and without NSSI

As shown in Table 2. participants in the NSSI group reported having experienced more childhood maltreatment than the non-NSSI group ($t = -2.85$, $p = 0.005$). In particular, participants who have experienced emotional abuse and emotional neglect were more likely to engage in NSSI ($t = -3.71$, $p < 0.001$; $t = -2.87$, $p = 0.005$). There was no significant difference in terms of any other types of childhood maltreatment (all $p > 0.05$).

With regards to gender differences, as shown in Table 3, the result of a binary logistic regression showed that emotional abuse was a

TABLE 2 CTQ scores of patients with and without NSSI.

	NSSI (*n*=109)	No NSSI (*n*=33)	*T*	*p*
CTQ total score	48.7 ± 14.2	41.0 ± 11.3	−2.853	0.005*
CTQ emotional abuse	11.6 ± 5.0	8.2 ± 2.9	−4.910	<0.001***
CTQ physical abuse	7.2 ± 4.0	6.5 ± 3.4	−0.879	0.381
CTQ sexual abuse	6.4 ± 3.6	5.5 ± 1.9	−1.773	0.079
CTQ emotional neglect	14.1 ± 4.9	11.5 ± 4.0	−2.871	<0.005**
CTQ physical neglect	9.4 ± 3.3	9.3 ± 3.3	−0.225	0.822

Bold values meet significance at *$P<0.05$; **$P<0.01$; ***$P<0.001$.

significant predictor of NSSI for females. For each additional point a female scored on emotional abuse scale, the odds of NSSI behavior increased by approximately 40%. However, there were no significant predictors for NSSI among male participants (All $p>0.05$).

4. Discussion

The present study examined the relationship between NSSI and childhood maltreatment in an adolescent inpatient sample with mood disorders, including an exploration of gender differences. The major findings showed that childhood maltreatment predicted the risk of NSSI, and this relationship was different for specific types of maltreatment. Additionally, gender moderated the relationship between childhood maltreatment and NSSI.

The present study showed that in an adolescent inpatient sample with mood disorders, 76.8% reported engaging NSSI in the past 12 months. The rate appears a little higher compared to some previous studies (60–72%) regarding inpatient samples (17, 28, 29). This might be due to the fact we used FASM to measure NSSI which also includes minor forms of NSSI (e.g., Bit yourself). In addition, our inpatient sample included more females than males compared to previous studies, and these participants were diagnosed with either major depressive disorder or bipolar disorder Previous studies have shown that patients meeting NSSI disorder criteria were significantly more likely to be female and to be diagnosed with a mood disorder (30). Our results showed that female participants were more likely to engage in NSSI than their male counterparts. This finding is consistent with previous observations that NSSI is more frequently seen in females and that this disparity is generally greater in clinical populations (31–33). One explanation is that females were more dependent on NSSI to regulate their negative emotions (34, 35). Another possibility is that males are less likely than females to report NSSI (36).

The NSSI group scored significantly higher in the emotional abuse and neglect subscales of CTQ, suggesting that mood disorder patients with NSSI behaviors were more likely to have experiences of emotional abuse and neglect. There is some support for these relations (17, 37, 38). A recent meta-analysis (11) found pooled ORs ranged from small-to-medium effects for emotional neglect to medium-to-large for emotional abuse. With regards to the relation between emotional abuse and NSSI, Glassman and colleagues suggested that this relation is partially explained by the presence of self-criticism: Experiencing emotional abuse in one's childhood may result in internalizing a negative critical thinking style toward the self and when these adolescents are faced with stressful events later in life, they are more likely to engage in NSSI for self-punishment (37).

In the present study, we found no statistically significant relationship between childhood sexual abuse and NSSI, which contradicted previous findings (17, 39, 40). This may be due to the low prevalence of sexual abuse in our sample rather than an indication of no relationship. Previous research showed that China has a lower incidence of sexual abuse than other countries (41). A meta-analysis showed that the prevalence of sexual abuse was 10.8% for Chinese women, which was lower than 19.7% for women in all countries, and for Chinese men, the rate was 4.8% compared to 7.9% globally (12). On the other hand, we did a further analysis showing that in those who engaged in NSSI, sexual abuse experience was positively correlated with NSSI frequency, suggesting that individuals may adopt NSSI as a coping strategy to sexual abuse.

There were some noteworthy gender differences. Emotional abuse seems to play an important role in NSSI behavior, especially for females. In unadjusted analysis, female patients with a history of NSSI behavior have significantly higher scores in the emotional abuse subscale, however, this was not found for males. This gender difference persisted even after adjusting for age and diagnosis. The results suggest that females are more sensitive to emotional abuse than their male counterparts, with a higher risk to result in NSSI behaviors. This finding is consistent with a previous study of clinical samples: Bernegger and colleagues showed in a clinical sample with mood disorders, emotional abuse was significantly associated with an increased odds ratio of NSSI for females but not for males (13). However, this finding is inconsistent with another previous study where researchers found little impact of emotional abuse on NSSI but physical abuse to be a significant risk factor for both genders (20). This might be due to the heterogeneity of the study cohorts. Our sample was recruited from inpatient clinics, which was similar to Bernegger's sample, whereas Swannell and colleagues recruited participants from the general population (13, 20). This may suggest different underlying mechanisms of effects of childhood maltreatment on NSSI behaviors between clinical samples and the general population, and future research is needed to clarify these differences. The findings highlight the importance to examine separate effects of subtypes of childhood maltreatment on NSSI behaviors and gender should be considered as a moderating factor.

Results from the present study suggest that it is important to screen for childhood maltreatment history as it is useful to predict the risk of NSSI. Although overall childhood maltreatment is linked with NSSI, specific subtypes have different associations with NSSI and should be viewed independently. Despite these findings, there were several limitations in the current study. Firstly, this study was cross-sectional with a relatively small sample size, and longitudinal studies with larger sample size are needed in the future to better understand the temporal relationship between child maltreatment and NSSI. Another potential limitation was that we used retrospective self-report of child maltreatment which may suffer from the natural process of forgetting. There is also a likelihood that people with depression or bipolar disorder may have memory bias that their cognitive styles may lead to exaggerating past negative events (42–44). In the current study, we have attempted to reduce bias by clearly explaining the definition of child maltreatment to participants. Furthermore, adverse childhood experiences include

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TABLE 3 Logistic regression of Non-suicidal Self-Injury (NSSI) on Childhood Trauma Questionnaire Subscale Scores.

Predictor	Male								Female							
	Incidents of NSSI (unadjusted)				Incidents of NSSI (adjusted)				Incidents of NSSI (unadjusted)				Incidents of NSSI (adjusted)			
	B	SE	OR	95%C.I.	B	SE	OR	95%C.I.	B	SE	OR	95%C.I.	B	SE	OR	95%C.I.
CTQ emotional neglect	0.1	0.12	1.1	0.88–1.38	0.09	0.12	1.1	0.87–1.40	0.08	0.09	1.09	0.09–1.31	0.05	0.1	1.06	0.87–1.28
CTQ physical abuse	−0.3	0.16	0.75	0.54–1.02	−0.3	0.16	0.76	0.56–1.04	−0.02	0.15	0.81	0.61–1.10	−0.2	0.16	0.8	0.59–1.10
CTQ emotional abuse	0.32	0.17	1.38	1.00–1.90	0.25	0.17	1.28	0.92–1.78	0.33	0.15	1.40*	1.04–1.87	0.35	0.16	1.42*	1.04–1.94
CTQ sexual abuse	0.42	0.37	1.52	0.74–3.11	0.39	0.32	1.47	0.79–2.75	0.06	0.14	1.06	0.81–1.38	0.05	0.14	1.05	0.81–1.37
CTQ physical neglect	0.08	0.15	1.08	0.81–1.43	0.13	0.16	1.14	0.84–1.54	−0.2	0.13	0.79	0.61–1.03	−0.02	0.13	0.81	0.53–1.05

OR, odds ratio; C.I., confidence intervals; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

many items other than childhood maltreatment such as parental separation and having family members in prison, whereas we did not include all these types in our study. Future studies may explore these items and to compare their effects on NSSI and mood disorders. Finally, our study subjects were inpatients, which may affect the prevalence of NSSI and the effects of childhood maltreatment. A healthy control cohort may help to compare the differences and improve the study.

Despite these limitations, our study highlights the importance of screening for subtypes of childhood maltreatment as it is a risk factor for NSSI in patients with mood disorders. In addition, clinicians should be aware of gender differences. Future research is needed to address the underlying mechanisms of gender difference.

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 Ethics committee of Suzhou GuangJi Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XD and YY designed the study. RY, FZ, XY, XL, PZ, ZL, and XZ collected materials from study participants and conducted the analysis of all data. YW drafted the initial manuscript. XD, YY, ZW and ZL contributed to the revision of the manuscript. All authors 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.

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Non-suicidal self-injury function: prevalence in adolescents with depression and its associations with non-suicidal self-injury severity, duration and suicide

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Background: Given that adolescents with depression are at the highest risk for non-suicidal self-injury (NSSI), a thorough understanding of their NSSI functions, as well as associations between functions and severe behavioral consequences, is essential for risk assessment and invention development.

Methods: Adolescents with depression from 16 hospitals across China, for whom data was available regarding their NSSI function, frequency, number of methods used, time characteristics, and suicide history were included. Descriptive statistical analyses were performed to determine the prevalence of NSSI functions. Regression analyses were conducted to explore the relationship between NSSI functions and behavioral characteristics of NSSI and suicide attempts.

Results: Affect regulation was the primary function of NSSI and followed by anti-dissociation in adolescents with depression. Females recognized automatic reinforcement functions more frequently than males, while males had a higher prevalence of social positive reinforcement functions. Automatic reinforce functions played the prominent role in associations between NSSI functions and all the severe behavioral consequences. Specifically, functions of anti-dissociation, affect regulation, and self-punishment were all associated with NSSI frequency, while higher levels of endorsements for anti-dissociation and self-punishment were linked to more NSSI methods, and greater level of endorsement for anti-dissociation was related to longer NSSI duration. Only the increase in endorsement of self-punishment was associated with a greater hazard of suicide attempts.

Conclusion: The dominant functions of NSSI in adolescents with depression was automatic reinforcement, specifically affect regulation. And prevalence of NSSI function differed between males and females. Anti-dissociation and self-punishment seemed to be the most risky factors as they were linked to severe NSSI or suicide behaviors. More attention should be given to these functions in risk evaluation, and the targeted interventions should be developed accordingly in a timely manner.

KEYWORDS

NSSI, self-harm function, adolescents, depression, suicide

1. Introduction

Non-suicidal self-injury (NSSI) is the "direct, deliberate destruction of one's own body tissue in the absence of suicidal intent" (1). Adolescents are a vulnerable population for NSSI. Meta-analyses have revealed that the prevalence of NSSI is 17.2% among community adolescents (2) and 35%–80% among clinical adolescents (3). NSSI not only inflicts immediate physical pain and injury but also significantly elevates the risk of suicide attempts (4). Given its high prevalence and damage, NSSI has emerged as a significant public health issue worldwide (5). Nevertheless, avoidance of pain and injury is an instinct for living beings and is vital for their survival and reproduction. The compelling motives behind self-injury that transcend biological resistance are worth exploring.

NSSI functions refer to the motives or reinforcers of NSSI behavior (6). The four-function model (FFM) proposed by Nock is often considered the conceptual base of NSSI function, which classified NSSI functions into four major categories based on the source (intrapersonal or interpersonal) and nature (positive or negative) of reinforcement: automatic negative reinforcement (ANR), automatic positive reinforcement (APR), social negative reinforcement (SNR), and social positive reinforcement (SPR) (7). However, subsequent studies have not consistently supported the FFM and Klonsky (8) adapted it and proposed a two-factor model, which divided NSSI functions into intrapersonal function (linked to automatic reinforcement in the four-function model) and interpersonal function (linked to social reinforcement in the four-function model). Further research found that while the source of function (i.e., intrapersonal or interpersonal) can always be divided, the positive or negative nature of the function, especially ANR and APR in AR, could not always be clearly distinguished (9, 10). However, this differentiation was more evident in the social domain (11, 12). Thus, a three-factor structure has emerged. A similar study (13) based on Chinese adolescents in a clinical setting supported the three-factor model and divided NSSI functions into automatic reinforcement (AR), SNR, and SPR. Therefore, this study also adopted the three-factor model. AR stems from inner needs, such as affect regulation, anti-dissociation, or self-punishment. SNR refers to the effect of NSSI on avoiding interpersonal interactions or social activities. SPR considers NSSI as a means of interpersonal communication or influence, such as attracting attention or seeking understanding. A meta-analysis (14) found that intrapersonal functions, with reported prevalence rates ranging from 66% to 81%, are the most frequently reported and higher than social functions (from 33%–56%).

The knowledge of NSSI functions is essential for understanding the behavior, identifying potential treatment targets, and developing effective therapies (15). Despite its significance, NSSI function has received less attention than other characteristics of this behavior. A meta-analysis that examined the prevalence of NSSI functions found that results varied across studies, a potential reason for which was the heterogeneity of samples (14). It suggested that NSSI function may differ among various groups. For instance, a research has reported correlations between borderline personality disorder (BPD) symptoms and NSSI functions (16), indicating that NSSI functions may differ across various disorders. Thus, investigating NSSI function in a specific disorder may be necessary, particularly under the trend of precision medicine. Patients with depression were found to comprise the largest population of NSSI, and adolescents are the most vulnerable people for NSSI. The prevalence of NSSI in adolescents with depression was reported to reach 42.50% in China (17), a significant amount considering the country's massive population and patients with mental disorders. Therefore, focusing on adolescents with depression would be a sensible approach to comprehensively understanding NSSI function and providing better medical services for this group.

Although NSSI is prevalent, its frequency and methods vary greatly among individuals (18). Given this high prevalence and diversity of NSSI, it is crucial to focus on the more severe aspects of NSSI for risk assessment and intervention in clinical practice. The severity of NSSI is usually measured by frequency and versatility, which refers to the number of methods used (19). Some studies suggest that automatic function (or intrapersonal function), rather than social function (or interpersonal function), is associated with more severe and enduring NSSI (20, 21). However, most of them have not investigated whether the association differs among specific functions (i.e., affect regulation, self-punishment, and anti-dissociation) within the automatic category. The value of such a conclusion is limited for both theoretical research and clinical work because automatic reinforcement function (AR) is just a broad and ambiguous category of NSSI function. So one aim of this study was to explore the relationship between specific AR functions and NSSI behavioral consequences, which may facilitate the accurate identification and effective treatment of individuals with severe NSSI, especially under the circumstance of commonly relative scarcity of medical resource.

Although NSSI is not primarily driven by suicidal intentions, it is closely associated with suicide. Numerous studies have confirmed the high comorbidity between NSSI and suicide such as (22). However little is known about the mechanisms underlying this association. Most studies have focused on the behavioral characteristics of NSSI and identified that the frequency and versatility of NSSI are the second strongest predictors of suicide attempts, just behind suicidal thoughts (23). This suggests that determining the characteristics of NSSI may be a promising avenue for estimating latent suicide risk, especially when suicide plans or attempts are private or sudden. Moreover, studies have found that NSSI and suicide may partly overlap in motivation (24), implying that individuals engaging in NSSI under certain functions are more likely to simultaneously develop or engage in suicidal behavior. Therefore, it would be worthwhile to explore the association between NSSI functions and suicide attempts, particularly in adolescents with depression, who are commonly considered as the most vulnerable and main group of NSSI and suicide behaviors (25).

This study has three main objectives: first, we aim to describe the prevalence of NSSI functions in adolescents with depression based on a large sample. Secondly, we intend to investigate the association between NSSI functions and its frequency, versatility, and duration. Based on previous research, we hypothesize that AR will play a prominent role. And in the subsequent step, the exploration of which specific AR functions are correlative to severe behaviour consequences will be conducted. Finally, we aim to investigate the potential association between NSSI functions and co-occurring suicide attempts.

2. Methods

2.1. Sample and procedure

Teenage patients were recruited from 16 hospitals' psychiatric outpatient clinics or inpatient departments in nine provinces of China

using convenience sampling between December 2020 and December 2021. Inclusion criteria for the study were as follows: (1) adolescents between the ages of 12–18 years old; (2) a diagnosis of depressive episode made by experienced clinical psychiatrists in accordance with the ICD-10; (3) at least one instance of NSSI behavior in the past year; and (4) having finished primary education. The exclusion criteria were as follows: (1) experiencing acute episode of obvious psychotic symptoms, and (2) presenting with cognitive or intellectual impairments.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Institutional Review Board (IRB) of Shenzhen Kangning Hospital (020-k021-02). Written informed consent was obtained from the participants and their legal guardians.

Participants completed the questionnaire independently, with a trained research assistant available to answer any questions they might have had. To ensure data quality, research assistants would check the questionnaires after completion, and any unusual answers would be confirmed.

A total of 1,101 participants were included, with 199 (18.07%) males and 902 (81.93%) females, and a mean age of 14.7 (SD = 1.63). Nearly half of the participants (44.96%) had experienced their first episode of depression. More than half (64.12%) lived in cities. Only about a quarter (25.16%) were only-child, whereas 74.84% had siblings. Nearly 20% had experienced being left-behind, which is a common social phenomenon in China, especially in the underdeveloped regions. It refers to children who are left behind in their hometowns while their parents work and earn money in larger cities. In this study, participants who had experienced being left-behind for over 1 year were classified as left-behind children. Most children (77.38%) had parents in marriage, while 19.62% had parents divorced or separated, and 3% had one or both deceased. In terms of educational status, the majority of adolescents with depression (79.75%) were enrolled in school, 18.17% were suspended, and 2.09% had dropped out of school. The demographic and clinical information of the participants has been shown in Table 1.

TABLE 1 Demographic and clinical characteristics.

	% or *M* (SD)
Gender	
Male	18.07%
Female	81.93%
Age	14.7 (1.63)
Course of disease	
First-episode	44.96%
<6 months	21.34%
6 months–1 year	11.26%
1 year-2 years	12.08%
≥2 years	9.81%
Residence	
Urban	64.12%
Rural	35.88%
Family structure	
Only-child	25.16%
Multi-child	74.84%
Left-behind experience	
Yes	19.26%
No	80.74%
Marital status of parents	
In marriage	77.38%
Divorced or separated	19.62%
One or both deceased	3.00%
Education status	
At school	79.75%
Suspend school	18.17%
Quit school	2.09%

2.2. Measures

2.2.1. Demographics

In the present study, participants were required to provide their basic personal information in a questionnaire, which included demographic characteristics such as gender, age, disease course, place of residence, family components, experience of being left behind, parents' marital status, and education status.

2.2.2. NSSI characteristics

NSSI behavior and function characteristics are often assessed by the functional assessment of self-mutilation questionnaire (FASM, 26), which has been demonstrated to possess good psychometric properties in both normal populations (27, 28) and clinical samples (29) across various countries. Qu et al. (13) translated and localized the scale and produced the Chinese version of FASM (C-FASM). In this study, all NSSI variables were measured using the C-FASM, which consists of three main parts. The first part evaluates 11 self-harm methods and their frequency in the past year. The second part inquires about age of the first NSSI episode, hesitation before action (from "not considered" to "greater than 1 week"), and degree of physical pain during NSSI (from "no pain" to "severe pain"). The last part measures the endorsement of 15 functions using a four-point Likert scale (from "never" to "often"), which can be categorized into three factors: AR, SNR, and SPR. AR includes three main individual functions: affect regulation ("to stop bad feelings" and "to feel relaxed"), anti-dissociation ("to relieve feeling numb or empty" and "to feeling something, even if it was pain"), and self-punishment ("to punish yourself"). The values of affect regulation and anti-dissociation function are the mean of the two items describing them, and the value of self-punishment function is the score of "to punish yourself" item. SNR primarily refers to avoiding social activities (e.g., "to avoid doing something unpleasant you do not want") or interpersonal interactions ("to avoid being with people"). SPR focuses on seeking positive interpersonal feedback (e.g., "to get your parents to understand or notice you"). All the three factors demonstrated acceptable internal consistency in this sample, AR-$\alpha = 0.71$, SNR-$\alpha = 0.72$, and SPR-$\alpha = 0.87$. NSSI behavior characteristics, including frequency and methods used, should be reported based on the fact in the past year.

2.2.3. Suicide attempts

Participants were queried regarding their history of suicidal thoughts or attempts, and if a suicidal behavior had occurred, the specific time should be noted. To investigate the co-occurrence of NSSI and suicide behaviour, only suicide attempts within the past year were considered to correspond with NSSI.

2.3. Data analysis

The measurement of NSSI versatility was based on the number of methods reported by participants, and the sum of NSSI frequency under each method was used to calculate the total NSSI behavior frequency. NSSI duration was defined as the difference between the current and first NSSI age and there were 64 cases with missing data in the first NSSI age were excluded from duration calculation and related data analyses. The scores of the AR, SNR, and SPR subscales were calculated as the mean of their respective items due to differences in the number of items included. The skewness of all metric variables (except NSSI frequency) was within an acceptable range [<2 (30),]. To address non-normality in NSSI frequency, a natural logarithmic transformation was applied, resulting in approximately normal distribution of the transformed frequency data for use in all relevant analyses.

Descriptive statistics, including percentages, means, and standard deviations, were used to provide a concise report of the basic characteristics of NSSI in this sample. The prevalence of NSSI functions was determined through the calculation of endorsement rates for each function. Gender differences were examined using Mann–Whitney *U* tests for every single function and *t*-tests for function categories. Linear regression was conducted to analyze NSSI frequency. As for the two count variables, negative binomial regression was used for NSSI versatility and Poisson regression was for NSSI duration. It was due to the overdispersion observed in NSSI versatility (but not in NSSI duration), with its variance (6.40) exceeding the mean (4.30) and the dispersion parameter (1.11) was over 1. And binary logistic regression was utilized to explore suicide attempts (yes/no). In all regression analyses, the three function categories were first entered to construct category models. And then, models of the individual AR functions were taken for further examinations. Control variables, including age, gender, and hospital site, were included in all regression analyses to eliminate potential confounding effects. All analyses were performed using SPSS version 26.0. Statistical significance was set at a two-tailed $p < 0.05$ (as the default value), and Bonferroni correction may be implemented in the event of necessity.

3. Results

3.1. NSSI characteristics

According to the criteria of Muehlenkamp et al. (31), patients were stratified into three groups based on the NSSI frequency they reported: low-frequency (<5), medium-frequency (5–25), and high-frequency (≥25), corresponding to proportions of 9.72%, 28.07%, and 62.22%, respectively. The mean number of methods employed was 4.30 (SD = 2.53), with the most common being "cut or crave on skin" (87.83%) and "hit self" (52.59%). The mean age of onset for NSSI was 13.31 (SD = 1.71) years, with an average duration of 1.41 (SD = 1.21) years. More than half of adolescents with depression (51.50%) engaged in the behavior without hesitation, while some (26.61%) hesitated for only a few minutes, and the majority (88.28%) did not hesitate for more than 1 h. Regarding the physical pain experienced during NSSI, more than half (51.23%) reported mild pain, nearly 30% did not feel any pain, 17.71% reported moderate pain, and only 2.45% reported severe pain.

3.2. Prevalence of NSSI functions

The most frequently reported functions were "to stop bad feelings" and "to feel relaxed," followed by "to relieve feeling numb or empty," all of which fell under the AR category. The most commonly reported functions of SNR were "to avoid doing something unpleasant you do not want" and "to avoid being with people." The function of "to let others know how desperate you were" and "to get your parents to understand or notice you" received the highest endorsement in SPR. Further elaboration on the prevalence of NSSI functions can be observed in Table 2.

Only 15.99% of participants endorsed a single function category, which was AR (15.44%) in most cases. Furthermore, 29.43% of participants endorsed two function categories, including AR + SNR (17.08%) and AR + SPR (11.99%). More than half of the participants (54.59%) endorsed all three function categories.

A significant difference was observed in the degree of recognition of the three function categories ($F = 650.73$, $p = 0.000^{***}$, $\eta_p^2 = 0.28$), with *post hoc* analysis indicating that all pairs significantly differed from each other ($p = 0.000^{***}$). And the results indicated that the most commonly endorsed function category of NSSI in adolescents with depression was AR, followed by SNR, and then SPR.

However, there were some differences between males and females in the prevalence of NSSI functions. Specifically, females endorsed AR > SNR > SPR ($F = 611.07$, $p = 0.000^{***}$, $\eta_p^2 = 0.31$; $p = 0.000^{***}$). Males endorsed AR > SPR and SNR ($F = 59.47$, $p = 0.000^{***}$, $\eta_p^2 = 0.17$) and no significant difference was noted between SPR and SNR ($p = 0.54$). Females endorsed each function of AR at a higher rate than males, with differences ranging from 1.34% to 12.61%. The mean score of AR category in females was significantly higher than in males, with a moderate effect size. The Mann–Whitney U test showed that females had higher endorsement in the function of "to punish yourself," "to feel relaxed," and "to stop bad feelings" than males. Males endorsed each function of SPR higher than females, especially "to try to get a reaction from someone, even negative," for which the rate was 20.01% lower in females, indicating a significant difference. This was where the greatest gender difference was observed. Males also gave more endorsement to the function of "to receive more attention from your parents or friends" and "to get attention" in SPR than females, and the score of SPR category was significantly higher in females than in males. However, no significant difference existed in SPR between males and females. Age did not correlate with social function and had a significant but weak negative correlation with AR ($r = -0.07$, $p = 0.018^{*}$).

3.3. Functions and the severity and duration of NSSI

Age, gender, hospital site, and the three function categories were inputted simultaneously (model 1) to conduct the linear

TABLE 2 Prevalence of NSSI functions.

Functions	Total	Male	Female	Total *M* (SD)	*t* or *z* (*p*)	Cohen's *d*
AR				1.76 (0.77)	**4.54 (0.000)**	0.36
To stop bad feelings	85.38%	78.89%	86.81%		**3.66 (0.000)**	0.30
To feel relaxed	81.65%	74.37%	83.26%		**3.76 (0.000)**	0.30
To relieve feeling numb or empty	80.47%	76.88%	81.26%		1.40 (0.162)	0.11
To punish yourself	75.66%	65.33%	77.94%		**4.38 (0.000)**	0.35
To feel something, even if it was pain	73.66%	70.85%	74.28%		1.89 (0.059)	0.15
SNR				0.79 (0.77)	0.08 (0.938)	0.01
To avoid doing something unpleasant you do not want	52.41%	54.77%	51.88%		0.76 (0.446)	0.05
To avoid being with people	47.59%	47.24%	47.67%		0.3 (0.764)	0.03
To avoid school, work, or other activities	40.42%	41.71%	40.13%		0.32 (0.750)	0.02
To avoid punishment or paying the consequences	32.97%	34.17%	32.71%		0.09 (0.929)	0.06
SPR				0.69 (0.77)	**−3.05 (0.002)**	0.24
To let others know how desperate you were	46.41%	52.26%	45.12%		−1.87 (0.061)	0.14
To get your parents to understand or notice you	40.69%	43.72%	40.02%		−1.12 (0.264)	0.09
To get help	38.24%	39.20%	38.03%		−0.09 (0.927)	0.02
To get attention	37.97%	48.74%	35.59%		**−3.54 (0.000)**	0.26
To try to get a reaction from someone, even negative	36.88%	53.27%	33.26%		**−5.38 (0.000)**	0.40
To receive more attention from your parents or friends	35.79%	47.24%	33.26%		**−3.99 (0.000)**	0.30

p after Bonferroni correction = 0.05/18 = 0.0028. Bold = significant after Bonferroni correction.

regression analysis of NSSI frequency. Result revealed that except age, only AR was significant after the Bonferroni correction. Although the *p*-value of SNR was below 0.05, it did not meet the Bonferroni correction and the beta weight was small. R^2 of the model was 0.23, which mean that the model accounted for approximately 23% variation of NSSI frequency. In Model 2, which focused on the three specific AR functions, affect regulation, anti-dissociation, and self-punishment were all independently associated with NSSI frequency, see Table 3.

In the negative binomial regression analysis for NSSI versatility, another indicator of NSSI severity, AR was also the only significant function category. And in model 2, only anti-dissociation and self-punishment survived the Bonferroni correction.

The same procedure was conducted for the Poisson regression of NSSI duration, and likewise only AR was significantly associated with enduring NSSI. However, only anti-dissociation survived in model 2, while self-punishment did not meet the Bonferroni correction and affect regulation failed to reach statistical significance totally.

3.4. NSSI functions and suicide attempt

Among adolescents with depression and NSSI, the vast majority (97.09%) reported having suicidal thoughts, and nearly half (49.59%) reported lifetime suicide attempts. Additionally, over 30% experienced both NSSI and suicide attempts in the recent 1 year.

Through binary logistic regression analysis, only affect regulation (AR) was found to be associated with an increased risk of suicide attempts. Specifically, an increase in the endorsement of self-punishment was independently relevant to concurrent suicide attempts (refer to Table 4 for detailed results).

4. Discussion

This study sought to investigate the primary functions of NSSI in adolescents with depression, and ascertain the risky functions associated with severe behavioral consequences. The main findings of the study are as follows: (1) affect regulation was the primary NSSI function in adolescents with depression, followed by an elevated function of anti-dissociation observed in this group. And gender difference observed in the prevalence of NSSI function was that Females recognized AR more frequently than males, while males had a higher prevalence of SPR. (2) AR played the prominent role in associations between NSSI functions and severe behavioral consequences. And within AR, functions of anti-dissociation, affect regulation, and self-punishment were all positively correlated with frequency of NSSI. And higher levels of endorsements for anti-dissociation and self-punishment were linked to more NSSI versatility. Only greater levels of endorsement for anti-dissociation were found to be linked to longer NSSI duration. (3) AR was also associated with a higher risk of suicide attempts, and only the increase in

TABLE 3 Regressions of NSSI functions and the severity and duration.

	NSSI frequency	NSSI versatility	NSSI duration
	β (*p*)	OR (*p*)	OR (*p*)
Model 1			
Age	**−0.12 (0.000)**	0.95 (0.009)	**1.18 (0.000)**
Gender[a]	0.01 (0.651)	1.02 (0.810)	1.18(0.046)
Hospital cite	0.03 (0.345)	1.01 (0.383)	1.01 (0.144)
AR	**0.43 (0.000)**	**1.41 (0.000)**	**1.22 (0.000)**
SNR	0.07 (0.016)	1.07 (0.187)	1.01 (0.839)
SPR	−0.03 (0.250)	1.00 (0.928)	1.05 (0.259)
Model 2			
Age	**−0.13 (0.000)**	**0.94 (0.005)**	**1.18 (0.000)**
Gender[a]	0.00 (0.998)	1.02 (0.799)	1.18 (0.047)
Hospital cite	0.03 (0.287)	1.01 (0.332)	1.01 (0.145)
Affect regulation	**0.18 (0.000)**	1.13 (0.012)	1.06 (0.167)
Anti-dissociation	**0.25 (0.000)**	**1.15 (0.000)**	**1.11 (0.003)**
Self-punishment	**0.14 (0.000)**	**1.13 (0.000)**	1.06 (0.031)

β(*p*), standardized regression coefficients with *p*-value. *p after* Bonferroni correction = 0.05/8 = 0.00625. Bold = significant after Bonferroni correction.
[a]Female

TABLE 4 Regressions of NSSI functions and suicide attempt.

	OR	*p*	95% CI	99.375% CI	χ^2
Model 1					**25.03**
Age	0.94	0.116	(0.87, 1.02)	(0.84, 1.05)	
Gender[a]	0.99	0.958	(0.70, 1.40)	(0.61, 1.60)	
Hospital cite	0.96	0.014	(0.93, 0.99)	(0.92, 1.00)	
AR	**1.35**	0.001	(1.13, 1.63)	(1.05, 1.75)	
SNR	0.90	0.267	(0.74, 1.09)	(0.69, 1.17)	
SPR	1.19	0.056	(1.00, 1.43)	(0.93, 1.53)	
Model 2					**25.67**
Age	0.94	0.125	(0.87, 1.02)	(0.84, 1.05)	
Gender[a]	1.04	0.819	(0.74, 1.47)	(0.65, 1.68)	
Hospital cite	0.96	0.021	(0.94, 0.99)	(0.92, 1.01)	
Affect regulation	1.11	0.273	(0.92, 1.34)	(0.86, 1.44)	
Anti-dissociation	1.03	0.661	(0.89, 1.20)	(0.84, 1.27)	
Self-punishment	**1.21**	0.002	(1.07, 1.36)	(1.02, 1.43)	

p after Bonferroni correction = 0.05/8 = 0.00625. Bold = significant after Bonferroni correction.
[a]Female.

self-punishment endorsement was independently related to a greater hazard of suicide attempts. Case-by-case discussions are presented below.

4.1. Prevalence of NSSI functions and gender difference

The most prevalent function was affect regulation ("to stop bad feelings" and "to feel relaxed"), which is in line with the prevailing view that NSSI is primarily used to alleviate negative emotions, reduce arousal levels, and simultaneously bring about positive feelings, such as relaxation or calmness (8, 32). The nature of NSSI, as a maladaptive emotion regulation strategy, has also been demonstrated in adolescents with depression (33). Anti-dissociation (e.g., "to relieve feeling numb or empty") was the second most common function, which was somewhat at odds with general findings. Meta-analyses (14, 34) and a study on BPD adolescents (16) reported that anti-dissociation was the relatively less endorsed function. However, our sample revealed a higher prevalence of it, which may be attributed to the association of depression with feelings of numbness and emptiness. NSSI can provide a person with physical and emotional sensations that facilitate a sense of authenticity and self-awareness, which could be the compensation and particularly reinforce the recognition of the anti-dissociation function in depression (6). In addition, a study using pathway analysis found that the relationship between post-traumatic stress, depression, and self-harm is mediated through dissociation, suggesting that anti-dissociation may be the crucial factor in the high co-occurrence of NSSI and depression (35).

Pronounced trait of avoidance was observed in NSSI function. Consistent with the hypothesis proposed by Nock and Prinstein (7), NSSI functions involve both decrease in negative outcomes and increase in positive outcomes, which often occur simultaneously and intertwine (36, 37). However, our results revealed a greater endorsement of negative aspects compared to positive ones (e.g., "to relieve feeling numb or empty" exceeded "to feel something, even if it was pain"). Similar findings have been reported in other studies (28, 38). These results suggested that avoiding unwanted internal states may be more desirable than inducing positive states or that negative reinforcement may be more potent in NSSI, which supports the experience avoidance model of NSSI (39). Individuals who engage in NSSI may be experiencing severe psychological distress and require urgent professional assistance.

The majority of adolescents with depression in this study had both automatic and social functions, and more than half recognized all three functional categories, which demonstrates the cross-functionality of NSSI. AR was consistently more prevalent than SNR and SPR, regardless of gender. However, females endorsed SNR more than SPR, while this difference was not observed in males. Males had significantly higher SPR scores than females, indicating a greater likelihood of self-harm to gain positive social feedback, such as attention or response. One theoretical perspective suggests that NSSI serves as a powerful form of communication to signal psychological distress and avoid abandonment or seek understanding (40, 41). (42) conducted a diary study and found that disclosing NSSI behaviors significantly increased perceived social support. NSSI may be a means of influencing the environment, reflecting the adaptability of this behavior, particularly in males who may experience difficulty expressing their emotions or needs. Additionally, we found that females had significantly higher AR scores than males, who might

be more likely to engage in NSSI as a means of self-punishment or affect regulation. This finding is consistent with previous research (43) and may be attributed to the greater prevalence of severe internal problems among females (44).

4.2. Individual automatic functions and the severity, duration of NSSI

AR was associated with more severe and persistent NSSI in this study, which is in line with the results of previous studies (42, 46). Although affect regulation was the most popular function, it no longer played the dominant role in the association between NSSI function and worse behavioral outcomes. Our study further confirmed that the three individual automatic functions, anti-dissociation, affect regulation, and self-punishment were associated with NSSI frequency, and anti-dissociation together with self-punishment were associated with NSSI versatility. Only anti-dissociation was independently associated with NSSI duration. Moreover, anti-dissociation beyond affect regulation showed the strongest overall association, which has also been partially reflected in Reinhardt's study (46) that reported correlation coefficients between them. And our study further confirmed these relationships through regression analysis.

Our findings partly confirmed and refined the findings of a preliminary study by Yen et al. (29) that it's anti-dissociation rather than affect regulation that was involved in the maintenance of NSSI. This can be understood in terms of stability. A follow-up study (47) found that affect regulation was the most variable function. Negative emotions easily subside as the internal or external environment improves, at which point there appears to be no reason to continue NSSI.

4.3. Individual automatic functions and suicide attempt

AR was identified as a significant factor associated with suicide attempts, consistent with prior research (42). However, our study revealed that only an increased in the self-punishment function was independently associated with an elevated risk of suicide attempt. Chapman et al. (39) posited that NSSI as a form of self-punishment could alleviate negative self-cognition, shame, and self-hatred. And it has been supported by the findings of experimental studies (48). However, unlike other functions, self-harm motivated by self-punishment implicates anger and aggression directed toward oneself. It can run through the continuum from NSSI to suicidal self-injury and escalate to the latter (49). That is, when the motivation to punish oneself expands to some extent, the most extreme form, suicide, may be the chosen course of action.

It is generally believed that intense psychological distress and despair are the primary drivers of suicide (50). Surprisingly, we did not observe a role of affect regulation in the co-occurrence of NSSI and suicide. This could be because affect regulation was already effectively achieved through NSSI. As reported by Saraff et al. (21), the majority of participants (94%) recognized the role of NSSI in emotional relief. Brausch and Muehlenkamp (47) also found that affect regulation was the most effective function in self-reporting. These findings demonstrate the value of NSSI as a coping strategy, as it may mitigate the risk of more serious consequences, even if doing so incurs costs.

4.4. Clinical implications

Our findings highlight the significance of conducting a comprehensive assessment of NSSI function. A high endorsement of automatic functions could indicate severe NSSI and underlying suicide attempts, which necessitate close monitoring and intensive treatment. In addition, given the multifacetedness NSSI function, mental health practitioners and clinicians should comprehend the NSSI functions that patients endorse and devise appropriate treatment plans. Currently, the primary therapy for NSSI is dialectical behavioral therapy [DBT (51),], which concentrates on affect regulation and enhancement of emotion regulation ability and distress tolerance. However, given our findings that functions of anti-dissociation and self-punishment might be the more important risky factors, we recommend that treatments targeting dissociation and negative self-cognition should be considered, such as behavioral activation (52), mindfulness (53), and cognitive behavioral therapy (CBT), particularly in individuals experiencing depression.

4.5. Limitations

This study has some limitations that should be considered when interpreting the findings. Firstly, the data were cross-sectional, which means that only associations between NSSI functions and behavioral outcomes were examined, and directionality and causality could not be clarified. Future longitudinal studies should be considered to verify these findings and explore the predictive role of NSSI functions in treatment effects or the transition from NSSI to suicide. Secondly, participants were only asked to report on NSSI that occurred within the past year. The lifetime data was unknown, which represents the overall level and may potentially impacting the results. Thirdly, self-reported data may be subject and exist bias. The use of ecological momentary assessment techniques could be considered to obtain more objective and impartial behavioral and physiological data. Finally, NSSI function is not necessarily equivalent to reinforcement, as sometimes the functions are not effectively satisfied. We suggest that future studies could include measures of function validity to gain a deeper understanding of associations between NSSI functions and behavioral outcomes from these subtle but essential perspectives.

4.6. Conclusion

In this study, we shed light on the significance of understanding the functions of NSSI in identifying prevalent motivations and potential risk factors associated with severe behaviors. Based on a large sample, we identified affect regulation as the most prevalent function, and found an increase in the endorsement of anti-dissociation function in adolescents with depression. We also found gender difference that females recognized AR more frequently than males, while males had a higher prevalence of SPR. AR was not only prevalent but also the risky function category linked to severe outcomes. However, function of affect regulation no longer played the

primary role in associations between NSSI function and behavioral consequences as it did in the prevalence aspect. Instead, anti-dissociation and self-punishment seemed to be more risky factors. Indicators of these functions should be given more attention to risk evaluation. We recommend that more attention should be given to these functions in risk evaluation of NSSI, and the targeted intervention or treatment should be developed accordingly in a timely manner.

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 Ethics Committee of the Institutional Review Board (IRB) of Shenzhen Kangning Hospital (020-k021-02). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YS and YZ: data collection. YS and YH: conceptualization, design and methodology. YH: data analysis and draft writing. YZ and XF: supervision, verification and editing. YZ and XF: project administration and funding acquisition. 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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Impaired behavioral inhibitory control of self-injury cues between adolescents with depression with self-injury behavior and those without during a two-choice oddball task: an event-related potential study

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Background: This study aimed to objectively evaluate the severity of impulsivity [behavior inhibitory control (BIC) impairment] among adolescents with depression. In particular, those involved in non-suicidal self-injury (NSSI) behaviors, compared with those engaged in suicidal behaviors and adolescents without any self-injury behavior, using event-related potentials (ERPs) and event-related spectral perturbation (ERSP) within the two-choice oddball paradigm.

Methods: Participants with a current diagnosis of major depressive disorder (MDD) engaged in repetitive NSSI for five or more days in the past year ($n = 53$) or having a history of at least one prior complete suicidal behavior ($n = 31$) were recruited in the self-injury group. Those without self-injury behavior were recruited in the MDD group ($n = 40$). They completed self-report scales and a computer-based two-choice oddball paradigm during which a continuous electroencephalogram was recorded. The difference waves in P3d were derived from the deviant minus standard wave, and the target index was the difference between the two conditions. We focused on latency and amplitude, and time-frequency analyses were conducted in addition to the conventional index.

Results: Participants with self-injury, compared to those with depression but without self-injury, exhibited specific deficits in BIC impairment, showing a significantly larger amplitude. Specifically, the NSSI group showed the highest value in amplitude and theta power, and suicidal behavior showed a high value in amplitude but the lowest value in theta power. These results may potentially predict the onset of suicide following repetitive NSSI.

Conclusion: These findings contribute to substantial progress in exploring neuro-electrophysiological evidence of self-injury behaviors. Furthermore, the difference between the NSSI and suicide groups might be the direction of prediction of suicidality.

KEYWORDS

event-related potential, behavior inhibitory control, P3, non-suicidal self-injury, suicidality, time-frequency analysis

1. Introduction

The global age-standardized suicide rate was 9.0 per 100,000 people with a sharp increase among young people aged between 10 and 20 years, according to the database published by WHO in 2022. The Chinese national suicide rates have decreased at a slow pace since 2006 (1). However, regional suicide mortality changed with a downward trend before 2009, followed by an upward trend as reported, based on reports (2). Clinical research has shown that cross-cutting constructs, such as affective and behavioral disorders, may be stronger predictors of suicidal events than single risk factors (e.g., past suicide attempts or psychiatric diagnoses) (3). Even if self-injury behaviors are not lethal, research also emphasized them (4). However, very few studies of suicidality focus on the affective combined with self-injury behaviors.

Self-injury behaviors, ranging from non-suicidal self-injury (NSSI) to suicidal behaviors, are a broad class of actions aimed at directly and deliberately injuring oneself (5). Although it is generally accepted that suicidal ideation confers a risk for later behaviors, extensive epidemiological and meta-analytical studies have found that it does not meaningfully differentiate individuals with a high risk of suicide attempts (6, 7). Theoretical models of suicide suggest that the factors for the development of suicidal ideation are distinct from those involved in the transition from thoughts to attempts (8–10). Among the meta-analytical studies, NSSI is one of the most robust predictors of future suicidal behaviors, even though it is defined as self-harm without the intent to die (11–15). How does NSSI increase the risk of suicidality? Notably, experiences of NSSI change the feelings and sensations of pain or such "risky behaviors" to provide emotional relief or balance more significant emotional dysregulation (16). In turn, such changes result in severe self-injury during future mental stress until the individual can no longer cope with it, and other suicidal behavior results (9, 11).

With immature and unstable impulse control, adolescents are a high-risk group for repetitive NSSI in the context of emotion dysregulation. A meta-analysis found that adolescents' aggregate prevalence rates of NSSI worldwide were 22.0% over their lifetime and 23.2% during 12 months (17). Simultaneously, a longitudinal study (18) found that self-injury frequency significantly predicts suicidal behavior among adolescents with NSSI. This effect is more pronounced among adolescents with depression (19, 20). Given that these two risk factors share a high common rate among the youth, we focused on adolescents with depression who engage in repetitive self-injury behaviors. This was to investigate whether there is a behavioral development spectrum from NSSI to suicide.

Therefore, it is necessary to highlight the common risk factors of NSSI and suicidal behaviors. Previous research (7, 10, 21, 22) indicated that impulsivity could be associated with the onset of a subsequent NSSI and suicide. In the behavioral dimension, impulsivity is regarded as maladaptive behavior and mainly manifested as deficits in behavior inhibitory control (BIC) (23). From the perspective of biobehavioral dispositions and biological behavior tendency, weak inhibitory control is an independent risk factor of suicidal behavior tendency (24). Its evidence comes from the study of impulsive–aggressive traits, one of the most promising endophenotypes (25), and manifested impairment of BIC showed a strong predictive relationship with suicidal behavior (26). Furthermore, laboratory tasks found that repetitive NSSI is associated with neurocognitive impulsivity (27), and strengthening inhibitory control would help reduce self-injury behaviors (including NSSI and suicidal behaviors) (28). Both from the motivation of self-injury addiction (28) and executive function (29), the impairment of BIC is positively correlated with the severity of NSSI (30). To further clarify the formation and development mechanism of NSSI and the subsequent suicidal behavior, it will be significant to focus research attention on the characteristics of BIC impairment. However, a few studies have focused on the BIC impairment difference between the two behaviors, which can be objectively measured. Thus, an essential next step in revealing the development of self-injury behaviors is to examine BIC impairment levels in both subjective and objective manners among depressive adolescents with repetitive NSSI and suicidal behaviors.

Benefitting from their excellent temporal resolution and goal-oriented evoked responses, event-related potentials (ERP) allow a high degree of target cognitive processes, such as inhibitory control (31). Although underutilized in studies of self-injury, ERP has been widely used in assessing cognitive process impairment in depression (32) and behavior using non-traditional approaches (33). Researchers frequently used the go or no-go task to investigate inhibitory control. Participants are typically asked to generate a motor response to the go trial and no motor response to the no-go trial. However, differences in motor response are likely to contaminate the inhibitory control effect because higher cognitive processes are particularly susceptible to motor potentials (34, 35). Therefore, the present study used a two-choice oddball task, in which participants were required to respond to both standard and deviant stimuli by pressing different keys as quickly as possible. Two ERP components have been suggested to reflect BIC activity, N2 and P3. N2, the negative component ∼200 ms after stimulation, operates as a detector of conflicts but not real inhibitory braking. P3, ∼300–500 ms after stimulation, is a slow centro-parietal positive component. It is closely related to motor inhibition in the premotor cortex (23). As reported, higher motor preparation represents more inhibition needed to withhold and more effort to respond correctly; consequently, a larger P3 is induced (36).

The present study randomized the onset sequence of standard and deviant stimuli for each participant. Compared with the 25% occurrence of deviant stimuli, standard stimuli were presented much more frequently to induce prepotent responses. Participants were required to inhibit the prepotent response and change to correct responses when they encountered deviant stimuli. To avoid overlap with adjacent ERP components, we used the different waves of the standard and deviant stimuli to isolate the components of interest. Subsequently, the difference waves to neutral cues minus self-injury cues were used as the target index. In addition to ERP, time-frequency decompositions were conducted for more BIC impairment details. Correlational studies have underlined the importance and potential of time-frequency-based indices in prospectively predicting adverse outcomes (37).

Altogether, the present study's primary goal was to explore the developmental spectrum from NSSI to suicidal behaviors among adolescents with depression, depending on the BIC impairment

level. Thus, we chose BIC's classic experimental paradigms to objectively evaluate the impulsive difference between neutral and self-injury cues through ERP or event-related spectral perturbation (ERSP). We hypothesized that these indicators would differentiate individuals with repetitive self-injury behaviors and that the difference in NSSI and suicidal behaviors would reflect the developmental spectrum. Due to limited knowledge about the severity of BIC impairment among adolescents with depression, we also collected the ERPs of adolescents with depression without any self-injury behavior as a control group. Finally, we employed time-frequency analyses to measure oscillatory neural activity in the theta frequency band. Although the present study focused on objective behavioral indicators, we utilized a correlation analysis to examine whether they share consistency.

2. Methods and materials

2.1. Participants

The participants of this study were 124 adolescents aged between 12 and 17 years from the outpatient department of The First Affiliated Hospital of Chongqing Medical University. All the participants were under the supervision of their parents. Guardians and participants themselves both had signed informed consent for this study. Participants with a current diagnosis of major depressive disorder (MDD) and a history of at least one prior complete suicide behavior history ($n = 31$) in the last year were eligible for the MDD+SA group, all of whom reported a history of prior NSSI. Participants with a current diagnosis of MDD and engaged in repetitive NSSI on five or more days ($n = 53$) in the past year were eligible for the MDD+NSSI group. Participants with a current MDD diagnosis and without self-injury behavior ($n = 40$) were included in the MDD group. Healthy controls (HC group) were age-matched adolescents recruited from the same community via advertisements ($n = 30$). The exclusion criteria for all groups comprised: (1) current diagnosis of other mental illnesses such as schizophrenia, bipolar disorder, or substance dependence; (2) previous brain organic mental disorders; (3) neurodevelopmental disorders; (4) other chronic or severe physical conditions. The demographic information of the four groups is presented in Table 1.

2.2. Measures

2.2.1. Diagnosis of major depressive disorder

The MINI-International Neuropsychiatric Interview (M.I.N.I. KID 5.0) was used to assess the current diagnosis of major depressive disorder (38) by two well-trained psychiatrists.

2.2.2. Non-suicidal self-injury and suicide behaviors history and characteristics

The Ottawa Self-injury Inventory was used to assess the lifetime and latest year NSSI history and its characteristics (39). Negative emotions induced all their NSSI behaviors, and the primary purpose of the behaviors was to aid emotional dysregulation. The Columbia Suicide Severity Rating Scale was used to assess lifetime and latest month suicide behavior history (40). Those with at least one suicidal behavior in recent years were recruited in the MDD+SA group. The Beck Scale for Suicide Ideation (BSSI) was used to assess suicidal ideation (41).

2.2.3. Impulsivity symptoms (self-report)

The Barratt Impulsiveness Scale (BIS) was used to assess behavior impulsivity (42). With the three dimensions of impulsivity, a higher score of motor impulsiveness and a lower score of non-planning impulsiveness will indicate impairment of behavior inhibitory control (43).

2.2.4. Behavior inhibitory control impairment (event-related potential)

Participants were required to complete a visually evoked task of the two-choice oddball paradigm for ERP use. This study chose Cz as the electrode of interest, referring to a previous study (23, 44) and the characteristics of P3 potential.

TABLE 1 Demographic and scale assessment.

Measure	HC group ($n = 30$)	MDD group ($n = 40$)	MDD + NSSI group ($n = 53$)	MDD + SA group ($n = 31$)	Test statistics
Demographics					
Age	15.2 ± 1.65	15.3 ± 1.47	14.4 ± 1.57	14.6 ± 1.43	$F_{(4,154)} = 2.055\ p = 0.109$
Female	18	23	37	24	
	60%	57%	69%	77%	$\chi^2 = 3.923\ p = 0.270$
Scale assessment					
PHQ-9		19 ± 4.994	19.47 ± 4.539	20.25 ± 3.640	$F_{(3,124)} = 0.481\ p = 0.619$
Beck_lately		0.7 ± 0.622	0.57 ± 0.607	1.2 ± 0.554	$F_{(3,124)} = 7.875\ p = 0.001$
Beck_lifetime		1.05 ± 0.850	0.97 ± 0.825	1.79 ± 0.358	$F_{(3,124)} = 8.612\ p < 0.001$
BIS_MI		27.24 ± 6.247	27.34 ± 6.941	27.25 ± 5.902	$F_{(3,124)} = 0.002\ p = 0.998$
BIS_CI		27.68 ± 6.196	25.85 ± 7.045	25.20 ± 5.935	$F_{(3,124)} = 0.924\ p = 0.401$
BIS_NPI		22.84 ± 5.242	21.63 ± 6.507	22.05 ± 7.265	$F_{(3,124)} = 0.280\ p = 0.757$

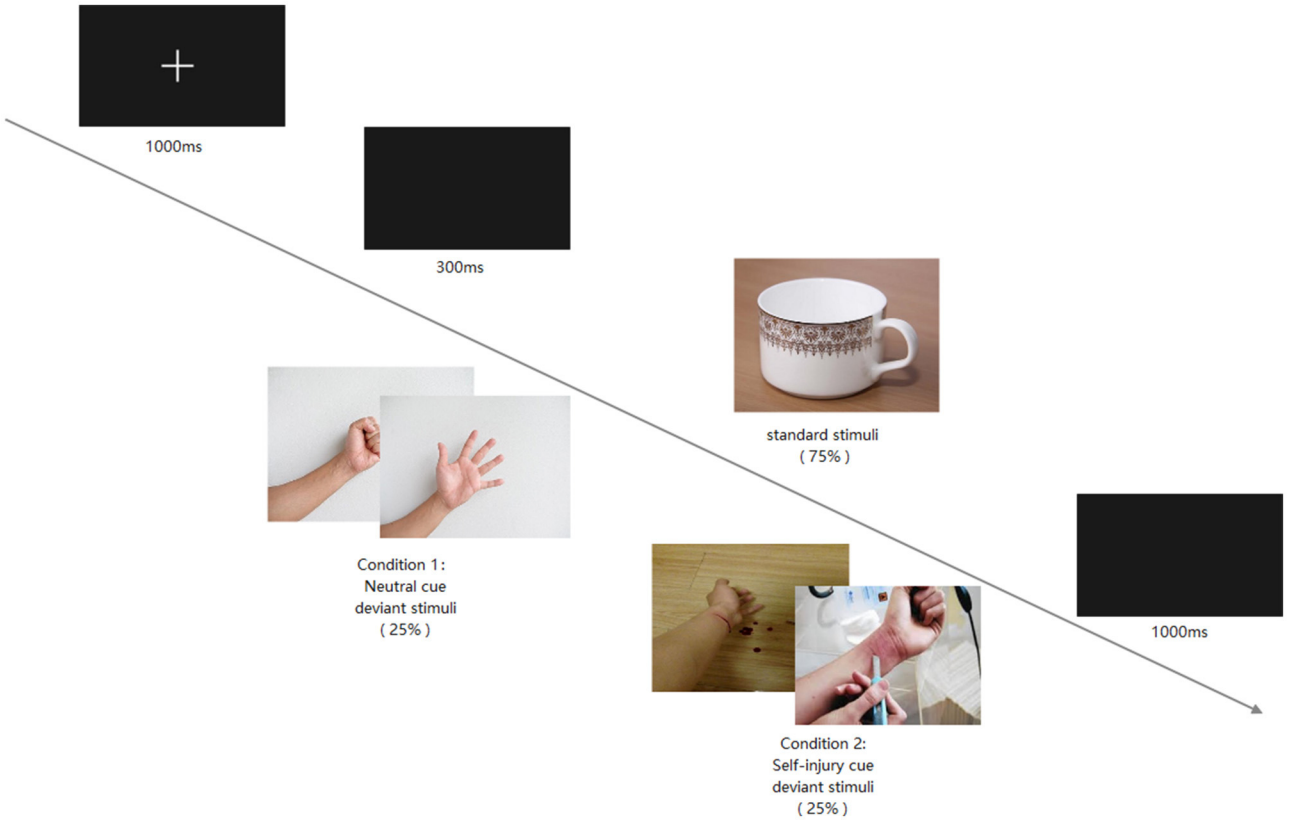

FIGURE 1
The processor of two-choice odd-ball paradigm.

TABLE 2 BSI scale comparison between groups.

Dependent variable		(I) group	(J) group	Mean difference (I-J)	Std. error	Sig.
Beck_lately	Bonferroni	MDD	NSSI	0.130	0.132	0.981
			SA	−0.497*	0.169	0.012
		NSSI	MDD	−0.130	0.132	0.981
			SA	−0.627*	0.159	0.000
		SA	MDD	0.497*	0.169	0.012
			NSSI	0.627*	0.159	0.000
Beck_mostly	Bonferroni	MDD	NSSI	0.082	0.169	1.000
			SA	−0.739*	0.216	0.003
		NSSI	MDD	−0.082	0.169	1.000
			SA	−0.821*	0.203	0.000
		SA	MDD	0.739*	0.216	0.003
			NSSI	0.821*	0.203	0.000

*$p < 0.05$.

The experimental environment was controlled for temperature, brightness, and noise. E-prime 3.0 was used to present the stimuli and experimental instructions. Furthermore, the two-choice oddball paradigm procedure is illustrated in Figure 1. The paradigm included two conditions: the deviant stimuli of one condition were neutral pictures, and the other was self-injury pictures. In both conditions, the standard stimuli were the same cup picture, and the standard and deviant stimuli frequencies were 75 and 25%, respectively. Participants were asked to press the "1" key in response to the standard stimuli and the "2" key in response to the deviant stimuli. Each participant was required to respond quickly and achieve at least 80% accuracy.

TABLE 3A One-Way ANOVA of P3d amplitude, group1 represent health control (HC) group; group 2 represent major depressive disorder (MDD) group; group 3 represent non-suicidal self-injury (MDD+NSSI) group; group 4 represent suicide behavior (MDD+SA) group.

Dependent variable		(I) group	(J) group	Mean difference (I-J)	Std. error	Sig.
CZ	Bonferroni	1	2	−3.78734	1.66814	0.153
			3	−8.45351*	1.78888	0.000
			4	−6.94707*	1.91349	0.003
		2	1	3.78734	1.66814	0.153
			3	−4.66617*	1.58254	0.024
			4	−3.15973	1.72214	0.418
		3	1	8.45351*	1.78888	0.000
			2	4.66617*	1.58254	0.024
			4	1.50644	1.83934	1.000
		4	1	6.94707*	1.91349	0.003
			2	3.15973	1.72214	0.418
			3	CPZ 1.50644	1.83934	1.000
CPZ	Bonferroni	1	2	CPZ 1.62599	1.73776	1.000
			3	CPZ 7.36322*	1.86354	0.001
			4	CPZ 5.71856*	1.99335	0.030
		2	1	1.62599	1.73776	1.000
			3	CPZ 5.73723*	1.64858	0.005
			4	CPZ 4.09257	1.79401	0.148
		3	1	7.36322*	1.86354	0.001
			2	5.73723*	1.64858	0.005
			4	1.64467	1.91610	1.000
		4	1	5.71856*	1.99335	0.030
			2	4.09257	1.79401	0.148
			3	CPZ 1.64467	1.91610	1.000

*$p < 0.05$.

A Neuroscan Quick cap with 64 scalp sites was employed to record brain electrical activities, and the EEGLAB toolbox in MATLAB 2013b was used for offline analysis. The sampling rate was 1,000 Hz, and the data were resampled to 500 Hz for analysis. The impedance of each electrode was controlled below 5 kΩ, and the M1 and M2 electrodes were chosen as offline references. The offline bandpass was 0.1–30 Hz, and all EEG data were epoched to 3,000 ms, including 1,000 ms of the pre-stimuli and 2,000 ms of the post-stimuli period. Only epochs of correct responses were used for the subsequent analysis. After artifact components by independent component analysis, epochs were overlapped and averaged for each condition. The pre-stimulus period was used as a baseline to correct the post-stimulus period.

2.2.5. Statistical analysis

Questionnaire data and the ERP index of BIC were analyzed using repeated-measures ANOVA. Spearman rank correlation was used to analyze the scale results and ERP index. *Post hoc* analyses were performed between the self-reported results and ERP index (latency and amplitude of P3) for the four groups (HC, MDD, MDD+NSSI, and MDD+SA). Bonferroni correction was used for multiple comparisons.

2.2.6. Ethics statement

The ethics committee of the University Town Hospital of Chongqing Medical University approved all experimental procedures.

3. Results

The four groups were almost equally distributed by sex ($\chi^2 = 3.923, p = 0.270$) and age [$F_{(4,154)} = 2.055, p = 0.109$]. Most of them were from middle school and were in the custody of their parents.

3.1. Self-reported results

The PHQ-9 was used to assess depressive symptoms. The scores of the three groups (MDD, MDD+NSSI, and MDD+SA) were not significantly different [mean (SD) score,19.00 (4.994) vs. 19.47

TABLE 3B One-Way ANOVA of P3d latency.

		Sum of squares	*df*	Mean square	*F*	Sig.
FC	Between groups	17,511.935	3	5,837.312	1.256	0.294
	Within groups	474,145.725	102	4,648.488		
	Total	491,657.660	105			
FCZ	Between groups	17,908.113	3	5,969.371	1.366	0.258
	Within groups	445,885.887	102	4,371.430		
	Total	463,794.000	105			
CZ	Between groups	19,140.205	3	6,380.068	1.334	0.268
	Within groups	487,908.700	102	4,783.419		
	Total	507,048.906	105			
CPZ	Between groups	32,166.524	3	10,722.175	2.166	0.097
	Within groups	504,943.854	102	4,950.430		
	Total	537,110.377	105			
PZ	Between groups	23,714.057	3	7,904.686	1.666	0.179
	Within groups	483,934.434	102	4,744.455		
	Total	507,648.491	105			

(4.539) vs. 20.25 (3.640); $F_{(3,124)} = 0.481$, $p = 0.619$]. Meanwhile, the assessment result of self-reported impulsivity (BIS, including the three dimensions) also showed no significant difference among the three groups [BIS_MI, $F_{(3,124)} = 0.002$, $p = 0.998$; BIS_CI, $F_{(3,124)} = 0.924$, $p = 0.401$; BIS_NPI, $F_{(3,124)} = 0.280$, $p = 0.757$]. Only the assessment result of suicide ideation (BSSI, including the latest week and lifetime) showed significant differences between groups [latest week, $F_{(3,124)} = 7.875$, $p = 0.001$; lifetime, $F_{(3,124)} = 8.612$, $p < 0.001$]; the details of the scales are presented in Table 1. *Post hoc* tests showed that the MDD+SA group was significantly higher both in the lifetime and the latest week of suicide ideation, but no significant difference between MDD and MDD+NSSI groups (Bonferroni-adjusted, $p < 0.05$); details are presented in Table 2.

3.2. Two-choice oddball task event-related potentials

As we required the participants to achieve 80% accuracy and respond as quickly as possible, the behavioral index (accuracy and latency for press response) was subject to intervention. Thus, the present study does not discuss behavioral indexes.

Regarding P3 amplitude and latency, we focused on the difference between the two cues, with the result of P3d (self-injury cue–neutral cue) as the target. We conducted two four groups (HC, MDD, MDD+NSSI, MDD+SA) × Channel mixed ANOVA of one variance with the P3d amplitude or latency serving as the dependent variable. As presented in Table 3A, the main effect of group [$F_{(4,154)} = 8.857$, $p < 0.001$, $\eta_p^2 = 0.21$] and the main and interaction [$F_{(4,154)} = 8.857$, $p < 0.001$, $\eta_p^2 = 0.78$] effects both showed significance. *Post hoc* tests showed that there was no significant difference in FC, and FCZ channels, but the parietal lobe channel showed a significant difference, indicating that the target channel is Cz. *Post hoc* tests indicated that the P3d amplitudes in the MDD + NSSI (Bonferroni-adjusted $p < 0.001$) and MDD + SA (Bonferroni-adjusted $p = 0.003$) groups were significantly larger than those in HC. Furthermore, the P3d amplitude in the MDD + NSSI group was considerably more extensive than in the MDD group (Bonferroni-adjusted $p = 0.024$). However, the main effect of group and interaction effects were not significant in the P3d latencies (Table 3B). Grand mean ERPs at the group level and P3d mean plots are presented in Figure 2.

3.3. Correlation analysis

For the three depressive groups (MDD, MDD + NSSI, and MDD + SA), correlation analysis was performed between the self-reported results (PHQ-9, BSSI, and BIS) and P3d amplitude. Interestingly, the amplitude in the MDD + NSSI and MDD + SA groups showed a significant correlation with some of the self-reported results, even with a smaller sample size, because some participants required a non-real name for their scale results. As shown in Table 4, the P3d amplitude was positively correlated with the PHQ-9 score ($r = 0.403$, $p = 0.006$, CI = 0.01) in the MDD + NSSI group and was positively correlated with the BSI (lifetime) score in the MDD + SA group ($r = 0.559$, $p = 0.01$, CI = 0.05). The scatter diagrams are shown in Figure 3.

3.4. Time-frequency analysis

The current time-frequency analyses were computed using short-term FFTs (MATLAB2013b eeglab toolbox). After baseline correction, the difference between two cues (self-injury-neutral)

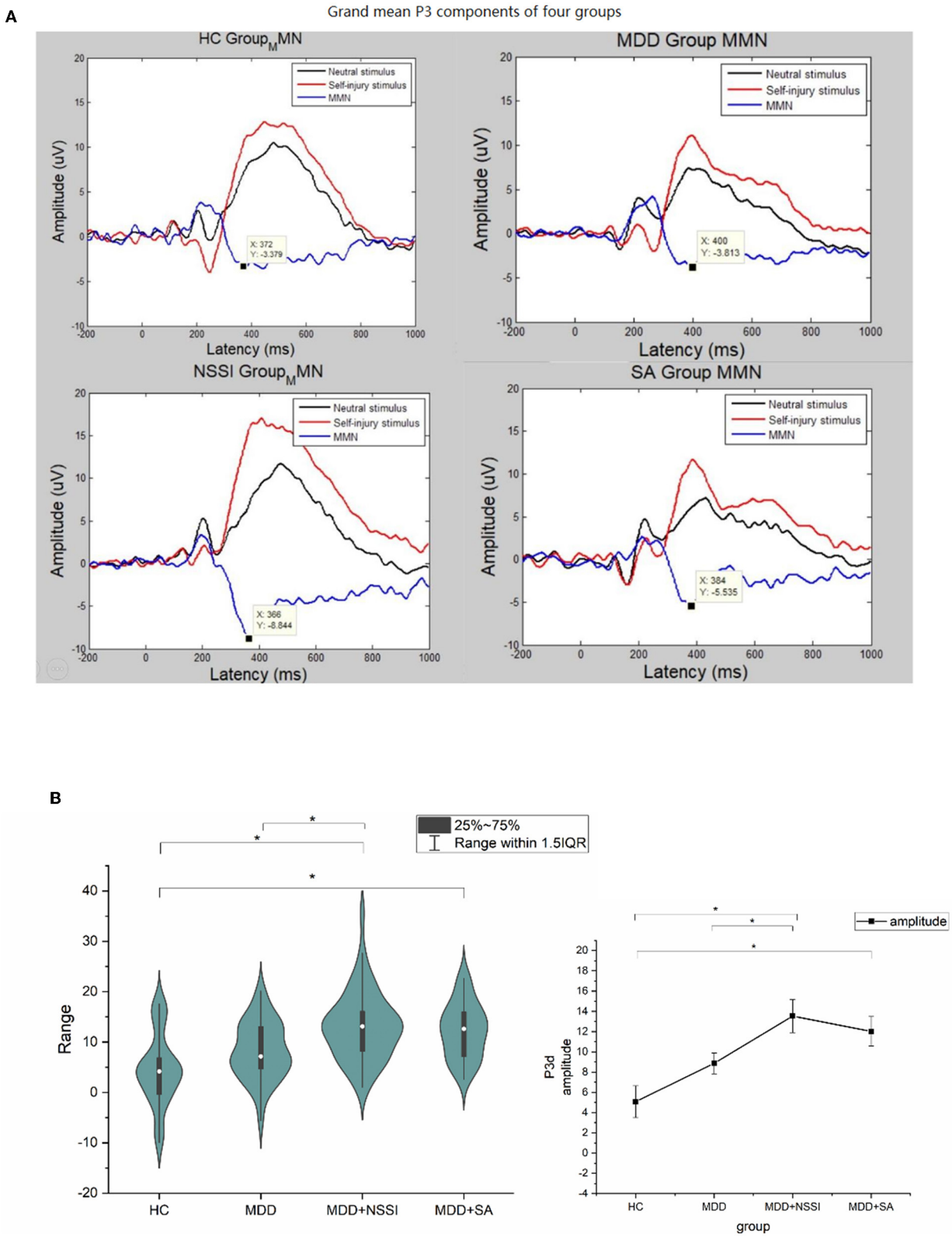

FIGURE 2
Grand mean ERPs at the group level **(A)** and P3d mean plots **(B)** on Cz channel, In order to avoid visual interference, P3d (blue curve) was changed to mirror negative curve (neutral - NSSI), P3d value remained unchanged in statistical analysis, *$p < 0.05$.

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TABLE 4 The correlation analysis between P3d amplitude and self-reported results.

			Amplitude
MDD group Spearman's rho	PHQ9	Correlation coefficient	0.215
		Sig. (2-tailed)	0.229
		N	33
	Beck_lately	Correlation coefficient	0.173
		Sig. (2-tailed)	0.320
		N	35
	Beck_lifetime	Correlation coefficient	0.145
		Sig. (2-tailed)	0.406
		N	35
	IBS_MI	Correlation coefficient	0.341
		Sig. (2-tailed)	0.095
		N	25
	IBS_CI	Correlation coefficient	−0.290
		Sig. (2-tailed)	0.159
		N	25
	IBS_NPI	Correlation coefficient	−0.260
		Sig. (2-tailed)	0.209
		N	25
	Amplitude	Correlation coefficient	1.000
		Sig. (2-tailed)	.
		N	39
MDD+NSSI group Spearman's rho	PHQ9	Correlation coefficient	0.403**
		Sig. (2-tailed)	0.006
		N	45
	Beck_lately	Correlation coefficient	−0.096
		Sig. (2-tailed)	0.527
		N	46
	Beck_lifetime	Correlation coefficient	0.108
		Sig. (2-tailed)	0.475
		N	46
	IBS_MI	Correlation coefficient	−0.091
		Sig. (2-tailed)	0.594
		N	37
	IBS_CI	Correlation coefficient	−0.112
		Sig. (2-tailed)	0.510
		N	37
	IBS_NPI	Correlation coefficient	−0.256
		Sig. (2-tailed)	0.126
		N	37
	Amplitude	Correlation coefficient	1.000
		Sig. (2-tailed)	.
		N	48
MDD+SA group Spearman's rho	PHQ9	Correlation coefficient	0.049
		Sig. (2-tailed)	0.836
		N	20
	Beck_lately	Correlation coefficient	0.425
		Sig. (2-tailed)	0.062
		N	20
	Beck_lifetime	Correlation coefficient	0.559*
		Sig. (2-tailed)	0.010
		N	20
	IBS_MI	Correlation coefficient	−0.055
		Sig. (2-tailed)	0.818
		N	20
	IBS_CI	Correlation coefficient	−0.382
		Sig. (2-tailed)	0.097
		N	20
	IBS_NPI	Correlation coefficient	−0.167
		Sig. (2-tailed)	0.483
		N	20
	Amplitude	Correlation coefficient	1.000
		Sig. (2-tailed)	.
		N	21

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

on the Cz channel for the four groups (HC, MDD, MDD+NSSI, and MDD+SA) is plotted in Figure 4A. The event-related spectral perturbation (ERSP) lasts for a period and induces oscillations (power value) that reflect important information regarding cognitive processes. Thus, we averaged the power value of the P3 time domain (250–450 ms) and frequency domain (5–7 Hz) of interest for statistical analysis. As shown in Table 5, during the P3 period there was a significant difference among the four groups [$F_{(4,154)} = 9.818$, $p < 0.001$, $\eta_p^2 = 0.18$]. As expected, the theta band power showed an upward trend from the HC group through the

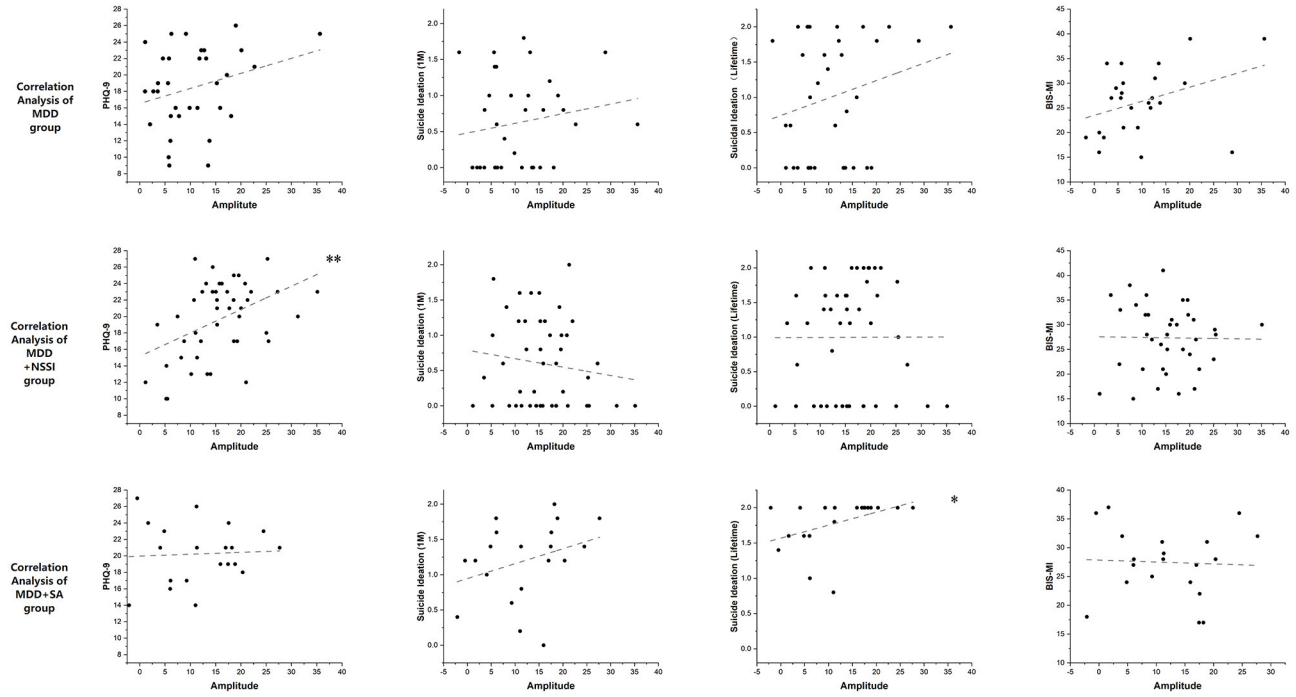

FIGURE 3
The scatter diagrams of the correlation analysis between P3d amplitude and self-reported scales, $*p < 0.05$, $**p < 0.01$.

TABLE 5 One-way ANOVA of P3d oscillating power at theta band of each group.

Bonferroni					
Dependent variable	(I) group	(J) group	Mean difference (I-J)	Std. error	Sig.
P300 theta	HC	MDD	−0.35730	0.25742	1.000
		NSSI	−0.79454*	0.23922	0.007
		SA	0.27740	0.26357	1.000
	MDD	HC	0.35730	0.25742	1.000
		NSSI	−0.43725	0.20165	0.191
		SA	0.63470*	0.23001	0.039
	NSSI	HC	0.79454*	0.23922	0.007
		MDD	0.43725	0.20165	0.191
		SA	1.07195*	0.20945	0.000
	SA	HC	−0.27740	0.26357	1.000
		MDD	−0.63470*	0.23001	0.039
		NSSI	−1.07195*	0.20945	0.000

*$p < 0.05$.

MDD group to the MDD+NSSI group and there was a significant difference between the HC group and the MDD+NSSI group (Bonferroni-adjusted $p = 0.007$). However, there was an obvious turning point between the NSSI group and the SA group. The theta energy of the SA group was lower than that of the MDD group, that is, there was a cliff decline from NSSI to SA, and there were significant differences between the SA group and NSSI group, and MDD group (Bonferroni correction, SA vs. NSSI, $p < 0.001$ vs. MDD, $p = 0.039$), as shown in Figure 4B.

4. Discussion

The primary goal of this study was to explore the behavioral development spectrum from MDD through NSSI to suicide. As self-injury behaviors share impulsivity as the common risk, the present study conducted an objective investigation of BIC impairment, expecting to find neuro-electrophysiological indicators to reflect the difference between adolescents with and without self-injury in the context of depression. We found

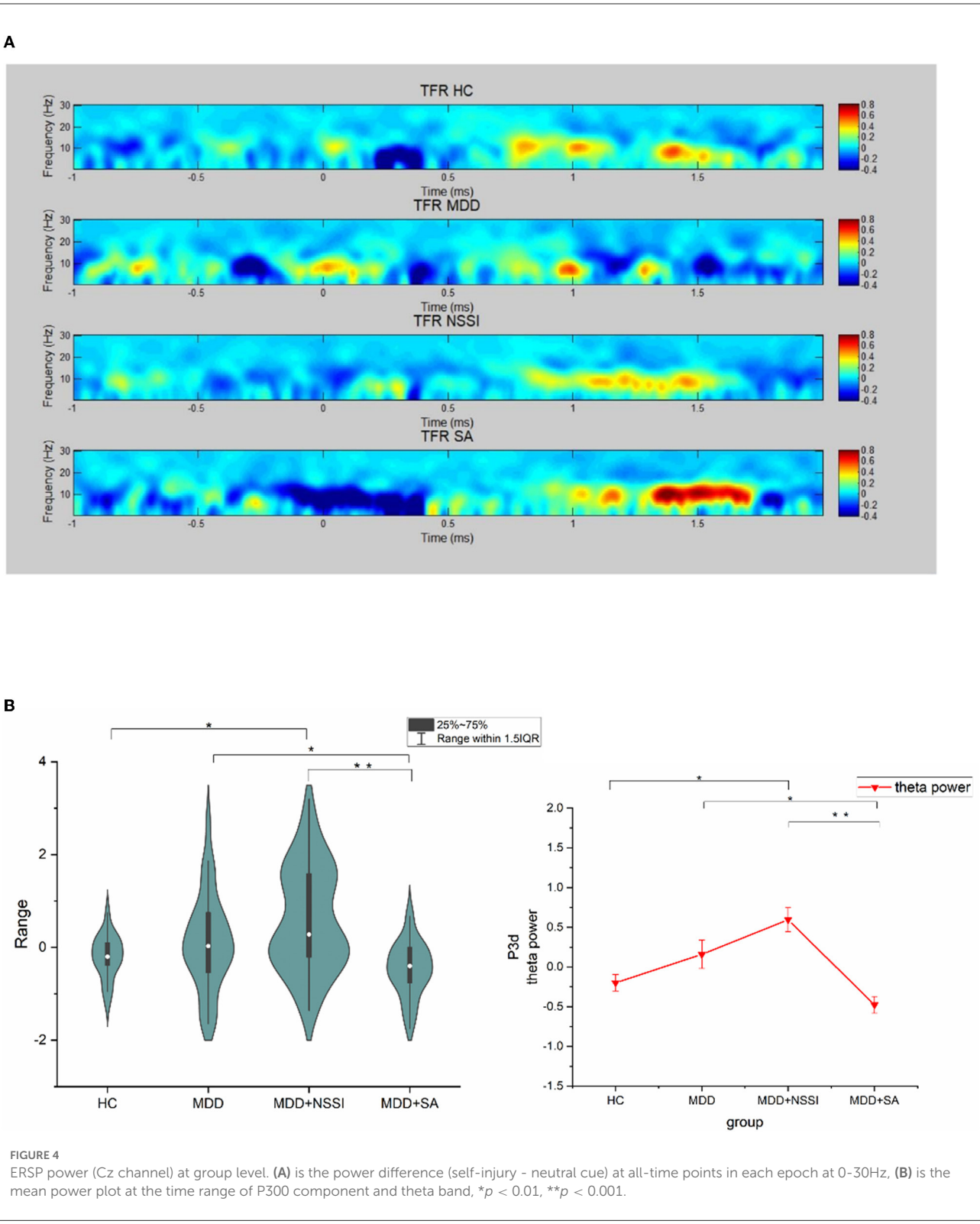

FIGURE 4
ERSP power (Cz channel) at group level. **(A)** is the power difference (self-injury - neutral cue) at all-time points in each epoch at 0-30Hz, **(B)** is the mean power plot at the time range of P300 component and theta band, *$p < 0.01$, **$p < 0.001$.

the specificity of BIC impairment in depressive adolescents with a history of suicidal behavior. Specifically, the MDD and MDD+NSSI groups exhibited higher power values than the HC group, showing a gradual upward trend. The trend turned between the MDD+NSSI group and the MDD+SA group, the MDD+NSSI group showed the highest power value among the four groups, and the SA group showed the lowest among the four groups (Figure 4B). These differences suggest that participants in the MDD+SA and MDD+NSSI groups both had deficits in their ability to inhibit the impulsivity of self-injury cues (45), but the different emotional responses to the self-injury cues. Regarding the theta rhythm continually enhancing emotional distress, the different power

values may further suggest that the self-injury cue brings emotional distress to the MDD+NSSI group but alleviates negative emotions for the MDD+SA group instead. Defective inhibitory processes lead to impulsive behavior, so in addition to neurodevelopmental diseases, the underlying causes of obsessive–compulsive disorder (OCD) and addiction are closely related to deficits in response-inhibitory control but they differ in the cognitive processes involved in the behavior inhibitory control. The results of functional imaging suggest that in patients with OCD, the combination of an overactive error processing mechanism and response inhibition disorder may be the basis of obsessive–compulsive behavior in disinhibited cues (23). When addicted patients face relevant cues, they are more inclined to the immediate gratification of strong desires in the motor response paradigm due to positive emotional stimulation and immediate desire gratification impulses (31). Findings above are consistent with the difference between NSSI and SA in this study. That is, for the MDD+NSSI group, the self-injury cues are more familiar to obsession, while for the MDD+SA group, the self-injury cues are familiar to addiction. In the presence of depression, the conclusion showed the potential to differentiate individuals who have attempted suicide from those who engaged in repeated self-injury behaviors.

We should also highlight that the participants included in the MDD+SA group had complete suicidal behavior within the last year; this time criterion is longer than the meta-analyses suggested (46). Although the between-group difference in P3d amplitude and theta power in the two-choice oddball task still requires replication and validation of longitudinal data, the findings suggest that, to a certain extent, neuro-electrophysiological indicators could extend the warning time of suicidality. Although any conclusion must remain tentative until a study with a larger sample confirms the reliability and a longitudinal study has confirmed its specificity, results from the present study highlight that time-frequency analyses might contribute to the recognition of suicide attempters in a specific way. Several previous studies have also demonstrated a vital link between psychopathology and the inhibitory control of theta oscillatory dynamics (47–49).

Although we did not find a significant difference between the MDD+NSSI and MDD+SA groups in the P3d amplitude, the NSSI group showed the most considerable amplitude differentiation among individuals without self-injury behavior. This suggests that depressive adolescents with repeated NSSI must expend tremendous effort to inhibit impulsive responses to self-injury cues. Nonetheless, this more significant effort did not act on faster responses (the main effect of the group was not effective in the P3d latencies). Although the results of previous studies of the two-choice oddball paradigm used on BIC impairment are mixed, the results of the present study were consistent with those of our previous study (50) and further, complementary to prior results, suggested that a larger amplitude may not simply be more salient to individuals addicted to self-injury behavior but those with compulsive self-injury behavior. As previous research found that P3 amplitude was negatively associated with no-go errors (51), we consider this greater effort to achieve the accuracy required by the study according to the compensatory mechanism (52), subsequently resulting in a larger amplitude of P3d. The time-frequency analyses of the MDD+NSSI group showed the highest power value, suggesting that the self-injury cue did cause emotional distress to the participants. Indeed, researchers have stated that the conceptual overlap between NSSI and obsessive–compulsive-related disorder (53) illustrates that the MDD+NSSI group did have BIC impairment when exposed to self-injury cues. Considering that participants in the MDD+NSSI group repetitively acted on NSSI behaviors on five or more days in the past year and the motivation was almost entirely to help regulate negative emotions, NSSI behaviors may be more related to obsessive–compulsive disorder than addiction.

In the present study, no significant group differences were found in self-reported levels of impulsivity or the correlation between self-reported impulsivity and P3d amplitude. In both the NSSI and SA studies, self-reported impulsivity seemed unreliable. A meta-analysis demonstrated that a large pooled effect size was evident only when the suicide attempt occurred within a month of behavioral impulsivity assessment. Even in the last month, highly behavioral impulsivity was less likely to make deliberate attempts (46). However, another longitudinal cohort study of children at risk for neurodevelopmental disorders in mid-adolescence suggested that impulsivity and inattention may be particularly important in understanding the onset of NSSI and suicidal behaviors (54). Specifically, adolescents are in the developmental stage of self-cognitive ability whose self-reported results vary significantly. Furthermore, it might not be easy for them, particularly those with a current depression diagnosis, to estimate their impulsivity level objectively and accurately. Interestingly, we found no significant difference among the three depressive groups in the PHQ-9 score, but the correlation analysis showed a significant positive correlation between the P3d amplitude and the PHQ-9 score in the MDD+NSSI group. It suggested that, in addition to the severity of BIC impairment, P3d amplitude also reflects the severity of depression among the NSSI individuals. The results indicated that neuro-electrophysiological indicators might be better and more objective in evaluating depression severity.

The present study achieves considerable homogeneity. In particular, the observation population in the experimental design might improve reproducibility; additionally, it is an indicator of self-injury and suicidality. Most previous suicidality studies have focused on suicidal ideation and suicide attempters compared with non-suicide populations. The commonly used binary classification did not adequately combine suicidality with high-risk factors, such as emotional dysregulation and maladaptive behaviors. Increasing evidence suggests that the onset of suicidal behavior has a long developmental process. As epidemiological surveys and meta-analyses declare, there is above 10 times the significant risk of suicidal behavior among self-injurers.

Previous studies report that multiple episodes of self-harm and psychiatric disorder are highly associated with an increased risk of suicide (10, 20, 55). The present study is one of the few to focus on the spectrum developed from repeated NSSI to suicidal behavior. Furthermore, the employment of ERP or ERSP enabled us to aim at the target cognitive function

(i.e., behavior inhibitory control impairment and impulsivity). Additionally, we were able to precisely examine the target component and frequency oscillation of BIC afforded by high temporal resolution. To the best of our knowledge, the present study is the first to objectively evaluate the distinction and correlation between NSSI and suicidal behavior. Moreover, all three depressive groups (MDD, MDD+NSSI, and MDD+SA) had similar depressive symptom levels, indicating a more robust specificity of BIC impairment to self-injury and suicide behavior history.

This study had some limitations. First, the sample size was relatively small, particularly in the MDD+SA group. Consequently, after some of the participants refused the real name of the scale, the correlation between self-reported score and ERP or ERSP index might appear to be a false negative. Second, because of the cross-sectional design of this study, whether the difference between NSSI and SA could predict the onset of subsequent suicidal behavior still requires larger samples for longitudinal studies. This is the next step in our ongoing research exploring suicidality. Third, examining all the related BIC impairment aspects within ERP or ERPS alone was challenging. Due to the poor spatial resolution of the EEG and ERP signal, it is challenging to recognize accurately the brain regions that may respond to the electrophysiological phenomena found in this study. It will be crucial for future research to be performed with neuroimaging data (e.g., fMRI or MEG) to further the understanding of the neuropathophysiological forming processes of suicidality. Finally, NSSI behaviors vary widely in behavioral patterns and severity, which is a major cause of heterogeneity in prediction studies of suicide. There is a strong association between the severity of self-injury and the onset of subsequent suicidal behavior, it is not rigorous enough to discuss NSSI behavior in general. Further studies must be conducted to investigate BIC impairment in different motivations, forms, and severity of self-injury.

5. Conclusion

Our study provided neuro-electrophysiological evidence that adolescents with depression involved in self-injury have impairment in BIC when exposed to self-injury cues. Furthermore, the difference in the self-injury between NSSI and suicide might be a warning marker predicting subsequent suicidal behavior in depressive patients combined with the NSSI population, and the warning time may extend longer. Our follow-up research will increase the sample volume for a longitudinal study to verify and replicate our results.

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 University Town 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

LM and D-DZ were involved in the study design. LM, LZ, JH, ZJ, XP, XH, SH, and WW were involved in the data collection and scale interviews. LM, D-DZ, and JH were involved in data and statistical analyses. LM wrote the manuscript. LK was involved in study supervision and the manuscript's senior editor. All authors had full access to all data in the study. Furthermore, they all take responsibility for the data's integrity and the data analysis's accuracy. 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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Abnormal brain spontaneous activity in major depressive disorder adolescents with non-suicidal self injury and its changes after sertraline therapy

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Background: Non-suicidal self-injury (NSSI) commonly occurs among adolescents with major depressive disorder (MDD), causing adverse effects on the physical and mental health of the patients. However, the underlying neurobiological mechanism of NSSI in adolescents with MDD (nsMDDs) remains unclear, and there are still challenges in the treatment. Studies have suggested that sertraline administration could be an effective way for treatment.

Methods: To verify the effectiveness and to explore the neurobiological processes, we treated a group of adolescents with nsMDDs with sertraline in this study. The brain spontaneous activity alteration was then investigated in fifteen unmedicated first-episode adolescent nsMDDs versus twenty-two healthy controls through the resting-state functional magnetic resonance imaging. Besides the baseline scanning for all participants, the nsMDDs group was scanned again after eight weeks of sertraline therapy to examine the changes after treatment.

Results: At pre-treatment, whole brain analysis of mean amplitude of low-frequency fluctuation (mALFF) was performed to examine the neuronal spontaneous activity alteration, and increased mALFF was found in the superior occipital extending to lingual gyrus in adolescent nsMDDs compared with controls. Meanwhile, decreased mALFF was found in the medial superior frontal in adolescent nsMDDs compared with controls. Compared with the pre-treatment, the nsMDDs group was found to have a trend of, respectively, decreased and increased functional neuronal activity at the two brain areas after treatment through the region of interest analysis. Further, whole brain comparison of mALFF at pre-treatment and post-treatment showed significantly decreased spontaneous activity in the orbital middle frontal and lingual gyrus in adolescent nsMDDs after treatment. Also, depression severity was significantly decreased after treatment.

Conclusion: The abnormal functional neuronal activity found at frontal and occipital cortex implied cognitive and affective disturbances in adolescent nsMDDs. The trend of upregulation of frontal neuronal activity and downregulation of occipital neuronal activity after sertraline treatment indicated that the therapy could be effective in regulating the abnormality. Notably, the significantly decreased neuronal activity in the decision related orbital middle frontal and anxiety-depression related lingual gyrus could be suggestive of reduced NSSI in adolescent MDD after therapy.

KEYWORDS

superior frontal, superior occipital, orbital middle frontal, lingual, mALFF, sertraline therapy, non-suicidal self-injury, adolescent depression

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder that is characterized by persistent low mood and loss of interest or pleasure in all activities, and these symptoms could finally lead to clinical sufferings (1). As a transitional stage from childhood to adulthood, the period of adolescence has a high prevalence of the psychiatric disorders such as MDD. And the adolescent depression could also increase the risk of depression later in the adulthood (2). Additionally, MDD has a significant association with self-injury and suicide (3). Non-Suicidal Self-Injury (NSSI) is defined as deliberately damaging one's own body without intention to die (4). According to the DSM-V, subjects with NSSI would be engaged in self-injury behavior five or more days within the past year to gain relief from the negative feelings or cognitive states (5). It has been further indicated that NSSI should be considered as a specific predictor of suicide (6). With the high incidence rate and suicide risk, NSSI has been attracted widespread attention among scholars. However, the underlying neurobiological mechanism is still unclear, and there are still challenges in the treatment for this group of population.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive neuroimaging technique which is based on the spontaneous fluctuations of the blood oxygen level dependent (BOLD) signal. It has been widely used in psychiatry disorder research as it could help uncover the neuronal activity pattern. The amplitude of low frequency fluctuation (ALFF) is one of the measurements commonly used to reflect the intensity of brain regional spontaneous activity (7). Moreover, ALFF could reflect the cyclic modulation of gross cortical excitability and long distance neuronal synchronization (8, 9). Previous studies on adolescent MDD have found impaired functional activation associated with emotional processing and regulation (10). Also, the deficits in developing neural systems such as visuo-spatial attention and sustained visual attention in adolescent MDD patients were also suggested (11, 12). While, there were few studies on adolescent MDD with NSSI.

In a functional study of NSSI in female adolescents without MDD, Plener et al. reported that NSSI patients showed altered neural activity pattern at limbic and fronto-occipital areas when watching the emotional and NSSI pictures (13). Our previous study also found that MDD adolescents with NSSI showed significantly increased ALFF signals in the frontolimbic brain regions compared with those patients without NSSI (14, 15).

Untill now, there is no recommended plan for NSSI treatment, and the optimal treatment for NSSI in adolescent MDD is still being explored. Several interventions appear to have an effect of reducing NSSI, including psychotherapy such as dialectical behavior therapy and emotion regulation group therapy, antipsychotics, and selective serotonin reuptake inhibitors (SSRIs). There remains a paucity of well-controlled studies investigating treatment efficacy of NSSI (16). Of the functional neuroimaging studies in NSSI, Santamarina-Perez et al. (17) Explored 4 weeks of psychotherapy among adolescents with NSSI, and they found that the strength of the amygdala-prefrontal connectivity could predict the efficacy of treatment. Cullen et al. (18) explored the circuit-level changes following an eight-week trial of N-acetylcysteine in female adolescents with NSSI, and they suggested that amygdala and nucleus accumbens-based circuits could serve as potential targets for treatment. These studies have demonstrated that NSSI in adolescents have neural circuits changes linked with the efficacy of treatment. However, these participants were not diagnosed with MDD.

Second-generation antidepressants are widely used for the treatment of MDD, including SSRIs, are recommended as the first-line medication for depression (19). Sertraline is an SSRI that has been used for the depression treatment. Studies have demonstrated that sertraline treatment for children and adolescents' MDD is effective and well-tolerated (20, 21). In the present study, we used the sertraline treatment for adolescent MDD with NSSI (nsMDDs). The rs-fMRI data was acquired at baseline and after treatment to explore the neurobiological mechanism and processes in adolescent nsMDDs. The mean ALFF (mALFF) analysis of imaging data was applied to improve the signal detection. Here, we hypothesized that: (i) The adolescent nsMDDs would have mALFF alterations at brain areas involved with cognitive and affective processing and (ii) The sertraline treatment would regulate the abnormal functional neuronal activity at the altered brain regions through the inhibition of selective serotonin reuptake in adolescent nsMDDs.

2. Materials and methods

2.1. Participants

Fifteen adolescents with nsMDDs were recruited from the outpatient clinic of the Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University, China, from January 2021 to March 2022. This study was approved by the Human Research and Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (no. 2021-546). Written informed consent was obtained from all adolescents and their caregivers.

All the patients were evaluated by two experienced psychiatrists using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-kid). The diagnostic criteria for NSSI were based on the Diagnostic and Statistical Manual of Mental Disorders, the fifth edition (DSM-V). These patients did not take any psychotropic drugs before participating in this study. The primary inclusion criteria were as follows: (i) Han nationality, aged 12–17 years, and right-handed, (ii) first-episode depression with no history of antidepressant treatment or psychotherapy, (iii) reported NSSI events five times or more in the past 12 months and at least once NSSI in the last month according to the Ottawa self-injury inventory (OSI), (iv) exhibited a Hamilton Depression Scale (HAMD-17) score > 17, (v) no MRI scanning contraindication such as metal implants, (vi) no history of brain trauma or other serious physical illnesses, (vii) no substance abuse or dependence, and (viii) no history of any other mental health disorders. The severity of depression was assessed using the 17-item Hamilton Depression Scale (HAMD) (all patients' score > 17). The patients were once assessed at baseline and then reassessed after 8 weeks of antidepressant medication treatment.

In addition, twenty-two healthy controls (HC) matched for age, gender and education level were recruited from the local school. The inclusion criteria were Han nationality, aged 12–17 years, right-handed, HAMD score < 7, and absence of any severe mental or physical illness.

2.2. Antidepressant medication protocol

Sertraline was selected as the main antidepressant drug with an initial dose of 50 mg per day, and the maximum dose was 100–200 mg per day depending on the patients' condition. The medication continued for 8 weeks.

2.3. Imaging protocol

All MR images were acquired with 3.0-T GE Signa HDxt (General Elecric Healthcare, Chicago, Illinois, United States) scanner equipped with a standard 8-channel head coil. Contiguous sagittal T1-weighted images across the entire brain were acquired with a fast gradient echo (FGRE) sequence: time of echo (TE) = 3.1 msc, time of repetition (TR) = 8 msc, flip angle = 12°, field of view (FOV) = 240 mm, voxel size = 0.938 × 0.938 × 1 mm^3, no gap. The rs-fMRI data were obtained using an echo-planar image (EPI) pulse sequence with the following parameters: 33 axial slices, TE = 40 msc, TR = 2000 msc, in-plane resolution = 64 × 64 pixels, flip angle = 90°, FOV = 240 mm, voxel size = 3.75 × 3.75 × 4 mm^3, no gap. A total of 240 time points was obtained over 8 min. All participants including both adolescent nsMDDs and HC underwent baseline MR scanning. After 8 weeks of treatment, the adolescent nsMDDs was scanned once again.

2.4. Imaging processing and analysis

Two experienced imaging professionals performed quality control of the original data, and no excessive head movements or abnormal signals were observed in any image. Then, imaging processing was performed with SPM12[1] and RESTplus toolkits[2] within MATLAB 2013b (MathWorks, Natick, MA, United States).

The procedures were as follows: (i) the original structural and functional image data were firstly converted into NII and NIFTI formats, (ii) the first 10 time points were removed to eliminate nonequilibrium effects of magnetization, (iii) slice timing and head motion correction were then performed to exclude the participants whose head movements exceeded 3 mm translation or 3 degree rotation in any direction, (iv) functional images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template and resampled as 3 × 3 × 3 mm^3, (v) a standardization smoothing through the Gaussian filter of 6-mm full width at half maximum (FWHM) was performed to reduce the influence of spatial noise and the differences of brain structure among subjects, and (vi) nuisance regression was performed using the six head motion parameters, white matter, and cerebral spinal fluid BOLD signal as covariates. Linear trends were removed.

ALFF was computed based on the fast Fourier transform (FFT) and the time series of each voxel was transformed to the frequency domain without band-pass filtering. The square root was first calculated at each frequency of the power spectrum, and the mean square root was then obtained across frequency band of 0.01–0.08 Hz for each voxel. Finally, the ALFF of each voxel was divided by the global mean to acquire the mALFF.

2.5. Statistical analysis

Differences in the clinical and demographic characteristics between patients and controls were assessed using SPSS (v26.0, IBM, Chicago, NY, United States). The whole brain analysis of mALFF alteration in adolescent nsMDDs compared to HC was conducted through the SPM using the two-sample *t*-tests. Age, gender and education level was entered into the general linear model as covariates. An initial voxel-wise threshold was set at $p < 0.05$ with subsequent family-wise error (FWE) corrected value of $p < 0.05$ at the cluster level. Then, region of interest (ROI) analysis was conducted to compare the mean signal at the altered brain regions at pre and post-treatment.

The other whole brain analysis of mALFF changes in adolescent MDD at post-treatment compared to pre-treatment was conducted through the SPM using the paired *t*-test. An initial voxel-wise threshold was set at $p < 0.05$ with subsequent family-wise error (FWE) corrected value of $p < 0.05$ at the cluster level. Also, ROI analysis was conducted to compare the mean signal changes at the altered brain regions at pre and post-treatment.

Depression severity changes were further assessed through the paired *t*-test. Also, Pearson correlation was carried out to examine relationship between the mALFF alteration and depression severity changes. The xjView toolbox[3] was used for imaging visualization.

3. Results

3.1. Participants and clinical characteristics

Fifteen adolescent nsMDDs (13 female/2 male, 14.60+/−1.35 years old) and twenty-two HC (13 female/9 male, 15.27 +/−1.05 years old) to be included into the analysis. The statistical analysis showed no significant differences of gender, age and education years between the two groups. More than half of adolescent nsMDDs had total HAMD scores higher than 24, corresponding to the severe status. The demographic and clinical characteristics of these individuals are shown in Table 1.

3.2. Whole brain comparison of mALFF in adolescent nsMDDs

At pre-treatment, significant differences were observed in regional mALFF between adolescent nsMDDs and HC groups. Compared to controls, adolescent nsMDDs showed significantly increased mALFF in the right superior occipital extending to left lingual gyrus (Peak value = 4.60; at [15, −87, 33]; k = 1,565 voxels) at $p < 0.05$ (corrected) (see Figure 1; Table 2). The hyperactivity at occipital cortex still remained significantly at $p < 0.001$ (corrected) (see Supplementary Figure S1; Table S1). Meanwhile, the mALFF was found decreased at right medial superior frontal gryus (SFG, Peak value = −3.95; at [9, 51, 6]; k = 607 voxels) extending to left medial orbital SFG at $p < 0.062$ (corrected) (see Figure 1; Table 2).

1 http://www.fil.ion.ucl.ac.uk/spm

2 http://www.restfmri.net/forum/REST

3 https://www.alivelearn.net/xjview

TABLE 1 Demographic and clinical characteristics of participants.

	nsMDDs (*n* =15)	HC (*n* =22)	Statistics
Gender, *n*			
Female	13	13	$p^a = 0.141$
Male	2	9	
Age, yrs	14.60 (1.35)	15.27 (1.05)	$t = -1.20$, $p = 0.24$
Education, yrs	9 (1.77)	9.36 (2.72)	$t = -0.49$, $p = 0.63$
HAMD[b]	23.53 (3.66)	1.59 (2.59)	$t = 23.21$, $p < 0.001$
N[c], %	8 (53.3%)		
HAMD[d]	14.47 (6.29)	–	–
N[e], %	1 (6.7%)		

HAMD, hamilton depression scale. [a]indicates the Chi-square test, [b]indicates the HAMD scores before treatment, [d]indicates the HAMD scores after treatment, [c,e]indicates the number of subjects with HAMD score > 24 before and after treatment, respectively.

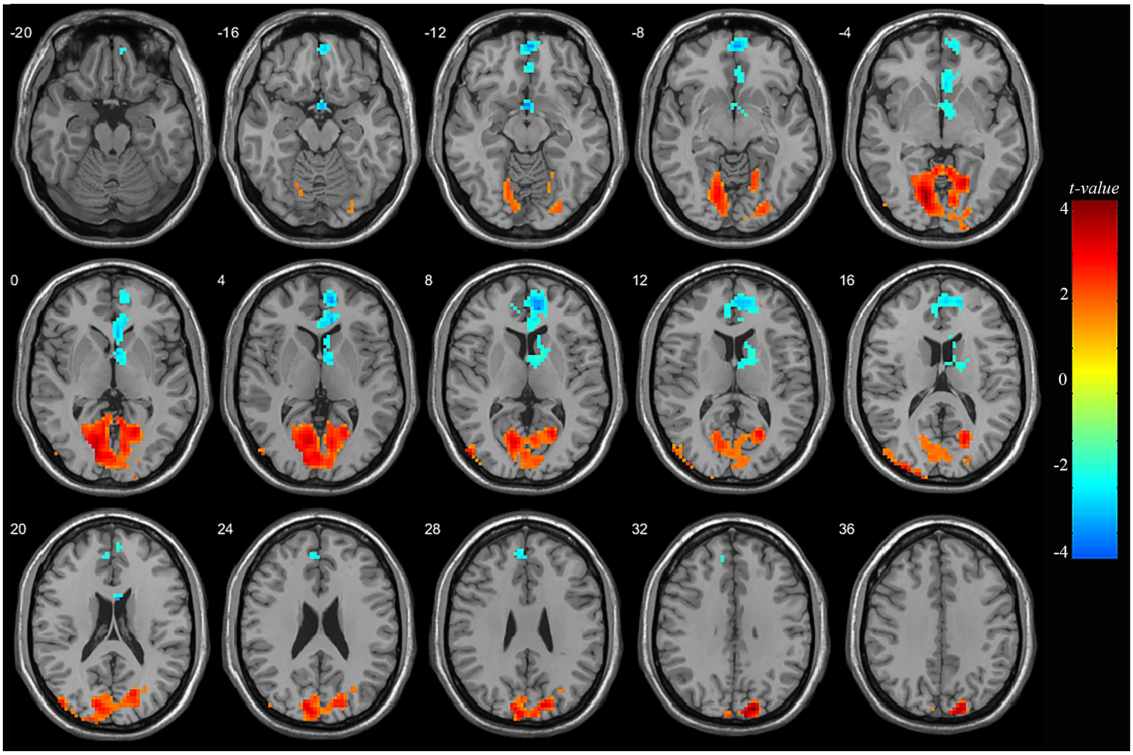

FIGURE 1
Adolescents with nsMDDs showed mALFF disturbances at frontal and occipital brain regions. Compared to controls, adolescent nsMDDs had significantly increased mALFF at right superior occipital extending to left lingual gyrus; Meanwhile decreased mALFF were found at right medial superior frontal extending to left medial orbital superior frontal. The color bar depicts the *t* value.

TABLE 2 Locations of regional mALFF alteration in adolescent nsMDDs compared to controls.

Brain region	MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous voxels)
	x	*y*	*z*		
nsMDDs>HC					
R. Superior occipital	15	−87	33	4.60	1,565
L. Lingual gyrus	−15	−75	−3	4.27	257
nsMDDs<HC					
R. Medial superior frontal	9	51	6	−3.95	607
L. Medial orbital superior frontal	0	57	−9	−3.29	37

3.3. Whole brain comparison of mALFF in adolescent nsMDDs before and after treatment

Compared to pre-treatment, significantly decreased mALFF was found at left orbital middle frontal gyrus (orbMFG, Peak value = −7.34; at [−18, 36, −15]; k = 1,638 voxels) extending to right triangular inferior frontal gyrus (IFG) in adolescent nsMDDs after treatment at $p < 0.05$ (corrected). The reduced neuronal activity at the orbMFG remained significantly at $p < 0.001$ (see Supplementary Figure S1; Supplementary Table S1). Also, the significantly decreased mALFF was found at the left lingual gyrus (Peak value = −4.44; at [−15, −54, 0]; k = 814 voxels) extending to right lingual gyrus at $p < 0.05$ (corrected) (see Figure 2; Table 3).

3.4. Comparison of mALFF at region of interests in adolescent nsMDDs before and after treatment

The ROI analysis found a trend of decreased mALFF at the hyperactive occipital cortex found in adolescent nsMDDs after sertraline treatment. Whereas, a trend of increased mALFF at the hypoactive medial SFG found in adolescent nsMDDs after treatment. Further, ROI analysis found significantly decreased mALFF at left orbMFG in adolescent nsMDDs compared to pre-treatment after sertraline treatment. Also, the mALFF at lingual gyrus in adolescent nsMDDs showed significantly decreased compared to pre-treatment (see Figure 3).

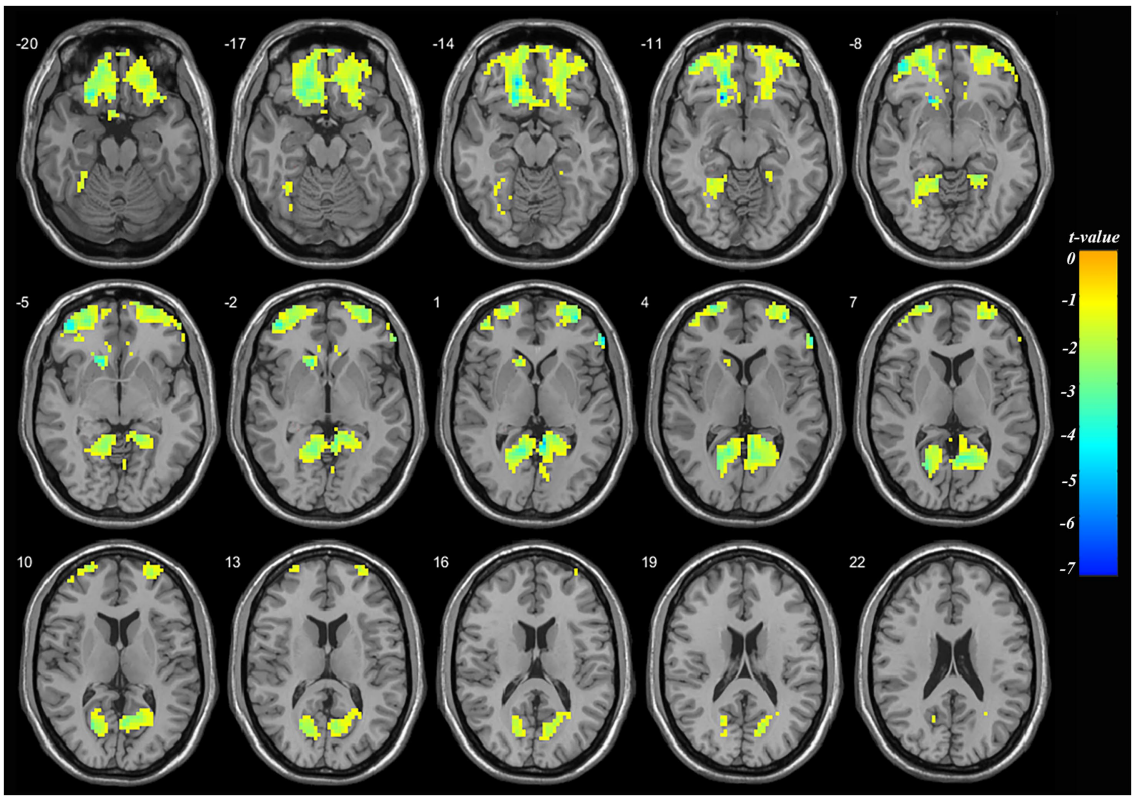

FIGURE 2
Adolescents with nsMDDs showed decreased mALFF at frontal and occipital brain regions after treatment. Compared to the pretreatment, adolescent nsMDDs had significantly decreased mALFF at left orbital middle frontal extending to right triangular inferior frontal, and bilateral lingual gyrus after treatment. The color bar depicts the *t* value.

TABLE 3 Locations of regional mALFF alteration in adolescent nsMDDs before and after treatment.

Brain region	MNI coordinates of peak			Peak *t*-value	Spatial extent (in contiguous voxels)
	x	*y*	*z*		
L. Orbital middle frontal	−18	36	−15	−7.34	1,638
R. Triangular inferior frontal	57	39	0	−5.41	15
L. Lingual	−15	−54	0	−4.44	814
R. Lingual	6	−60	6	−4.18	122

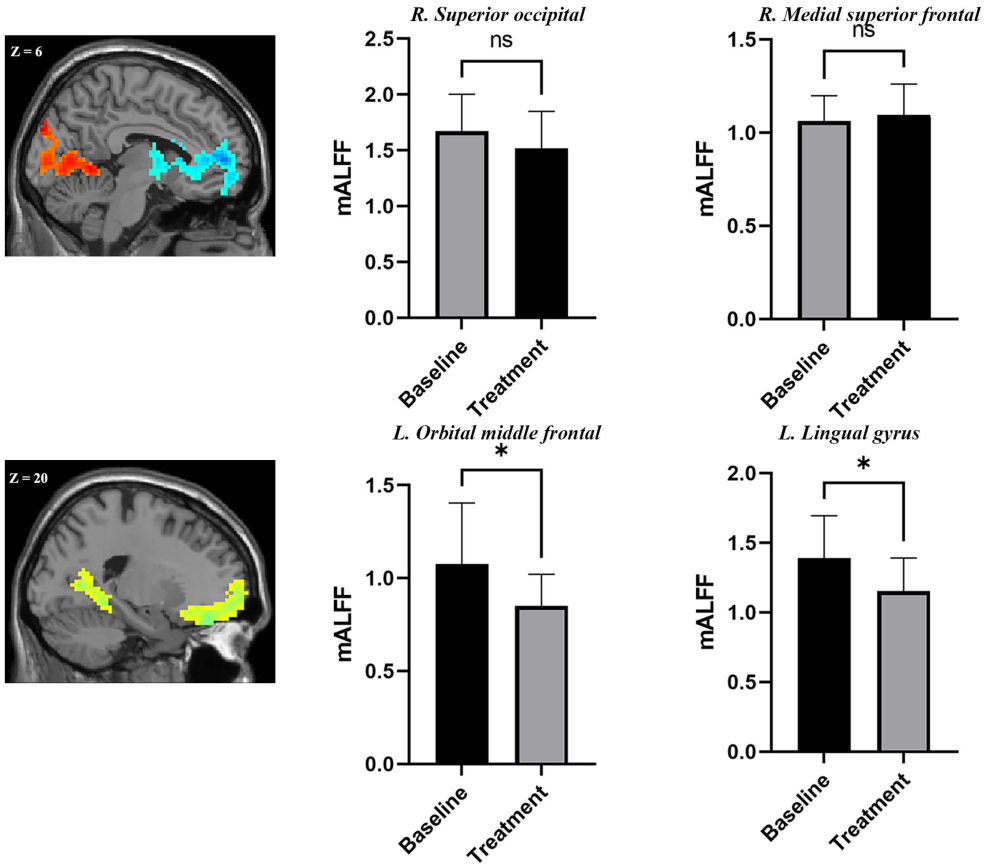

FIGURE 3
Adolescents with nsMDDs showed mean mALFF signal changes after treatment. The upper panel showed a trend of downregulation of mALFF at the occipital areas. At the mean time, a trend of upregulation of mALFF at the frontal areas. Further, compared to the pre-treatment, the adolescent nsMDDs showed significantly decreased mALFF at left orbital middle frontal and lingual gyrus after treatment. *$p < 0.05$.

3.5. Correlation with clinical severity changes in adolescent nsMDDs after treatment

After sertraline treatment, the HAMD scores were significantly decreased in adolescent nsMDDs ($t = 5.86$, $p < 0.001$) (see details in Supplementary Table S2). Further, Pearson correlation analysis showed no significant correlation between the HAMD changes with mALFF alteration in adolescent nsMDDs. But the correlation between the changes of mALFF at occipital cortex and HAMD was achieved nearly significant ($r = -0.295$, $p = 0.287$ for superior occipital; $r = -0.357$, $p = 0.192$ for lingual gyrus) (see Supplementary Table S3). Finally, the NSSI measured by OSI was 1.47 +/−0.64 before treatment, and after therapy, it showed a decrease (1.27 +/−0.96) but no significant difference was observed ($t = 0.716$, $p = 0.486$) (see Supplementary Table S4). Pearson correlation showed no significant correlation of the alteration in changes of mALFF and NSSI after treatment (see Supplementary Table S5).

4. Discussion

Through the rs-fMRI technique, the present study identified the abnormal neuronal activity pattern in adolescent nsMDDs. Further, we elaborated the changes of this activity pattern after the eight-week sertraline therapy. Compared with healthy individuals, adolescent nsMDDs had increased neuronal spontaneous activity at superior occipital cortex, and decreased activity at medial SFG. Further, no significant differences but a trend of decreased activity were observed at the superior occipital cortex in adolescent nsMDDs after treatment. At the same time, a trend of increased activity was observed at the medial SFG after treatment. The changes of neuronal activity at fronto-occipital areas reflect the downregulation and upregulation of antidepressant effects. Moreover, the neuronal activity at left orbMFG and lingual gyrus was significantly decreased after treatment, which might indicate the decreased NSSI behaviors or thoughts, and anxiety-depression level in adolescent nsMDDs. Finally, significantly decreased HAMD scores were found in adolescent nsMDDs after the sertraline therapy.

4.1. Findings of mALFF alteration in adolescent nsMDDs

The occipital cortex is involved in primary visual stimulation and is associated with facial emotional awareness and working memory

(22). Previous studies have provided evidences of the decreased concentration of gamma-aminobutyric acid (GABA) at the occipital cortex (23–25). As GABA is an inhibitory neurotransmitter, the deficits might cause the abnormal spontaneous activity found in nsMDDs.

Located at the occipital cortex, lingual gyrus plays an important role in emotional processing, logical reasoning, and visual information integration (26, 27). Previous studies proposed the activation in the lingual gyrus in MDD patients may be a sign of dysfunction in emotion processing and involved in suicidal behavior (28, 29). Furthermore, Yan et al. (30) demonstrated that nsMDDs have increased ALFF in the lingual gyrus and they speculated that increased resting-state activity in the lingual gyrus was associated with NSSI behavior. In this study, we found that nsMDDs exhibited increased mALFF in the right superior occipital gyrus and left lingual gyrus compared with HC, which was consistent with previous studies. Besides, the left lingual gyrus is involved in linguistic processing (31, 32) and an additional study indicated that the changes in speech characteristics could predict depression severity (33). These findings could explain the language expression problems such as reduced speech rate and decreased volume of tone in MDD patients.

Moreover, we found that nsMDDs exhibited decreased mALFF in the medial SFG. The SFG is the core region of the default mode network (DMN), involved in memory-related cognitive and motor control tasks, as well as self-related processing (34). Previous studies have reported abnormalities in DMN of MDD patients, and this abnormality could be related with suicidal ideation and NSSI behavior (15, 35). The decreased levels of glutamatergic (Glu) metabolites in the medial frontal cortex were linked with the pathophysiology of depression (36). Contrary to GABA, Glu is an excitatory neurotransmitter, and the deficits might cause the decreased neuronal activity found in the study.

4.2. Findings of mALFF changes in adolescent nsMDDs after sertraline treatment

The left orbMFG is located in the prefrontal lobe, and belongs to the reward network involved with decision making processes. Sun et al. (37) found that the decreased activation in this region was associated with the efficacy of antidepressant treatment, which was similar to our results. NSSI behavior is associated with decision making, the decreased activation found in this region might indicate the reduction of NSSI behaviors or thoughts. It is inferred that the significantly reduced HAMD score after treatment might be associated with the reduced NSSI behaviors or thoughts.

The IFG plays an important role in emotional and cognitive control. As an important component of the IFG, the right triangular part is suggested taking part in language comprehension (38). Also, this region was involved in unconscious information processing (39). Further, it was also associated with the early-onset depression (EOD) and late -onset depression (LOD). Zhang et al. (40) found the EOD patients exhibited increased activation in the right triangular IFG compared with the LOD patients. They indicated that the specific brain alterations of EOD and LOD patients could be associated with different clinical symptoms. EOD patients are associated with more suicidal behaviors and thoughts, slower treatment response and higher prevalence of co-morbid personality disorders (40–42). According to these reports, we speculated that the decreased activation in the right triangular IFG was linked with the reduced suicidal behaviors and the efficacy of the sertraline therapy.

Also, nsMDDs exhibited decreased mALFF at the bilateral lingual gyrus after sertraline therapy, which could indicate that the abnormal activation in the occipital gyrus of the patient was relieved after treatment. It has been demonstrated that SSRI treatments could increase the GABA concentration at the occipital cortex in depressed patients (43, 44). With the increased GABA concentration, it could further lead to the decreased functional neuronal activity in the occipital cortex. Therefore, this GABA concentration improvement could be a potential mechanism underlying the sertraline therapy in nsMDDs to diminish the hyperactivity at the occipital cortex.

Moreover, the ROI analysis found downregulation of hyperactivity at the superior occipital cortex and upregulation of hypoactivity at the medial SFG in adolescent nsMDDs after treatment. It is widely acknowledged that the breakdown in brain serotonin (5-HT) signaling is closely related to depression symptoms, and antidepressants have been developed according to this basis (45, 46). Sertraline is an SSRI, which plays an important role in treating depression through regulating the abnormal 5-HT. Therefore, the changes of neuronal activity might indicate the efficacy of sertraline therapy.

Over all, our findings of neuronal activity alteration pattern in nsMDDs were consistent with the previous studies. Also, there were few studies that used the rs-fMRI technique to examine the efficacy of sertraline treatment in adolescent nsMDDs. But there were still some limitations in this study. First, our sample size was relatively small and some participants could not endure long-term MRI examinations. The future study with large sample size could be carried out to replicate and validate our findings. Second, nsMDDs exhibited changes of neuronal activity as well as HAMD scores after the therapy, but there was no significant correlation between these changes. While a previous study based on structural imaging has indicated that the alterations in the first week of treatment might be associated with long-term treatment efficacy (47). Thus, a longitudinal observation would be conducted in the future study. Lastly, some participants did not fully understand the OSI report, thus, we could not exactly determine the frequency of NSSI. We would optimize the procedure in the future study.

5. Conclusion

In summary, this study revealed that sertraline was an effective way to treat nsMDDs in adolescents through the direct insight into sertraline-induced brain spontaneous activity changes using the rs-fMRI technique. Specifically, it exhibited downregulation of the hyperactivity at superior occipital cortex and upregulation of the hypoactivity at medial SFG in adolescent nsMDDs. Alongside the regulation effects, significantly decreased neuronal functional activity in the decision related orbMFG, and anxiety-depression related lingual gyrus implied the reduced NSSI behaviors or thoughts in adolescent nsMDDs.

Data availability statement

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

Ethics statement

This study was approved by the Human Research and Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (no. 2021-546). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LD: conceptualization, formal analysis, and writing – original draft. XZ: formal analysis, visualization, and writing – review and editing. RY and XW: imaging scanning. FD and XL: data collection. LK: project administration, funding acquisition, and writing – review and editing. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1177227/full#supplementary-material

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Interactive effect between sleep and exercise on depressive symptoms in Chinese adolescents

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Objectives: The study aimed to investigate the effects of sleep and exercise, individually and jointly, on depressive symptoms in Chinese adolescents.

Methods: Cluster sampling was used to conduct a cross-sectional, electronic survey among 11,563 students from five primary and high schools in Sichuan Province in Western China. The questionnaire contained custom-designed items concerning sleep and exercise, while it used the Center for Epidemiologic Studies Depression Scale to assess depressive symptoms and the Core Self-Evaluations Scale to assess core self-evaluation. Data were analyzed using descriptive statistics and multivariate linear regression.

Results: A total of 10,185 valid questionnaires were collected, corresponding to an effective response rate of 88.1%. Among the respondents in the final analysis, 5,555 (54.5%) were boys and 4,630 (45.5%) were girls, and the average age was 15.20 ± 1.72 years (range, 11–18 years). Only less than half of the respondents (4,914, 48.2%) reported insufficient sleep, while the remainder (5,271, 51.8%) had adequate sleep. Nearly one-quarter (2,250, 22.1%) reported insufficient exercise, while the remainder (7,935, 77.9%) reported adequate exercise. More than half of the respondents (5,681, 55.7%) were from vocational high school, 3,368 (33.1%) were from junior high school, 945 (9.3%) were from senior high school, and 191 (1.9%) were from primary school. The prevalence of depressive symptoms among all respondents was 29.5% (95% CI 28.7%–30.4%). When other variables were

controlled, the depression score did not vary significantly with gender ($B = -0.244$, SE = 0.127, $P = 0.054$), but it decreased by 0.194 points per 1-year increase in age ($B = -0.194$, SE = 0.037, $P < 0.001$). Students getting adequate sleep had depression scores 2.614 points lower than those getting insufficient sleep ($B = -2.614$, SE = 0.577, $P < 0.001$), while students who engaged in adequate exercise had depression scores 1.779 points lower than those not exercising enough ($B = -1.779$, SE = 0.461, $P < 0.001$). The depression score decreased by 0.919 points per 1-point increase in the core self-evaluation score ($B = -0.919$, SE = 0.008, $P < 0.001$). In regression controlling for gender, age, and core self-evaluation, sleep and exercise were found to be related significantly to influence depressive symptoms ($B = 0.821$, SE = 0.315, $P = 0.009$).

Conclusion: Adequate sleep and adequate exercise are individually associated with milder depressive symptoms in Chinese adolescents. Our results further highlight the need for researchers and clinicians to take into account not only the individual but also the joint effects of sleep and exercise on depression in adolescents when conducting research and designing interventions. If sleep or physical exercise has substantially reduced the risk of depressive symptoms, further reductions by improving sleep and exercise become difficult and may even have opposite effects.

KEYWORDS

sleep, exercise, interactive effect, adolescent, depressive symptoms

1. Introduction

Depression often begins in adolescence, and a meta-analysis of 37 studies of high school students in China indicated a prevalence of 28% for depressive symptoms (1), while a meta-analysis of 72 studies of adolescents worldwide indicated a prevalence of 34%. The prevalence may be even higher among adolescents in the Middle East, Africa, and Asia (2). Thus, depression is a major disease, threatening the physical and mental health of adolescents. Identifying more influencing factors of depression may help to provide more options for the prevention and treatment of depression.

The National Sleep Foundation in the USA and the 24-Hour Movement Guidelines for Children and Youth in Canada recommend that children aged 5–13 years should sleep 9–11 h per night, while adolescents aged 14–17 years should sleep 8–10 h per night (3, 4). A survey on adolescent sleep in the USA found that only 26% of adolescents had adequate sleep (5). A lack of sleep affects the growth and development of adolescents and increases the risk of hypertension, diabetes, obesity, and other diseases (6, 7). It also increases the risk of depression and anxiety symptoms (8–10).

Regular, moderate physical exercise has been observed to reduce the risk of depression in adolescents and improve their mental health (11). The World Health Organization recommends that teenagers spend more than 1 h per day on average exercising at moderate intensity (12). In fact, a meta-analysis of prospective cohort studies found that physical exercise can reduce the incidence of depression among people of all ages (13). Among adults who did not exercise, those who completed half the recommended amount of exercise were at an 18% lower risk of depression, while those who completed the full amount were at a 25% lower risk (14).

Many studies have reported a correlation between core self-evaluation (CSE) and depression. CSE is an individual's basic evaluation of self-worth and ability, and it comprises mainly four traits: self-esteem, generalized self-efficacy, locus of control, and emotional stability (low neuroticism) (15–17). One study among Chinese university students found that fatalism and CSE mediated the relationship between stressful life events and depression (18). Another study reported that depression among Chinese adolescents correlated negatively with CSE and self-efficacy in expressing positive emotions and managing negative ones (19).

In addition to the effects of sleep and exercise individually on the risk of depression among adolescents, several studies have pointed to a potential interaction between them. For example, a 2-year longitudinal study of Estonian adolescent girls indicated an association between increased sleep disturbance and decreased physical activity with increased depressive symptoms (20). In addition, higher levels of depressive symptoms at the baseline in that study were associated with less physical activity and more sleep disturbance 2 years later. A systematic review study found that sleep deprivation contributed to the risk of depressive mood, while exercise reduced that risk (21). A study of high school students in Eastern China found that sleep duration and the number of days when respondents completed 60 min of physical exercise mediated the relationship between academic stress, anxiety, and depression (22). A study of Japanese high school students detected an interactive effect of sleep and exercise on depression (23).

This literature suggests that sleep and exercise act individually and jointly to influence the risk of depression among adolescents. However, large studies are needed to verify this hypothesis and

begin to explore the causes. Therefore, we conducted a cross-sectional survey of more than 10,000 adolescents in Sichuan Province in Western China to explore relationships among sleep, exercise, and depressive symptoms.

2. Objectives and methods

2.1. Sample

Using PASS software, we calculated a minimal sample size of 8,165 assuming a prevalence of 30% for depressive symptoms among adolescents (2, 24, 25), tolerance error of 0.01, type I error of 0.05, and statistical power of 0.8. We increased the sample size by 10% to 9,072 in order to account for invalid questionnaires or lack of consent to participate. From October 2020 to March 2021, five primary and high schools in Chengdu (one junior high school, one primary school, and two vocational high schools) and Leshan (one high school containing a junior high school department and a senior high school department) were selected using cluster sampling. Teachers at each school sent electronic questionnaires to all students who are at least 11 years old. The final sample of 10,185 exceeded the minimal sample size, suggesting good statistical power.

2.2. Tools

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), which contains 20 self-report items to which subjects respond using a 4-point scale from 0 to 3 based on the frequency of depression emotion or mood during the previous week. The CES-D can be divided into four factors: (1) physical symptoms, (2) negative emotion, (3) positive emotion, and (4) interpersonal relationships. Higher scores indicate higher levels of depression (26, 27). We defined a CES-D score of at least 20 as indicating the presence of depressive symptoms; this cutoff was found to balance sensitivity and specificity better in a systematic review study (28).

CSE was evaluated using the Core Self-Evaluations Scale (CSES), which contains 10 self-report items to which subjects respond on a 5-point scale from 1 to 5 according to how much they agree with a statement (1 = "completely disagree" and 5 = "completely agree") (15, 29).

Data on sleep and exercise were obtained through a custom-designed set of questionnaires asking about the average number of hours of sleep per day, for which possible responses were "4 h or less," "5 h," "6 h," "7 h," "8 h," "9 h," "10 h," "11 h," or "12 h or more." Subjects were also asked to report the average number of hours of medium- or high-intensity exercise in which they engaged daily, for which possible responses were "<1 h," "1 h," "2 h," "3 h," "4 h," and "5 h or more."

We defined adequate sleep as at least 9 h per day if the subject was 13 years old or younger or at least 8 h per day if the subject was at least 14 years old (3, 4). We defined adequate exercise as at least 1 h per day (12).

2.3. Research permission and informed consent

This study was approved by the Ethics Committee of West China Hospital, Sichuan University. The legal guardians (parents) of the minors were informed of the significance, confidentiality, and safety of the study through an electronic informed consent form, which they signed electronically. Only subjects whose legal guardians signed the informed consent were included in the analysis.

2.4. Statistical analysis

All data were analyzed using SPSS 23.0 software. Descriptive statistics were used to describe demographic information, depression scores, and proportions of students reporting sufficient sleep or sufficient exercise. Multivariate linear regression was used to identify factors influencing depression and to detect a potential joint influence of sleep and exercise on depression (30, 31).

3. Results

3.1. Characteristics of the sample

Of the 11,563 questionnaires distributed, 10,185 valid questionnaires were returned, corresponding to an effective response rate of 88.1%. Among those respondents, 5,555 (54.5%) were boys and 4,630 (45.5%) were girls; their average age was 15.20 ± 1.72 years (range, 11–18 years; Table 1). Only less than half of the respondents (4,914, 48.2%) reported insufficient sleep, while the remainder (5,271, 51.8%) had adequate sleep. Nearly one-quarter (2,250, 22.1%) reported insufficient exercise, while the remainder (7,935, 77.9%) reported adequate exercise. More than half of the respondents (5,681, 55.7%) were from vocational high school, 3,368 (33.1%) were from junior high school, 945 (9.3%) were from senior high school, and 191 (1.9%) were from primary school. The prevalence of depressive symptoms among all respondents was 29.5% (95% CI 28.7–30.4%), which had been reported in our previous article (32).

3.2. Factors influencing depressive symptoms

Multivariate linear regression was used to assess the effects of age, sex, CSE, sleep, and exercise on CES-D scores. In the case of sleep and exercise, we examined these factors individually and jointly. Before an interaction between sleep and exercise was specified, the inclusion of the five variables in the regression led to a significant model ($F = 2{,}733.161$, $P < 0.001$), which explained 57.3% of the observed variation in CES-D scores. No multicollinearity was observed among the included variables. Including interaction between sleep and exercise in the regression led to a model that was also significant ($F = 2{,}280.072$, $P <$

TABLE 1 Demographic information (number of students, %/$X \pm S$).

Items	Distribution
Gender	
Male	5,555 (54.5%)
Female	4,630 (45.5%)
Age	15.20 ± 1.72 years
Ethnic group	
Han nationality	9,792 (96.2%)
Tibetan	178 (1.7%)
Yi nationality	112 (1.1%)
Other nationalities	103 (1.0%)
Grade	
Primary school	191 (1.9%)
Junior high school	3,368 (33.1%)
Senior high school	945 (9.3%)
Vocational high school	5,681 (55.7%)
Sleep	
Insufficient sleep	4,914 (48.2%)
Adequate sleep	5,271 (51.8%)
Exercise	
Insufficient exercise	2,250 (22.1%)
Adequate exercise	7,935 (77.9%)
CSES score	35.04 ± 7.81
CES-D score	15.95 ± 9.59
Physical symptoms	3.20 ± 3.20
Negative emotion	5.12 ± 5.05
Positive emotion	6.65 ± 3.33
Interpersonal relationships	0.99 ± 1.39

0.001) and that explained 57.3% of the observed variation in the CES-D scores.

When other variables were controlled, the depression score did not vary significantly with gender ($B = -0.244$, SE = 0.127, $P = 0.054$), but it decreased by 0.194 points per 1-year increase in age ($B = -0.194$, SE = 0.037, $P < 0.001$). Students getting adequate sleep had depression scores 2.614 points lower than those getting insufficient sleep ($B = -2.614$, SE = 0.577, $P < 0.001$), while students who engaged in adequate exercise had depression scores 1.779 points lower than those not exercising enough ($B = -1.779$, SE = 0.461, $P < 0.001$). The depression score decreased by 0.919 points per 1-point increase in the core self-evaluation score ($B = -0.919$, SE = 0.008, $P < 0.001$). In regression controlling for gender, age, and core self-evaluation, sleep and exercise were found to interact significantly to influence depressive symptoms ($B = 0.821$, SE = 0.315, $P = 0.009$) (Table 2).

4. Discussion

In this study, 10,185 adolescents aged 11–18 years old from five primary and high schools in Chengdu and Leshan, China were investigated for depressive symptoms and influencing factors. Our data indicated a higher prevalence of depressive symptoms among students who lacked sleep or exercise. We also found that depressive symptoms correlate negatively with age and CSE.

The proportion of respondents in our study who reported insufficient sleep was 48.2%, which is similar to that reported among Saudi adolescents (33) but lower than that reported among USA and Chinese adolescents (34, 35). The proportion of respondents in our study who reported insufficient exercise was 22.1%, which is lower than that in studies in India and similar to that in the ABCD cohort study in the USA (36, 37), which may reflect that more than half of our respondents were in vocational high school, where academic demands are less than in other types of high school, leaving students more time and opportunities to engage in sports.

Our results are consistent with previous studies linking lower physical activity with a greater risk of depressive symptoms in the Avon Longitudinal Study of Parents And Children (ALSPAC) cohort from the University of Bristol (38), a meta-analysis of 23 randomized trials showing physical exercise to be effective for treating depression (39), and a longitudinal study in Europe showing that regular leisure-time exercise of any intensity reduced risk of depression during an 11-year follow-up (40). Our results are also consistent with a previous study linking adequate sleep to a lower risk of depressive symptoms (41, 42). Finally, our detection of an interactive effect of sleep and exercise on depression among Chinese adolescents mirrors the results from a similar study in Japan (23). These observations suggest the robustness of the effects of sleep and exercise, individually and jointly, on the risk of depression among adolescents.

Interestingly, the interactive effect of sleep and exercise in our study was in the opposite direction as their individual effects on depressive symptoms. The Japanese study reported a similar finding (23). This may reflect an overlap in how sleep and exercise influence such symptoms, such that if sleep or physical exercise has substantially reduced the risk of depressive symptoms, further reductions by improving sleep and exercise become difficult. The finding may also reflect the influence of other factors that we did not take into account, such as negative life events, school bullying, family history of mental illness, or personality traits.

Since this was a cross-sectional study, we could not make a causal inference. We did not objectively measure sleep or exercise but relied on self-report, increasing the risk of memory and reporting bias. It may be more objective to survey subjects using the Pittsburgh Sleep Quality Index or to monitor their sleep or exercise directly using, for example, a wearable device (38, 43, 44). We did not collect data about the history of mental illness, which may have contributed to depressive symptoms. All subjects in this study were adolescents from Sichuan province, so whether our results can be generalized to other ethnic and age groups is unknown. We did not rigorously determine whether students had depression or not, but only examined their depressive symptoms, which means that our findings should be confirmed in adolescents diagnosed with

TABLE 2 Multiple linear regression analysis of depressive symptoms-related factors.

Independent variables	*B*-value	SE	*B*-value 95% CI	*P*-value
Constant	56.316	1.089	(54.181, 58.451)	<0.001
Gender (male/female)	−0.244	0.127	(−0.493, −0.004)	0.054
Age	−0.194	0.037	(−0.267, −0.120)	<0.001
Sleep	−2.614	0.577	(−3.746, −1.482)	<0.001
Exercise	−1.779	0.461	(−2.683, −0.874)	<0.001
CSES	−0.919	0.008	(−0.935, −0.903)	<0.001
Sleep * exercise	0.821	0.315	(0.205, 1.438)	0.009

depression. Indeed, these limitations mean that our results should be interpreted with caution.

Despite these limitations, our study, together with an increasing number of other studies, suggests that ensuring adequate sleep duration and increasing physical activity in adolescents can mitigate and even prevent depressive symptoms. Our results further highlight the need for researchers and clinicians to take into account not only the individual but also the joint effects of sleep and exercise on depression in adolescents when Conducting research and designing interventions. If sleep or physical exercise has substantially reduced the risk of depressive symptoms, further reductions by improving sleep and exercise become difficult and may even have opposite effects. In future, we hope to conduct a large, longitudinal study and analyze more factors related to depressive symptoms in order to explore how sleep and exercise affect such symptoms.

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 Ethics Committee of West China Hospital, Sichuan University. Written informed consent to participate in this study was provided by the participants' 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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Adjunctive repetitive transcranial magnetic stimulation for adolescents with first-episode major depressive disorder: a meta-analysis

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Objective: This meta-analysis of randomized clinical trials (RCTs) was conducted to explore the therapeutic effects, tolerability and safety of repetitive transcranial magnetic stimulation (rTMS) as an adjunct treatment in adolescents with first-episode major depressive disorder (FE-MDD).

Methods: RCTs examining the efficacy, tolerability and safety of adjunctive rTMS for adolescents with FE-MDD were included. Data were extracted by three independent authors and synthesized using RevMan 5.3 software with a random effects model.

Results: A total of six RCTs involving 562 adolescents with FE-MDD were included. Adjunctive rTMS was superior in improving depressive symptoms over the control group [standardized mean difference (SMD) = −1.50, 95% confidence interval (CI): −2.16, −0.84; I^2 = 89%, $p < 0.00001$] in adolescents with FE-MDD. A sensitivity analysis and two subgroup analyses also confirmed the significant findings. Adolescents with FE-MDD treated with rTMS had significantly greater response [risk ratio (RR) = 1.35, 95% CI: 1.04, 1.76; I^2 = 56%, p = 0.03] and remission (RR = 1.35, 95% CI: 1.03, 1.77; I^2 = 0%, p = 0.03) over the control group. All-cause discontinuations were similar between the two groups (RR = 0.79, 95% CI: 0.32, 1.93; I^2 = 0%, p = 0.60). No significant differences were found regarding adverse events, including headache, loss of appetite, dizziness and nausea (p = 0.14–0.82). Four out of six RCTs (66.7%), showed that adjunctive rTMS was more efficacious over the control group in improving neurocognitive function (all $p < 0.05$).

Conclusion: Adjunctive rTMS appears to be a beneficial strategy in improving depressive symptoms and neurocognitive function in adolescents with FE-MDD. Higher quality RCTs with larger sample sizes and longer follow-up periods are warranted in the future.

KEYWORDS

repetitive transcranial magnetic stimulation, adolescent, depression, first episode, meta-analysis

1. Introduction

As a common mental disorder, major depressive disorder (MDD) affects approximately 5–15% of children and adolescents (1). Depression during adolescence is associated with a high risk of academic failure and behavioral problems (2), suicidal ideation and attempts (3), and adverse mental health consequences (i.e., anxiety disorder and substance use disorder) in the future (4–6). As a result, developments in treating adolescents suffering from MDD may have a positive influence on public health.

The usual treatment modalities for adolescents with MDD, mainly psychotherapy (e.g., cognitive behavioral therapy [CBT]), pharmacotherapy (e.g., selective serotonin reuptake inhibitors [SSRIs]) or both (7, 8), remain limited. Previous studies have found that at least 40% of adolescents with MDD showed unsatisfactory responses to those treatments (9, 10). For instance, psychotherapy may involve substantial time and financial costs, which lead to poor treatment compliance (11), while pharmacotherapy for adolescent patients may be associated with adverse events and even increased suicide risk (12). Therefore, there is an urgent need to explore more efficient and acceptable therapeutics for adolescents with MDD in clinical practice.

Repetitive transcranial magnetic stimulation (rTMS), as a noninvasive physical therapy, can modulate brain network functioning by producing a local magnetic field that acts on the local cerebral cortex and depression-related areas (13). rTMS has received the US Food and Drug Administration (FDA) approval to treat MDD among adults rather than adolescents (9). Accumulating randomized controlled trials (RCTs) have revealed the positive therapeutic effects of rTMS in adult patients suffering from treatment-refractory depression (TRD) (14, 15). Growing evidence has shown that rTMS can also improve drug efficacy in adult patients with first-episode major depressive disorder (FE-MDD) (16). For adolescents with MDD, several open-label studies (17, 18) have shown adjunctive rTMS to be a potentially effective treatment. However, the findings of RCTs (19–24) examining the therapeutic effects and safety of adjunctive rTMS in the treatment of adolescents with FE-MDD were inconsistent.

Therefore, the main aim of this meta-analysis was to investigate the therapeutic effects, tolerability and safety of adjunctive rTMS for adolescents with FE-MDD. We hypothesized that active rTMS plus antidepressants would be more efficacious than sham rTMS plus antidepressants or antidepressant monotherapy in improving depressive symptoms in FE-MDD patients among adolescents.

2. Methods

2.1. Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25), three authors (CHS, XHY and ZMS) independently retrieved RCTs examining the efficacy, tolerability and safety of adjunctive rTMS for adolescents with FE-MDD in international (Cochrane Library, PubMed, PsycINFO, and EMBASE) and Chinese (Wan Fang and Chinese Journal Net databases) databases from the establishment of the database to 9 November 2022. The detailed search strategy is presented in Appendix S1. Furthermore, the reference lists of meta-analyses and review articles (1, 9, 26) and the included RCTs (19–24) were searched manually and independently by the same three investigators to identify additional studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were conducted based on the following *PICOS* principle. *P*articipants: the study subjects must be adolescent patients (aged ≥12 years and ≤18 years) with a diagnosis of FE-MDD based on standardized diagnostic interviews. Following the methodology of a recent systematic review (27), adolescents were defined as those who were 12–18 years old. According to the recommendations of a previous meta-analysis (28), the sample was considered an FE-MDD group if the literature showed explicit characteristic descriptions (e.g., first-episode depression, first-episode depressive disorder, early depression) for the enrolled patients. *I*ntervention: active rTMS plus antidepressants. *C*omparison: antidepressants plus sham rTMS or antidepressant monotherapy. *O*utcomes: the primary outcome was the improvement of depressive symptoms at the post-rTMS time point measured with standardized instruments, such as the Hamilton Depression Rating Scale (HAMD) (29). The secondary outcomes were (1) study-defined response (i.e., at least 50% reduction in HAMD scores) and remission (i.e., at least 75% reduction in HAMD scores); (2) discontinuation due to any reason; (3) adverse events; and (4) neurocognitive function. ***S***tudy design: only published RCTs targeting the efficacy and safety of adjunctive active rTMS versus sham rTMS or antidepressant monotherapy for adolescents with FE-MDD were included. Thus, studies examining the efficacy and safety of active rTMS alone versus antidepressants (30) or sham rTMS alone (31) were excluded. Furthermore, studies involving of other inventions such as any kind of psychotherapy were excluded. Case reports/series, non-RCTs and reviews were excluded.

2.3. Data extraction

We established a standardized Microsoft Excel table to extract essential information from selected studies. This process was independently conducted by the same authors (XHY, CHS and ZMS). If there were some inconsistencies, they were resolved by discussion within the team or the involvement of a senior investigator WZ (from Guangzhou). If relevant data were missing in the included literature, the first and/or corresponding authors were contacted by email or telephone for accurate information. If the eligible RCT consisted of a mixture of FE-MDD and multiepisode MDD, only data from the FE-MDD group were extracted.

2.4. Quality assessment

Three authors (XHY, CHS, and ZMS) independently assessed the quality of each RCT using the Cochrane risk of bias (32) and the Jadad scale (33). A Jadad scale score < 3 was rated as 'low quality', and a Jadad

scale score ≥ 3 was rated as 'high quality'. The overall evidence level of meta-analyzable outcomes was evaluated by the grading of recommendations assessment, development, and evaluation (GRADE) system (34, 35).

2.5. Statistical analyses

We used Revman software (version 5.3) to compute primary and secondary outcomes through a random effects model (36). For dichotomous data and continuous data, the risk ratio (RR) and standardized mean difference (SMD) and their 95% confidence intervals (CIs) were calculated. Heterogeneity among different studies was determined using Cochrane's Q and I^2 test, with $Q < 0.1$ or $I^2 \geq 50\%$ suggesting significant heterogeneity (37). We conducted a subgroup analysis for the primary outcome: high-frequency (>1 Hz) rTMS (HF-rTMS) targeting the left dorsolateral prefrontal cortex (L-DLPFC) versus low-frequency (≤1 Hz) rTMS (LF-rTMS) targeting the right dorsolateral prefrontal cortex (R-DLPFC). For the primary outcome, a sensitivity analysis was performed to explore the source of heterogeneity by removing one study (23) with an outlying effect size of −2.53. Publication bias was assessed using funnel plots and Egger's regression interanalyses (38). In all analyses, $p < 0.05$ was defined as a significant difference (two-sided).

3. Result

3.1. Literature search

According to the search strategy, 621 studies were retrieved. After screening the title, abstract and full text, six RCTs (19–24) fulfilled the inclusion criteria and were analyzed in this meta-analysis (Figure 1).

3.2. Participant and study characteristics

As shown in Table 1, six RCTs were conducted in China covering 562 patients (281 patients in the rTMS group and 281 patients in the control group). The mean age was 15.0 years (range = 12–18 years). Male patients accounted for 36.5% (range = 18.6–51.3%) of the total sample. The use of antidepressants included sertraline (4 RCTs) (19, 21–23) and fluoxetine (1 RCT) (24). Participants underwent 1 Hz frequency rTMS (LF-rTMS) in 2 RCTs (20, 24) and 10 Hz frequency rTMS (HF-rTMS) in 4 RCTs (19, 21–23) (Table 1). The treatment duration of rTMS ranged from 2 to 6 weeks. The detailed treatment parameters of rTMS among the included RCTs are summarized in Table 1.

3.3. Quality assessment

As displayed in Supplementary Figure 1, four RCTs (4/6, 66.7%) were rated as 'low risk' regarding random sequence generation. Three RCTs (3/6, 50.0%) were rated 'low risk' regarding the blinding of participants and personnel the blinding of outcome assessment. Selective reporting was rated as 'low risk' in all of the included RCTs. The mean Jadad score was 3.7 (range = 2–5), and five out of the six RCTs (5/6, 83.3%) were classified as high-quality studies (Jadad score ≥ 3) (Table 1). Following the GRADE approach (Supplementary Table 2), the overall evidence quality was rated as 'low' (2/8, 25%), 'moderate' (5/8, 62.5%) and 'high' (1/8, 12.5%).

3.4. Primary outcomes

As shown in Figure 2, adjunctive active rTMS outperformed the control group in improving depressive symptoms (5 RCTs, $n = 464$, SMD = -1.50, 95% CI: −2.16, −0.84; $I^2 = 89\%$, $p < 0.00001$), as measured by the HAMD-24 (3 RCTs) (20, 21, 23) and HAMD-17 (2 RCTs) (19, 24). Similarly, significant findings remained in a sensitivity analysis after excluding one RCT with an outlying effect size (23) (4 RCTs, $n = 342$, SMD = −1.22, 95% CI: −1.70, −0.73; $I^2 = 75\%$, $p < 0.00001$). In addition, the superiority of adjunctive rTMS was retained when divided into two subgroups by frequency, which included HF-rTMS (3 RCTs, $n = 327$, SMD = −1.63, 95% CI: −2.67, −0.60; $I^2 = 94\%$, $p = 0.002$) and LF-rTMS (2 RCTs, $n = 137$, SMD = -1.22, 95% CI: −1.78, −0.65; $I^2 = 43\%$, $p < 0.0001$).

3.5. Secondary outcomes

3.5.1. Study-defined response and remission

Adjunctive rTMS was superior to the control group regarding response (4 RCTs, $n = 406$; RR: 1.35, 95% CI: 1.04, 1.76; $I^2 = 56\%$, $p = 0.03$) and remission (3 RCTs, $n = 306$; RR: 1.35, 95% CI: 1.03, 1.77; $I^2 = 0\%$, $p = 0.03$) (Table 2).

3.5.2. Discontinuation due to any reason

As shown in Table 2, discontinuation due to any reason was similar between the two groups (6 RCTs, $n = 562$, RR = 0.79, 95% CI: 0.32, 1.93; $I^2 = 0\%$, $p = 0.60$). The reasons for discontinuation of each included RCT were summarized in Supplementary Table 2.

3.5.3. Adverse events

Four studies (19, 20, 22, 24) reported adverse events. As displayed in Table 2, no significant differences were found regarding adverse events, including headache, loss of appetite, dizziness and nausea ($p = 0.14$–0.82).

3.5.4. Neurocognitive function

Five out of six RCTs (83.3%, 5/6) (19–21, 23, 24) examine the effect of adjunctive rTMS on neurocognitive function in adolescents with FE-MDD. Among them, 4 RCTs (80.0%, 4/5) (19–21, 23) found that active rTMS group outperformed the comparator in improving neurocognitive function as measured by different measurement tools (Table 3). However, one RCT (20.0%, 1/5) (24) found no significant differences between the two groups.

3.6. Publication bias

Given that the number of included RCTs was less than 10, publication bias could not be analyzed as recommended (39).

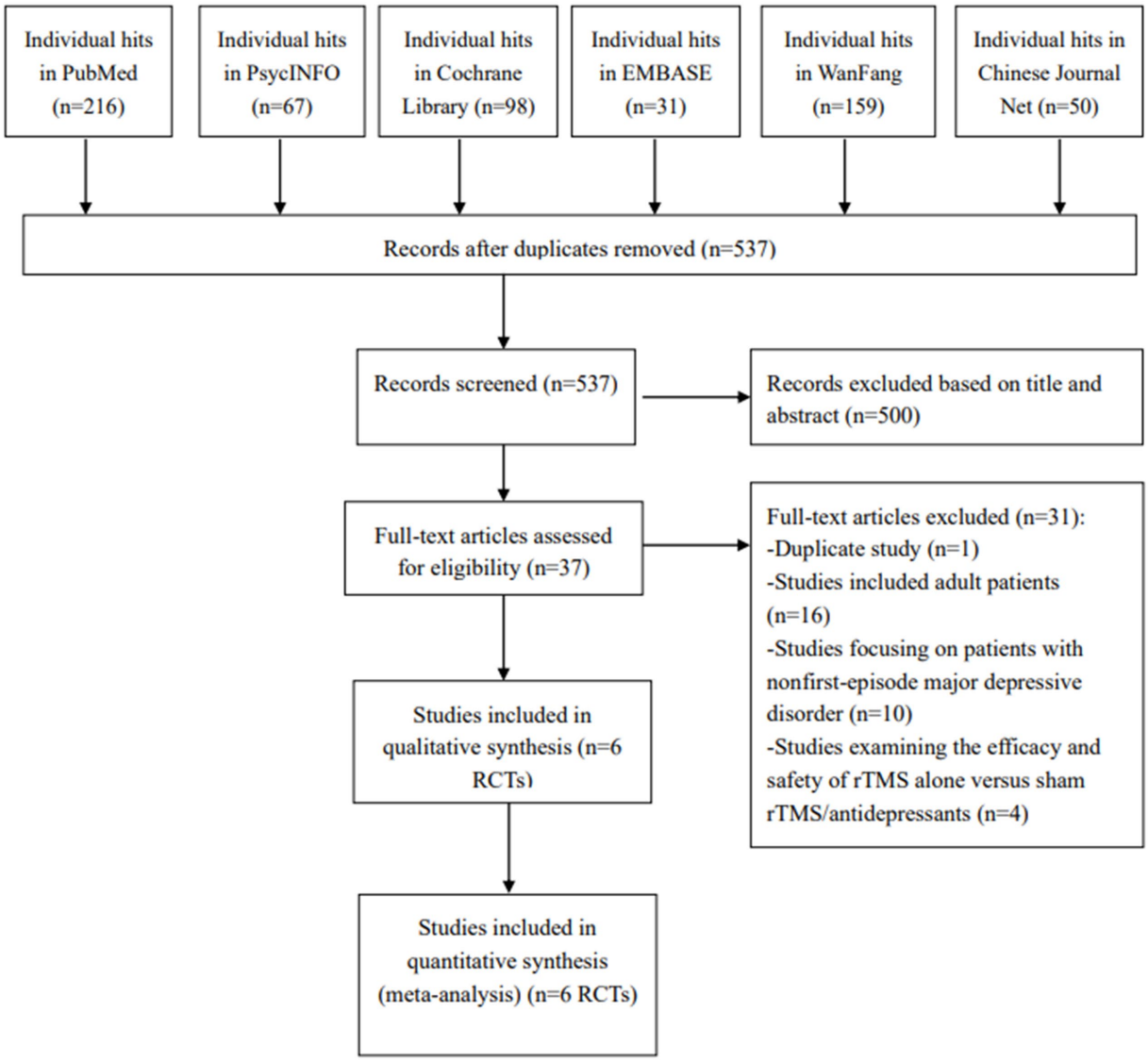

FIGURE 1
PRISMA flow diagram.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to examine the efficacy, tolerability and safety of rTMS as an adjunct treatment for adolescents (12–18 years) with FE-MDD. Six RCTs (19–24) involving 562 adolescents with FE-MDD were included in this meta-analysis. The main findings are as follows: (1) adjunctive rTMS was superior in improving depressive symptoms over the control group; (2) adolescents with FE-MDD treated with rTMS had a significantly greater response and remission over the control group, suggesting that rTMS may have beneficial effects for adolescents with FE-MDD; (3) rTMS appeared to be safe and tolerable as an adjunct treatment for adolescents with FE-MDD; and (4) adjunctive rTMS appears to be effective in improving neurocognitive function in adolescents with FE-MDD.

Although no meta-analysis has investigated the therapeutic effects, tolerability and safety of adjunctive rTMS for adolescents with FE-MDD, several systematic reviews (31, 40, 41) have preliminarily explored the efficacy of adjunctive rTMS for adolescents with MDD. For example, a systematic review (40) found that rTMS could reduce depressive symptoms in adolescents with MDD. However, this systematic review (40) included RCTs consisting of a mixture of FE-MDD and multiepisode MDD. Additionally, a systematic review (41) also suggested that rTMS is an effective and well-tolerated treatment for adolescents with TRD. Therefore, the findings of our study provided further support for the utility of rTMS treatment (either HF-rTMS or LF-rTMS) combined with antidepressants for adolescents with FE-MDD. Importantly, adjunctive rTMS appeared to be safe and tolerable for adolescents or adults with FE-MDD (16).

The underlying mechanism of the effect of rTMS on depressive symptoms may be that it can generate repeated pulses that act on the cerebral cortex and then transform neural functional activities in the brain circuits related to the pathophysiology of depression (42, 43). More specifically, HF-rTMS (> 5 Hz) has an excitatory effect on neural

TABLE 1 Participant characteristics and rTMS parameters of each included study.

Study (country)	Number of Participants[a]	-Diagnostic criteria -Setting	Mean age (years)[b] (range)	-Illness duration (months)[b] -Male (%)	Treatment duration of rTMS (weeks)[c]	Intervention versus control groups: (dosage of antidepressants); the number of patients (n)	-Intensity (%MT) -Frequency (Hz)	Site	-Number of trains per day -Train duration (s) -Intertrain duration (s)	-Pulses per session -Number of sessions -Total pulses	Jadad score
Chen et al., 2022 (China)	100	-DSM-IV -In- and outpatients	15.0 (12–18)	-16.6 -18.6	2	1. Sertraline (50–100 mg/day) + rTMS; $n = 50$ 2. Sertraline (50–100 mg/day); $n = 50$	-90 -10	L-DLPFC	-60 -4 -15	-2400 -10 -24000	4
Fu et al., 2022 (China)	104	-ICD-10 -Inpatients	15.5 (12–18)	-5.7 -27.9	4	1. SSRIs[d] + rTMS; $n = 52$ 2. SSRIs[d] + sham; $n = 52$	-100 -1	R-DLPFC	-40 -5 -20	-2000 -20 -40000	5
Lu et al., 2020 (China)	116	-ICD-10 -Inpatients	14.2 (12–18)	-5.3 -47.2	4	1. Sertraline (100–150 mg/day) + rTMS; $n = 58$ 2. Sertraline (100–150 mg/day) + sham; $n = 58$	-80 -10	L-DLPFC	-30 -2 -28	-NR -20 -NR	3
Ma et al., 2021 (China)	80	-ICD-10 -NR	16.1 (13–18)	-NR -51.3	6	1. Sertraline (50 mg/day) + rTMS; $n = 40$ 2. Sertraline (50 mg/day); $n = 40$	-80 -10	L-DLPFC	-NR -1 -20	-NR -30 -NR	3
Zhang et al., 2019 (China)	40	-DSM-IV -Inpatients	15.7 (13–17)	-10.8 -36.4	6	1. Fluoxetine (20 mg/day) + rTMS; $n = 20$ 2. Fluoxetine (20 mg/day) + sham; $n = 20$	-100 -1	R-DLPFC	NR	-1200 -30 -36000	5
Zhu et al., 2021 (China)	122	-CCMD-3 -Inpatients	14.5 (12–18)	-5.6 -37.7	4	1. Sertraline (100–150 mg/day) + rTMS; $n = 61$ 2. Sertraline (100–150 mg/day); $n = 61$	-80 -10	L-DLPFC	-30 -2 -28	-NR -20 -NR	2

[a]Data were extracted based on random assignment.

[b]Available data were extracted based on the mean baseline value of each included trial.

[c]The treatment duration was defined as the entire period from begin of the first rTMS treatment to the endpoint of the last rTMS treatment.

[d]Participants of active or sham groups were treated with selective serotonin reuptake inhibitors, but the authors did not specify which antidepressant they received.

CCMD-3, Chinese Classification and Diagnostic Criteria of Mental Disorders 3rd edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; L-DLPFC, left dorsolateral prefrontal cortex; MT, motor threshold; NR, not reported; R-DLPFC, right dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; s, second; SSRIs, selective serotonin reuptake inhibitors; yrs, years.

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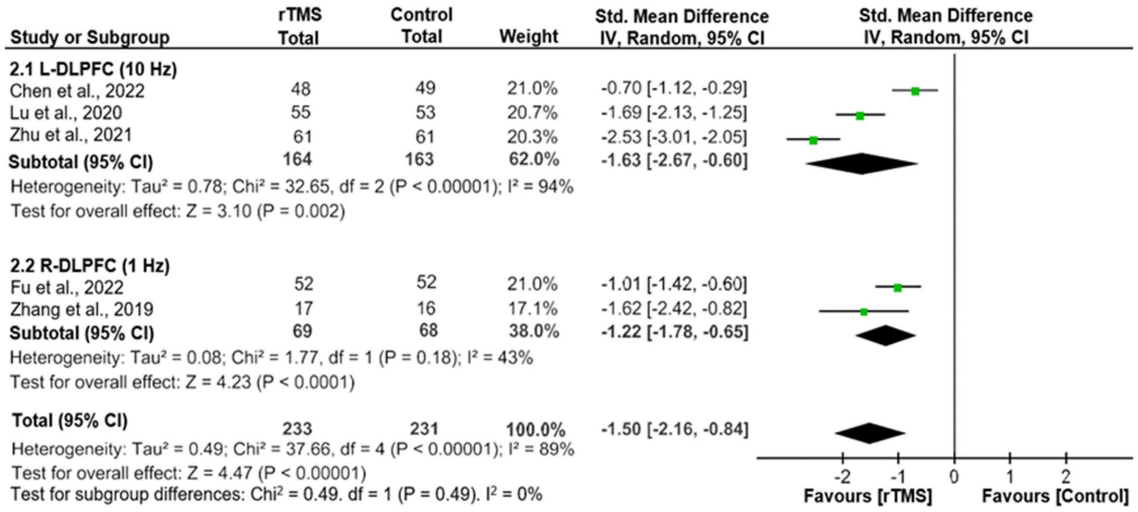

FIGURE 2
Adjunctive rTMS for adolescents with FE-MDD: forest plot for the improvement of depressive symptoms assessed by the HAMD. CI, confidence interval; FE-MDD, first-episode major depressive disorder; HAMD, Hamilton Depression Scale; L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, right dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

TABLE 2 Adjunctive rTMS for adolescents with FE-MDD: secondary outcomes.

Variables	Number of studies (sample size)	RRs/ SMDs	95% CI [Lower, Upper]	I^2 (%)	*P*
Study-defined response and remission					
Response	4 (406)	1.35	[1.04, 1.76]	56	**0.03**
Remission	3 (306)	1.35	[1.03, 1.77]	0	**0.03**
Discontinuation rate					
Discontinuation due to any reasons	6 (562)	0.79	[0.32, 1.93]	0	0.60
Adverse events					
Headache	4 (324)	3.07	[0.70, 13.37]	0	0.14
Loss of appetite	2 (180)	0.43	[0.07, 2.88]	0	0.39
Dizziness	2 (184)	1.30	[0.14, 12.29]	29	0.82
Nausea	2 (120)	0.26	[0.03, 2.24]	0	0.22

$P < 0.05$ is in bold. CI, confidence interval; FE-MDD, first-episode major depressive disorder; RRs, risk ratios; rTMS, repetitive transcranial magnetic stimulation; SMDs, standardized mean differences.

functional activities, and LF-rTMS (≤ 1 Hz) has the opposite effect on depression, which is characterized by reduced neural functional activity in the L-DLPFC and increased neural functional activity in the R-DLPFC (40). Previous research has found that HF-rTMS on L-DLPFC and LF-rTMS on R-DLPFC both have similar mechanisms that induce equivalent functional changes in the brain associated with antidepressant efficiency in MDD patients, including a decrease in brain limbic activity within the left perirhinal cortex (44). In addition, rTMS has a certain potential for modulating pathologic imbalances in GABAergic and glutamatergic neurocircuitry (45, 46), which play an important role in depression (47, 48).

Previous meta-analyses have found that rTMS appears to be effective in improving neurocognitive function in adults with FE-MDD (49, 50). For example, Martin et al. (49) found that rTMS courses administered to the prefrontal cortex for depression may produce modest neurocognitive enhancing effects specific to psychomotor speed, visual scanning, and set-shifting ability. A possible reason is that the improvement of neurocognitive function may be a secondary effect after emotional improvement (49). Although the findings of the neurocognitive effects of adjunctive rTMS for adolescents with FE-MDD are mixed in the included five RCTs (19–21, 23, 24), four out of five RCTs (80.0%) found the significant superiority of adjunctive rTMS over the comparator in improving neurocognitive function after rTMS (19–21, 23). Only one RCT (24) included in this meta-analysis found no deterioration or significant improvement in neurocognitive function with a small sample size ($n = 40$). Taken together, adjunctive rTMS appears to be effective in improving neurocognitive function in adolescents with FE-MDD, although further studies focusing on adjunctive rTMS on neurocognitive function in adolescents with FE-MDD are warranted.

There are several limitations of this present study. First, the sample size of the meta-analysis was relatively small ($n = 562$), which might reduce the statistical power. Second, all of the included RCTs had relatively short observation periods (2–6 weeks) and lacked long-term follow-up. Third, all included studies were conducted in China and involved only Chinese adolescents. Thus, the findings of the present study are not generalizable to other countries or populations. Fourth, the confounding effects of antidepressant medications could not be detected due to insufficient information in the included studies. Fifth, the significant heterogeneity for primary outcome ($I^2 = 89\%$)

TABLE 3 Adjunctive rTMS for adolescents with FE-MDD: neurocognitive function.

Study	Neurocognitive function	Findings
Chen et al., 2022	IVA-CPT THINC-it	Compared with sham stimulation, rTMS can significantly improve neurocognitive function including the attention quotient (listening, visual and full-scale) of IVA-CPT as well as the Spotter of THINC-it in adolescents with FE-MDD (all $p < 0.05$).
Fu et al., 2022	MoCA TMT-A	Compared with sham stimulation, rTMS can significantly improve neurocognitive function as measured by the MoCA and TMT-A in adolescents with FE-MDD (all $p < 0.05$).
Lu et al., 2020	WCST TMT	Compared with sham stimulation, rTMS can significantly improve neurocognitive function as measured by the WCST and TMT in adolescents with FE-MDD (all $p < 0.05$).
Ma et al., 2021	NR	NR
Zhang et al., 2019	CPT SCWT MCCB	No differences were found regarding the CPT, SCWT and MCCB tests between active rTMS and sham stimulation group in adolescents with FE-MDD (all $p > 0.05$).
Zhu et al., 2021	MoCA CMS[a]	Compared with the control group, adjunctive rTMS appeared to be effective in improving neurocognitive functions measured with MoCA and CMS in adolescents with FE-MDD ($p < 0.05$).

[a]An assessment scale for memory function adapted for the Chinese population compiled and revised by the Institute of psychology, Chinese Academy of Sciences.
CMS, Clinical Memory Scale; CPT, continuous performance test; IVA-CPT, Integrated Visual and Auditory Continuous Performance Test; MCCB, MATRICS Consensus Cognitive Battery; MoCA, Montreal Cognitive Assessment; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SCWT, Stroop Word-Color Interference Test; TMT, Trail Making Test; TMT-A, Trail Making Test-A; WSCT, Wisconsin Card Sorting Test.

remained, even in a sensitivity analysis ($I^2 = 75\%$), which may partly attribute to the significant heterogeneity of the rTMS protocols used in the included RCTs.

5. Conclusion

Adjunctive rTMS appears to be a beneficial strategy in improving depressive symptoms and neurocognitive function in adolescents with FE-MDD. Higher quality RCTs with larger sample sizes and longer follow-ups are warranted in the future.

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.

Author contributions

C-HS, Z-MS, J-XM, and X-HY selected studies and extracted the data. WZ from (Guangzhou) reviewed all the data and helped to mediate disagreements. C-HS wrote the first draft. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1200738/full#supplementary-material

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Appendix S1. Methods

("Transcranial Magnetic Stimulation"[MeSH] OR Transcranial Magnetic Stimulation OR rtms OR tms) AND ("depression"[MeSH] OR depression OR depressive OR depressed OR melancholia) AND (child OR childhood OR children OR adolescent OR adolescents OR puberty OR pubertal OR juvenile OR teen* OR youth OR preschool OR preschool child OR school age OR high school OR student OR pediatric* OR paediatric* OR minors OR boys OR boy OR girl*) AND (first episode OR early phase OR early-phase OR FEP OR recent onset OR untreated OR unmedicated OR non medicated OR undiagnosed OR first diagnosed OR first diagnosis OR drug-free OR antidepressant-free OR medication-free OR drug-naïve OR antidepressant-naïve OR medication-naïve OR treatment-naïve OR never-medicated) AND (random OR random* OR control OR RCT).

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Analysis of self-healing of depression by helping others in adolescents from the perspective of constructivism

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Purpose: This study aims to explore the mechanism of psychological qualities constructed in helping others with depression and guide adolescents to actively participate in the practical activities of helping others to prevent and self-heal depression.

Method: Symptom self-rating scale, trait coping style questionnaire, and self-administered helper scale were employed. A total of 1,086 valid on-site questionnaires were collected from adolescents.

Result: The depression levels of adolescents were negatively correlated with helping beliefs, behaviors and total scores (r = −0.500, −0.401, and −0.530). Helping others had a significantly negative predictive effect on depression, effectively inhibiting depression levels. Although the positive coping style had an inhibitory effect on depression, it exerted no predictive effects on depression under the influence of helping others. In contrast, the negative coping style had a significantly positive predictive effect on depression.

Conclusion: Proactively participating in helping others is an important way to prevent and eliminate depression in adolescents. They should be instructed to give full play to their initiatives to participate in social practice and assist others actively, thus constructing positive psychological qualities, improving mental health, and achieving self-healing of depression and self-help through helping others.

KEYWORDS

constructivism, adolescents, depression, helping others, self-healing

1. Introduction

Constructivism emphasizes that knowledge is not passively received but actively constructed (1), and it can only be actively constructed by individuals and internalized into their knowledge system or life experience instead of being transferred from the mind of teachers to that of students (2). Similarly, the mental health of a person is constructed by their practice, comprising creative and harmonious thinking abilities when solving practical problems in life, and is the healthy self-created through personal participation, interactions, and behavioral feedback (3, 4). However, the positive impact of practical activities on the mental health of adolescents is not valued, especially for the treatment of serious mental health problems such as anxiety and depression. People often only focus on the effect of medication (5–7) and neglect the role of

psychological counseling and self-construction. Psychiatric patients are increasingly vulnerable when hospitalized and living in the community and engaging in interpersonal interactions are helpful for emotional regulation (8). Psychotropic drugs are reportedly damaging to the hearts of patients (9, 10), and medical medication increases the risk of sudden cardiac death in psychiatric patients (11). Medication alone cannot eradicate depression (12, 13) and performs poorly (14). There is no panacea for depression, and the fundamental way to eliminate depression requires the self-reconstruction of a positive psychological system (15). Helping others is important for individuals to construct a positive psychological system through interactions with people. Psychological counseling emphasizes "helping people and helping themselves" (16), which means that the dedicator achieves self-help by helping the recipient to learn to solve problems (17–19). In other words, in offering help to others, the inner emotional experience of the helpers is enriched, their aspirations are satisfied, and joy and happiness are gained; additionally, the helpers sublimate their spiritual realm, enrich their minds, and improve the way to deal with setbacks and difficulties and the ability to solve problems (20, 21). This idea is consistent with that advocated by constructivism to realize the development of individual knowledge systems, mental health and ability through self-construction (22, 23). Kant also proposed that human knowledge and psychological qualities were constructed by combining intellectual categories and perceptual experience. Without subject construction, the formation of knowledge and psychological qualities was not possible [(24), p. 7]. Such proposals as discovery learning by Bruner [(25), p. 5], generative cognition theory by Piaget [(26), p. 17], and cooperative learning and educational practice by Vygorsky [(27), pp. 82–83] reflect that human knowledge and psychological qualities are constructed through practice. Only by actively participating in activities with social significance can individual behavioral patterns and knowledge systems be constructed [(28), p. 355], and helping others fully meets this requirement. In helping others, people construct their positive mentality and reduce depressive mood through experience [y3–(29), y4–(30)], and thus promote the self-healing of depression. Studies noted that mutual help effectively addressed mental health and addiction problems (31). Considering that helping others is an altruistic behavior, people with high altruistic behaviors are mentally healthier than those with low altruistic behaviors (32). Put differently, helping others willingly is a manifestation of mental health and is recognized as an important way to cultivate a healthy personality. People with a high propensity to help others show high life satisfaction and few problem behaviors. People who are willing to provide help can quickly shorten their distance from others, establish harmonious interpersonal relationships (33), be easily accepted by others, and perceive interpersonal relationships with an increasingly positive mindset (34); the mindset, in turn, has an impact on the different coping styles individuals choose (35, 36). Moreover, another factor also draws attention to adolescents' psychological development. Studies showed that cell phone use can influence their social and emotional development (37, 38). Excessive use of social media platforms and video games can lead to feelings of anxiety, depression, and loneliness (39–41). Cyberbullying can have severe psychological consequences. The use of cell phones before bedtime can lead to sleep deprivation, which results in a negative impact on adolescents' mental health, cognitive functioning, and overall well-being (42–44). Cell phone addiction may make them experience withdrawal symptoms, anxiety, and irritability when they are separated from their phones (45, 46). In a nutshell, cell phone use among adolescents can reduce their face-to-face communication, which makes them struggle with interpersonal interactions, empathy and effective communication techniques. In addition, several studies found that crucial factors such as gender, study pressure, and family background can affect adolescents' depression levels. This study hypothesized that the levels of depression are negatively correlated with the helpfulness and positive coping styles; helping others and positive coping styles can effectively reduce or negatively predict depression levels.

2. Research method

2.1. Research tools

The coping style questionnaire, developed by Qianjin Jiang, contains 20 items of positive coping (PC) and negative coping (NC) dimensions. The scale ranges from 1 to 5 (1 not; 2 generally not; 3 not sure; 4 generally yes; 5 definitely yes). PC > 40 indicates that the individual adopts a positive coping style, and NC > 35 implies a negative coping style. The retest reliability of the two dimensions was 0.75 and 0.65, respectively; the correlation coefficients of PC and NC between the subjects and the family test were 0.75 and 0.73, respectively (47). The study showed a Cronbach's alpha coefficient of 0.78 for the coping style questionnaire total scale.

The symptom self-rating scale, designed by Derogatis and Savitz (48), includes 90 items, and only depressive symptoms were analyzed in this study. The questionnaire was a five-point scale (1 = never, 2 = mild, 3 = moderate, 4 = quite severe, and 5 = severe). Any factor score reaching 2 indicated a positive item (48).

The help scale was devised using a self-administered 5-point Likert scale (1 = very unsuitable, 2 = not very suitable, 3 = uncertain, 4 = quite suitable, 5 = very suitable). In accordance with the requirements and procedures of the scale, 12 items were designed to predict 425 adolescents, and 9 items were retained after analysis. Two dimensions were determined and named "helping beliefs" and "helping behaviors." The former comprised perceptions and attitudes toward helping others, and the latter constituted behavioral activities that benefit or help others. After the scale was performed, 1,086 adolescents were surveyed. It was revealed that the eigenvalues of the two dimensions were 4.193 and 1.524, respectively, and the contribution rates were 46.592 and 16.934%, respectively, with a cumulative contribution rate of 63.526%. The higher scale score represents a higher propensity to help people; those with a median score of 27 or less have a low propensity to help others, and those with a score of 36 or more show a high propensity to help people. The Kaiser-Meyer-Olkim test and Bartlett's sphericity test was conducted on the 9-item scale to examine the appropriateness of the factor analysis of "helping people." The results showed that the Kaiser-Meyer-Olkim coefficient was 0.858 > 0.5, indicating relatively large common factors among the variables; the chi-square value of Bartlett's sphericity test was 4169.115, with a degree of freedom of 36 and a significance of 0.000 < 0.05 (at a significance level), indicating that common factors exist among the items and the sample is suitable for factor analysis. The reliability and validity were verified to be relatively good. The final internal consistency coefficient (Cronbach's alpha coefficient) was 0.852, and the coefficients of the two dimensions were

TABLE 1 Detailed analysis of factors on the help scale.

Dimension name	Question number and item	Factor 1	Factor 2	Common degree
Helping beliefs	T1, I believe in giving roses and leaving fragrance in my hands	0.838		0.734
	T2, I think people need to help each other	0.834		0.712
	T9, I believe helping others is one of the most attractive qualities in a person T4, I believe that to help others is to broaden the road for yourself	0.832 0.716		0.747 0.561
	T3, I always trust others	0.669		0.480
Helping behaviors	T6, I often participate in volunteer services or peer support activities		0.873	0.775
	T7, It's always a pleasure to help others		0.772	0.619
	T5, I often help my classmates to do what I can		0.749	0.602
	T8, I always donate some pocket money to events that require donations		0.629	0.487
	Eigenvalue	4.193	1.524	
	Contribution rate (%)	46.592	16.934	
	Cumulative contribution rate (%)	46.592	63.526	

0.860 and 0.786, respectively. The specific factor analysis is shown in Table 1.

2.2. Research object

According to the survey design, from September 1 to 30, 2021, subjects were selected in several middle schools and universities in Hefei, Anhui Province, and the survey was implemented in the classroom with the assistance of mental health education teachers. A total of 1,086 valid questionnaires were collected, including 531 middle school students (270 junior middle school students and 261 high school students) and 555 college students (258 sophomores and 297 juniors). There were 480 male students (44.2%), 606 and female students (55.8%). Among them, 387 students (35.6%) came from urban areas and 699 (64.4%) from rural areas. Regarding the mobile phone use duration, four types were divided: within 1 h, 1–2 h, 2–3 h, and more than 3 h. The number of people using mobile phones within 1 h and more than 3 h is relatively small, mainly concentrated between 1 and 3 h in a normal distribution, and thus the median value was taken. The mobile phone use time was categorized into two parts: within 2 h and more than 2 h. A total of 411 students used mobile phones within 2 h, accounting for 37.4%, and 675 utilized their phones for more than 2 h, contributing to 62.2% (Table 2).

3. Results

3.1. Differences in depression levels, helping others, and coping styles

Analysis of variance showed significant differences between genders in helping beliefs and positive coping styles. Female students had significantly higher helping beliefs and more positive coping styles than male students, and no differences were found in other aspects. Concerning grades, helping beliefs did not differ, while depression levels, helping behaviors, and coping styles differed significantly. Specifically, college students were more inclined to choose positive coping styles than middle school students, and they exhibited higher helping behaviors and tendencies and significantly lower depression levels than those of middle school students. The details are depicted in Table 3.

Concerning the duration of mobile phone use, participants who used mobile phones for more than 2 h showed high levels of depression and were inclined to choose negative coping styles. In contrast, those utilizing mobile phones for less than 2 h displayed lower levels of depression, more helping beliefs and behaviors, and higher tendencies to help others and choose positive coping styles. Excerpt for helping beliefs and positive coping styles among students of different sources, significant differences were observed in depression levels, helping behaviors, tendencies to help people and negative coping styles, indicating that urban students have higher levels of depression and more tendencies to negative coping styles than rural students, and significantly lower helping behaviors and tendencies than rural students.

3.2. Correlation of depression levels, helping others, and coping styles

As shown in Table 4, depression levels were significantly and negatively correlated with helping beliefs, behaviors and tendencies and positive coping styles ($r = 0.500$, -0.401, -0.530, and -0.347, respectively), and significantly and positively correlated with negative coping styles ($r = 0.494$). The positive coping style was significantly and positively correlated with helping beliefs and behaviors, and the total helping score ($r = 0.386$–0.582), and the negative coping style was significantly and negatively correlated with the three helping indicators ($r = -0.349$ to -0.421). An increase in helping tendencies was consistent with a rise in positive coping styles and the opposite direction of an increase in depression levels. In contrast, the increasing negative coping styles conformed with the high depression levels and oriented oppositely with the upgrading helping tendencies. It is reflected that helping tendencies and positive coping styles can reduce depression levels and promote mental health.

3.3. Regression of helping others and coping styles on depression levels in adolescents

The stepwise regression analysis with depression level as the dependent variable and helping beliefs and behaviors, and positive and negative coping styles as the independent variables showed an R2 of 0.376 and an adjusted R2 of 0.374, reflecting a high explanation degree of the predictive effect of independent variables on the dependent variable, and the regression equation is as follows:

$$Y = a + b1^{*}X1 + b2^{*}X2 + b3^{*}X3 + b4^{*}X4 + e$$

As shown in Table 5, helping beliefs and behaviors had a significant negative predictive effect on depression levels, positive coping styles had a non-significant predictive effect on depression levels, and negative coping styles had a positive predictive effect on depression levels. Regression models are developed as follows:

$$\text{Depression level} = 1.975 - 0.048^{*}\text{Helping beliefs} + 0.03^{*}\text{Negative coping styles} - 0.025^{*}\text{Helping behaviors}$$

It can be seen from the regression model that helping behaviors and beliefs had a negative predictive effect on depression levels, significantly inhibiting the increase in depression. Specifically, each increase of one variable in helping beliefs decreased depression levels by a 0.048 variable, and each additional variable in helping behaviors reduced depression levels by a 0.025 variable. Furthermore, helping beliefs had a more significant inhibitory effect on depression than helping behaviors. In contrast, the negative coping style had a positive predictive effect on depression levels, with each increase elevating depression levels by a 0.03 variable.

TABLE 2 Sample composition distribution.

Classification	Standard	Number (*N*)	Percentage (%)
Gender	Male	480	44.2
	Female	606	55.8
Grade	Middle school	531	48.9
	University	555	51.1
Student source	Rural area	699	64.4
	Urban area	387	35.6
Mobile phone usage time	Within 2 h	411	37.8
	More than 2 h	675	62.2

3.4. The regulation of the effect of coping styles on depression by helping tendencies

In the influence of coping styles on depression levels, helping tendencies exhibited a certain moderating effect. As shown in Table 6, the effect of negative coping styles on depression levels was moderated by helping tendencies, the moderating effect was −0.002, and R2 was 0.03. Figure 1 showed that under negative coping styles, the higher tendencies to help others suggested the faster depression reduction. In other words, in the case of negative coping styles, increasing the tendency to help others is conducive to improving mental health,

TABLE 3 Differences in depression levels, helping others and coping styles among adolescents ($M \pm SD$).

	Gender		*t*	*p*	Grade		*t*	*p*
	Male *N* = 480	Female *N* = 606			Middle school *N* = 531	University *N* = 555		
A	1.528 ± 0.595	1.546 ± 0.518	−0.524	0.600	1.587 ± 0.601	1.491 ± 0.499	2.821	0.005
B	19.319 ± 3.709	19.762 ± 3.513	−2.017	0.044	19.446 ± 3.812	19.681 ± 3.393	−1.070	0.284
C	14.394 ± 3.138	14.446 ± 3.114	−0.271	0.786	13.853 ± 3.407	14.968 ± 2.720	−5.942	0.000
D	33.713 ± 5.883	34.208 ± 5.655	−1.408	0.159	33.299 ± 6.249	34.649 ± 5.169	−3.868	0.000
E	34.069 ± 4.980	34.936 ± 5.462	−2.700	0.007	34.175 ± 5.545	34.914 ± 4.971	−2.307	0.021
F	28.431 ± 6.380	28.767 ± 5.795	−0.908	0.370	29.655 ± 5.987	27.627 ± 5.968	5.590	0.000

	Mobile phone use duration		*t*	*p*	Student source		*t*	*p*
	Within 2 h *N* = 411	More than 2 h *N* = 675			Urban area *N* = 387	Rural area *N* = 699		
A	1.427 ± 0.587	1.606 ± 0.520	−5.220	0.000	1.614 ± 0.608	1.497 ± 0.516	3.204	0.001
B	19.971 ± 3.556	19.320 ± 3.614	2.896	0.004	19.504 ± 3.757	19.601 ± 3.519	−0.424	0.671
C	15.299 ± 3.097	13.889 ± 3.019	7.393	0.000	13.597 ± 3.395	14.880 ± 2.864	−6.296	0.000
D	35.270 ± 5.842	33.209 ± 5.570	5.805	0.000	33.101 ± 6.261	34.481 ± 5.405	−3.648	0.000
E	35.015 ± 5.138	34.271 ± 5.332	2.259	0.024	34.279 ± 5.357	34.704 ± 5.219	−1.273	0.203
F	26.854 ± 6.202	29.693 ± 5.715	−7.535	0.000	29.364 ± 6.309	28.206 ± 5.881	3.028	0.003

A, depression; B, helping beliefs; C, helping behaviors; D, helping total score; E, positive coping; F, negative coping; same below.

TABLE 4 Correlation coefficients of depression levels, helping indicators and coping styles among adolescents.

	A. Depression levels	B. Helping beliefs	C. Helping behaviors	D. Helping scores	E. Positive coping styles	F. Negative coping styles
A	1.000	1.000	1.000	1.000	1.000	
B	−0.500**	0.463**	0.832**	0.573**	−0.321**	
C	−0.401**	0.877**	0.386**			
D	−0.530**	0.582**				
E	−0.347**					
F	0.494**	−0.370**	−0.349**	−0.421**		1.000

**Indicates significant correlation at 0.01 level (both sides).

TABLE 5 Regression analysis with depression level as the dependent variable.

Dependent variable	Independent variables	*B*	*β*	*t*	*p*	VIF	*F*	p	R^2
Depression levels	Constant	1.975		14.917	0.000		216.862	0.000	0.376
	Helping beliefs	−0.048	−0.312	−11.160	0.000	1.358			
	Negative coping styles	0.030	0.330	12.451	0.000	1.215			
	Helping behaviors	−0.025	−0.141	−5.069	0.000	1.335			

realizing the elimination and self-healing of depressive disorder. The influence of positive coping styles on depression levels was moderated by helping tendencies, the moderating effect was 0.003, and R2 was 0.046. Figure 2 demonstrated that in the positive coping state, low helping tendencies led to a rapid decline in depression levels, and high helping tendencies slowly increased depression levels.

4. Analysis and discussion

According to the results, the levels of depression in adolescents were not influenced by gender. Previous studies have shown that women suffered from mental illness more than men (8), yet gender differences may not appear in depression levels during adolescence. This may be related to the growth and educational experiences of the adolescents. The learning tasks and family and social responsibilities undertaken by adolescents are no longer differentiated by gender, and the environment and requirements for their growth are highly consistent. In this sense, gender differences may simply be misunderstood (49).

In terms of educational levels, middle school students had higher levels of depression and were more prone to negative coping styles than college students, and college students were more likely to choose positive coping styles than middle school students. College students had a higher propensity to help others with significantly more helping behaviors than middle school students. Grade differences were not detected in helping beliefs between the two groups, indicating that middle school students also have high helping ideas and beliefs. Due to the limited learning environment and external conditions, they cannot fully participate in practice, resulting in restricted helping behaviors. In contrast, college students have more time and energy to devote to helping behaviors, participate in more social practices, are more capable of dealing with psychological confusion and stress, and have lower levels of depression. Research has pointed out that participating in practical activities, interpersonal communication, and collective or interactive tasks can improve the positive mentality and reduce the "Buddha-like mentality" (50). College students have more freedom than middle school students in their studies since their academic burdens and pressure are relatively small. These factors may affect the difference in helping behaviors and depression levels among adolescents in different grades.

Teenagers who spent more time using mobile phones had higher levels of depression, more negative coping styles, fewer helping behaviors, and smaller tendencies to positive coping styles. This is consistent with the studies that the longer mobile phone use time of adolescents indicated higher anxiety levels, lower verbal adequacy, and more serious verbal exhaustion (51). In other words, adolescents devoting more time to the virtual world inevitably reduce the behavior of helping others and interpersonal interactions, thus lacking the opportunities to gain pleasure in practice and having difficulties alleviating depression (52). Although cell phones bring convenience to people, they also inhibit adolescents from social participation and development and self-construction of psychological qualities, reflecting the importance of helping others and active participation in social practices for constructing positive psychological qualities and self-healing psychological problems.

The depression levels of urban adolescents were significantly higher than those of rural adolescents, the helping behaviors and tendencies were significantly lower in urban adolescents than those in rural adolescents, and urban adolescents were more inclined to choose negative coping styles. It is reflected that the freer environment of rural areas is more suitable for the healthy growth of adolescents, allowing for more face-to-face contact, practical exercises, and opportunities to be involved in helping others and interpersonal interactions, thus constructing positive ideas through their own experiences. Positive psychological qualities promote individuals to easily internalize knowledge or information into their cognitive system (53), thereby changing their own cognitive and behavioral results (54), and effectively promoting the prevention and self-healing of depression.

TABLE 6 The regulation of depressive mood by helping others.

Dependent	Independent	β	t	R^2	ΔR^2	F
Depression levels	Negative coping styles	0.030	12.845	0.401	0.030	54.614**
	Helping others	−0.035	−14.117			
	Help*negative	−0.002	−7.390			
	Positive coping styles	−0.008	−2.467	0.330	0.046	74.879**
	Helping others	−0.042	−14.186			
	Help* positive	0.003	8.653			

**Indicates significant correlation at 0.01 level (both sides).

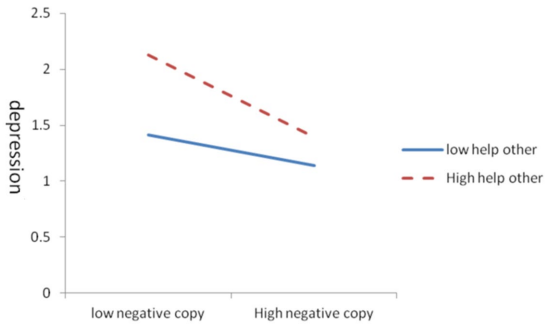

FIGURE 1
Moderation of the effect of negative coping styles on depression by helping others.

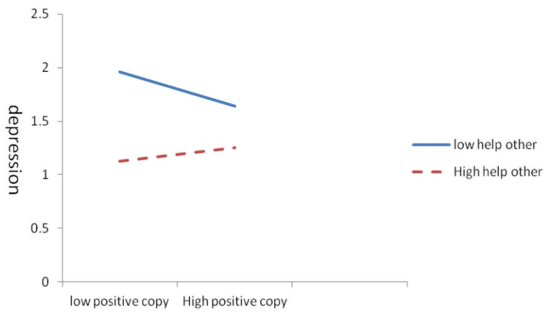

FIGURE 2
Moderation of the effect of positive coping styles on depression by helping others.

The depression levels, helping tendencies, and positive coping styles of adolescents were mutually inhibited, while depression and negative coping styles were mutually promoted. The tendency to help others can promote the development of positive psychological qualities and active coping manners towards adversity, thus establishing a buffer between events and physical and mental reactions when encountering negative stimuli (55). Additionally, the goal of reducing depression can be achieved as a result of improved mental health and coping manners with life by helping others. The result agrees with previous studies which pointed out that helping others could arouse the biological mechanism of the social perception of individuals and promote them to actively deal with events in life (56). Participating in practical activities with a positive attitude was argued to promote the formation and development of positive psychological qualities and change the subconscious cognition and positive psychological experience of participants (57, 58). A positive attitude also contributed to the therapeutic effect of major diseases (59). In this sense, guiding young people to proactively participate in voluntary services and helping activities can promote them to devote themselves to practical activities and interpersonal interactions, thus enhancing their abilities to learn cooperation and mutual assistance, construct positive psychological qualities, and face various challenges and difficulties with a positive attitude and coping style.

Helping people and depression had two-way predictive effects, helping beliefs and behaviors had significantly negative predictive effects on depression, and negative coping styles had a positive predictive effect on depression. Although the changes in helping others exerted a small negative predictive effect on depression, this prediction was still significant, and depression was effectively suppressed by helping others. The negative coping style can increase depression levels, and its enhancement effect on depression was much greater than the inhibitory effect of the positive coping style on depression. Individuals in a depressive state are inclined to choose an avoidant coping style (60). In contrast, adolescents interested in helping others are more likely to adopt positive coping styles, and the positive psychological qualities they develop in the process play a decisive role in their mental health. Helping others promotes the self-construction of positive psychological qualities in adolescents (61). In addition, it manifests individual integration and harmony with the collective (62) and is regarded as an important way of constructing interpersonal alliances and cooperation (63), and self-construction of healthy psychological qualities from the perspectives of interpersonal relationships and social adaptation. The construction of these positive psychological qualities has significance for the self-healing of depression.

Helping tendencies had a moderating impact on the effect of coping styles on depression; whether using positive or negative coping styles, the depression levels can be reduced to some extent with helping tendencies. In the case of a negative coping state, high helping tendencies were helpful to reduce depression, indicating that actively helping others or public welfare social activities is beneficial to improve mental health. Whereas for adolescents with a positive coping state, a low helping tendency contributed to reduced depression, and a high helping tendency slowly increased levels of depression. Helping others is a manifestation of peer support, which improves mental health (64), in people with mental illness, thereby inhibiting and eliminating depression or achieving self-healing of depression. Notably, being excessively involved in actively helping activities is not recommended to avoid overwhelming burdens.

5. Conclusion

In the prevention and treatment of depression, medication alone may not necessarily be enough for depression. The positive psychological qualities through helping others and practical activities are key to self-healing of depression. Helping people can be beneficial in alleviating depression. People can construct the ability for social engagement, mental resilience, and sound interpersonal skills in the process, effectively reducing the occurrence of depression. Consultation and social work emphasize "helping others is self-help." For one thing, as the old Chinese saying goes "teaching people to fish is a lifetime benefit"; for another, the giver achieves self-help by helping others. In offering help to others, young people enrich their inner emotional experience, sublimate their spiritual realm, and construct positive psychological qualities, thus forming immunity against depression, which is consistent with the proverb "the only way to help oneself is to help others." In the devoting process, adolescents acquire the ability to cope with difficulties and frustrations, positive self-efficacy, lasting inner happiness, the skills to serve others and deal with their interests and cooperate with others, and the virtues and self-healing of depression. According to the constructivist view on knowledge acquisition and healthy psychological formation, instructing teenagers to proactively participate in helping others, doing something useful for their classmates, and serving society to their best will help develop their abilities to help others and inspire their positive psychological qualities of integrating into the group and undertaking social responsibility, and suppress the negative effects of depression and realize self-healing of depression in the process.

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 Chaohu University Teacher Education College, Academic Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YJ and HY: study design. ZX: collection, analyses, interpretation of data, and draft of the manuscript. SL: critical revision of the manuscript. 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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Hard-to-treat or hard-to-catch? Clinical features and therapeutic outcomes of help-seeking foster care youths with mood disorders

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Introduction: The high level of emotional problems in youths placed in foster care contrasts with the limited use of evidence-based treatments. This study aims to better characterize the clinical features and therapeutic outcomes of foster care youths with mood disorders.

Methods: A secondary analysis of data collected in the context of a French-Canadian clinical research network on pediatric mood disorders in four sites was conducted to compare three groups of patients with depressive or bipolar disorder: those without exposure to child welfare intervention (WCWI, *n*=181), those who received non-placement psychosocial intervention (NPI, *n*=62), and those in placement interventions (PI, *n*=41).

Results: We observed a very high rate of academic problems in patients in the groups NPI/PI compared to those in the WCWI group. Patients in the PI group had more disruptive behavioral disorders (OR=6.87, 95% CI [3.25–14.52]), trauma-related disorders (OR=3.78, 95% CI [1.6–8.94]), and any neurodevelopmental disorders (OR=2.73, 95% CI [1.36–5.49]) compared to the other groups (NPI/WCWI). Among inpatients, the Clinical Global Impression-Improvement scale and the change in the Children Global Assessment Scale during the hospital stay did not differ across the three groups. We observed a higher prescription rate of antipsychotics in the PI group compared to the NPI/WCWI groups, but no significant difference for antidepressants and mood stabilizers.

Discussion: These findings support the view that, when provided with dedicated support, fostered inpatient youths can improve in a range comparable to other inpatients. Undetected neurodevelopmental disorders and academic problems are likely important contributors of the burden of mood disorders in these youths.

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KEYWORDS

depressive disorder, early-onset bipolar disorder, disruptive mood dysregulation disorder, child adversity, complex psychotrauma, developmental psychotrauma, adverse chilhood experiences

1. Introduction

1.1. Mental health difficulties in foster care

Young people in the foster care system are identified as a high-risk group for emotional and behavioral problems as well as psychiatric disorders (1, 2). These youths are especially prone to trauma and stressors-related disorders, disruptive behavioral disorders, substance abuse, and suicidal behaviors (1, 2). The global mental health burden of youths in foster care stems from multiple factors including exposure to repeated adverse childhood experiences (ACEs) (including the ones which led to the placement decision), abrupt life transitions, and associated environmental and neurodevelopmental factors (3–6).

The evaluation of the effectiveness of mental health interventions in youths in foster care received surprisingly little scrutiny considering the number of patients concerned. Several reports note that youths in foster care are over-represented in pediatric mental health services, with almost 25–53% of them having already been in contact with mental health professionals (7–9). Yet, the mental health care provided to these patients is usually regarded as suboptimal by health professionals with a high use of emergency services and a low access to evidence-based interventions targeting emotional and trauma-related symptoms (5, 6, 10) and learning disability if any (4).

1.2. Clinical presentations of mood disorder in youths in foster care

Foster care patients with mood disorders are expected to present more severe forms of mood disturbances compared to those without exposure to child welfare intervention, considering the very high rate of major ACEs reported in this population (6). The exposure to major ACEs (i.e., physical, sexual, emotional abuse and/or physical, emotional neglect) is correlated with more severe depressive symptoms, more severe suicidal behaviors, more frequent psychotic symptoms, earlier age of onset, and more recurrent and chronic course of the disorder with a decreased rate of remission (11–14). Comparable trends have also been observed in adults with bipolar disorder (BD) where a history of major ACEs is associated with more frequent suicidal behaviors and more frequent psychotic and mixed features (15).

The clinical challenges of assessing mood symptoms in pediatric patients may be particularly exacerbated in patients in foster care (16, 17). Among the most common pitfalls, youths with trauma-related symptoms may exhibit manic-like symptoms (e.g., emotional lability, behavioral disinhibition) or ADHD-like symptoms (e.g., increased distractibility, hyperkinetic) in response to acute stressors (18–20). A large overlap exists between symptoms of post-traumatic and depressive disorders, such as self-injurious behaviors in response to trauma-related stimuli, social withdrawal, and impaired sleep (19). Finally, even in the absence of post-traumatic symptoms, a history of life trauma may influence a youth's ability to trust and share concerns and emotional experiences with mental health professionals (21).

The identification of mood symptoms in foster care youths is also important as it may influence placement prognosis. Longitudinal studies have shown that the level of a youth's mood symptoms at admission into the welfare system often predicts the onset of behavioral problems in foster care (22–24). This is an issue of particular significance for careers considering the interplay between foster care youth's emotional and behavioral problems and placement instability (22–24). Anderson (22) noted that the likelihood of suicidal ideation increased by 68% each time a child experienced a change in placement situation. Effective interventions on mood symptoms in this population are therefore opportunities to break this vicious circle (23, 24).

1.3. Therapeutic outcomes of mood disorder in youths in foster care

While childhood maltreatment has been found to be associated with a lower probability of response to antidepressant pharmacotherapy and psychotherapy in depressed (14) and bipolar adults (25), these findings have not been replicated in pediatric samples. Secondary analyses of data from clinical trials of antidepressants have shown that a history of sexual violence did not significantly influence the response rate of provided medications in children and adolescents (26–29). ACEs status did not influence the average response to mood stabilizers during the acute treatment of manic or mixed episodes in 81 adolescents in the study conducted by Benarous et al. (30).

Discrepancy also exists regarding how ACEs status could influence the functional improvement during the hospital stay of inpatient adolescents with mood disorders. In a chart-review with over 10 years of follow-up, Serim Demirgoren, Ozbek, and Gencer (31) noted that high familial risk scores at admissions are associated with lower functional improvement during the stay of 308 Turkish children and adolescents. However, the exposure to ACEs or child welfare interventions did not influence the average change in CGAS, the average Clinical Global Impression-Improvement scale, or the average length of stay in 106 adolescents hospitalized for severe or treatment-refractory mood disorders (32). Some authors have even suggested that youths exposed to ACEs or child welfare interventions could benefit more in terms of their general functioning during inpatient treatment compared to other patients as they are removed from potential ongoing stressors (31, 33).

While these findings could be mitigated when considering the impact of ACEs on the therapeutic outcomes of psychotherapies (34), they suggest that mood disorders should not be left untreated even in patients who are usually regarded as "complex." In this vein, the American Academy of Pediatrics recommends that the general guideline for the use of antidepressant should apply to youths indistinctly of the context of exposition to childhood maltreatment (5).

1.4. Aims

This research is a secondary analysis of data initially collected in three observational cross-sectional studies conducted within a French-Canadian clinical research network on pediatric mood disorder and suicidal behavior. These researches aimed to test a series of hypotheses on the clinical features and therapeutic outcomes of different subtypes of pediatric mood disorders, in particular the category of Disruptive Mood Dysregulation Disorder (DMDD). Here, we aim to compare the clinical features and therapeutic outcomes of patients with mood disorders in three groups of patients: those without exposure to child welfare intervention (WCWI), those in non-placement psychosocial intervention (NPI), and those in out-of-home placement interventions (PI). The comparison between youths in the NPI and in the PI groups would help to better distinguish the effect of risk factors related to placement (involving family separation) from the effect of co-occurring environmental risk factors (i.e., demographic, perinatal, and psychosocial) (3, 6). It is indeed worth remembering that the possible separations from the youth's close relationships (e.g., siblings, grand-parents, friends, teachers) in out-of-home placements could result in the loss of protective factors for mood disorders (35).

Regarding clinical outcomes, we tested whether patients with mood disorders in foster care present on average a higher severity of mood symptoms and a poorer level of functioning compared to those WCWI, in line with the literature about ACEs (11, 12, 14) and foster care patients (16, 17). We also hypothesized that patients in the NPI group would have an "intermediate" severity profile compared to the two other groups, and that a higher rate of school problems would be observed in youths in PI compared to those in NPI and WCWI, in line with previous findings (36, 37). Patients with mood disorders in the PI group were expected to present higher comorbidity rates of psychiatric and neurodevelopmental disorders compared to patients from the two other groups. This would be consistent with previous reports stressing the importance of perinatal factors in this population and the high rate of neurodevelopmental disorders generally reported in PI youths (1).

Regarding therapeutic outcomes, we expect that the treatment provided for pediatric mood disorders would differ between inpatients in the PI, NPI, and WCWI groups in line with the previous studies conducted in youths with ACEs mentioned above (4, 5, 10). A higher rate of antipsychotic treatment is to be expected in the PI group as well as a lower access to specific treatment (i.e., antidepressants, and mood stabilizers) (5). No *a priori* hypotheses were made regarding the clinical and functional effectiveness of the treatment provided for inpatient adolescents with mood disorders considering the discrepant reports in the literature mentioned above (30–32).

2. Methods

2.1. Settings and study design

This research consists of a secondary analysis of data collected in three observational cross-sectional studies conduct in the framework of a university French-Canadian clinical research network on pediatric mood disorders and suicidal behaviors. The research network was developed in view of studying in view of studying the specific clinical features and predictors of treatment response of youths with pediatric mood disorders and/or severe suicidality to guide policy decisions and preventive strategies. The context for the hospitalization and the main intervention provided were previously detailed in published papers (32, 38–40).

- Site 1: inpatients referred to two adolescent inpatient units (for 12- to 15 years-old and for 15- to 18 years-old patients, with 30 beds) at the Pitié-Salpêtrière Hospital, Paris, France, between January 2017 and December 2018.
- Site 2: inpatients referred to pediatrician-psychiatric crisis-center inpatient unit with 12 beds at the Amiens University Hospital, France, between February 2020 and April 2021.
- Site 3: outpatients referred to psychiatric outpatient unit specialized in pediatric mood disorders at the Rivière des Prairies Hospital, Montréal, Canada, between November 2006 and December 2010
- Site 4: outpatients referred to psychiatric outpatient unit specialized in pediatric mood disorders at the Douglas Mental Health University Institute, Montréal, Canada, between November 2006 and December 2010.

Prior authorization and approval from independent ethics committee were previously received from each competent local authority in line with national legislation as presented in previous studies, i.e., for site 1, for site 2, for sites 3–4. No new data was collected for the current research.

2.2. Participants

For this study, we extracted information from patients with a discharge psychiatric diagnosis of mood disorders. The psychiatric diagnoses had been defined according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) categories (American Psychiatric Association 2013); that is, a major depressive disorder (MDD), a persistent depressive disorder (PDD), a DMDD, and BD. No exclusion criteria were used. The flow chart presents the selection of participants (Figure 1). Taking into account the debate about the wide spectrum of pediatric bipolar disorder (41), only type-I bipolar disorder was included in the BD category.

In France and in Canada placement in foster care is decided when that child is no longer able to live safely at home. A court grants legal guardianship for the child to the state, and Child Protective Services (*Aide Social à l'Enfance* in France, *Direction de la protection de la jeunesse* in Canada) is subsequently granted temporary legal possession to place the child in foster care. The decision can made in an emergency or after a period when non-placement psychosocial interventions had been provided to the family.

For all participants, child welfare interventions were systematically sought during a clinical interview with the child, parent, health professionals and, if needed a social worker in line with previous studies in youths with mood disorders (4, 42, 43). We distinguished between PI and NPI. PI encompassed out-of-home psychosocial interventions, such as short-term shelter, foster home, rural living facility, and foster family. NPI also included in-home psychosocial intervention usually required by judiciary and legal services to investigate suspicion of maltreatment. Patients referred to the hospital by administrative or legal authorities for immediate protection or when parental consent was not received were classified as PI. The classification was based on current or lifetime prior involvement in the child welfare system. For example, a 12 years old child who lived in a

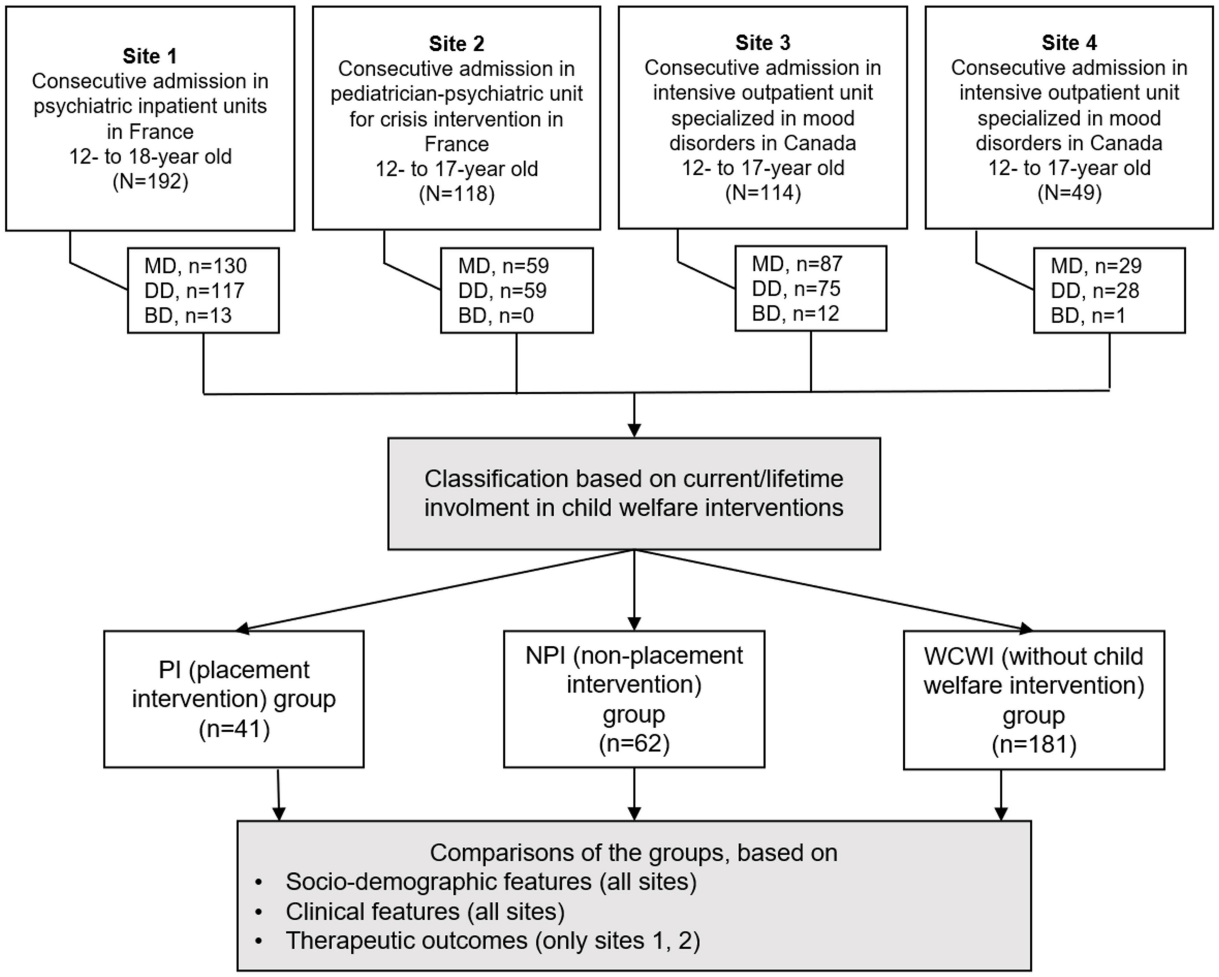

FIGURE 1
Flow chart of the study. MD, mood disorders; DD, depressive disorders; BD, bipolar disorders.

short-term shelter during 6 months had at 8 years old been included in the PI group. Participants in the WCWI group represented patients who had never been involved in psychosocial interventions (placement or non-placement) in child welfare system.

Participants were classified as having experienced "maltreatment" if they were ever exposed to at least one form of major ACEs, i.e., physical abuse, sexual abuse, emotional abuse and/or severe physical or emotional neglect. The category was rated by the clinicians involved in the patient's care based on all information available. The external validity of this measure compared to information based on social services evaluations was empirically supported in a previous study (30, 44). Information about the type of maltreatment was only available for sexual abuse. No other information was available concerning the age at onset, frequency, the duration or the setting of experienced major ACEs, in particular the involvement of other family members and the contribution to the placement decision.

2.3. Assessments

The data collected encompassed sociodemographic characteristics; school performance; psychosocial factors; developmental history and associated medical conditions; clinical characteristics, including the discharge psychiatric diagnoses; symptom severity, level of functioning, and treatment response.

2.3.1. Clinical features and associated disorders

The discharge psychiatric diagnoses were selected among a list of the most frequently used categories. The Schedule for Affective Disorders and Schizophrenia for School-Age Children PL (K-SADS-PL) (45) was included in the clinical assessment at the sites 3 and 4, but only in case of uncertainty in the sites 1 and 2. In these cases, the psychiatric diagnoses retained were the ones made by treating clinicians based on all information available. As this instrument refers to the DSM-IV-TR classification the following changes have been made. All participants meeting criteria for dysthymia have been identified as PDD. Concerning the DMDD diagnosis, symptoms reported in the patient's medical file were compared with the DSM-5 criteria for DMDD. The psychometric properties of this retrospective assessment was estimated to be very good (Cronbach's α for internal validity: 0.90; κ for test–retest reliability: 0.87) (41).

The severity of clinical symptoms was measured with the Clinical Global Impression-Severity (CGI-S) scale (46), and the level of functioning was assessed using the Children-Global Assessment Scale

(CGAS) (47). The CGI-S and the CGAS were only available in sites 1 and 2 as it was not used in routine practice at Canadian sites. The CGAS was systematically measured the first and the last week of stay by a senior psychiatrist (respectively, "CGAS admission" and "CGAS discharge").

2.3.2. Therapeutic outcomes in inpatients (site 1 and 2)

Classes of psychopharmacological treatments prescribed at discharge were classified into five categories (i.e., anxiolytics, hypnotics, antidepressants, mood stabilizers, antipsychotics). Therapeutic outcomes were assessed using two proxy measures available for sites 1 and 2. Clinical improvement during the hospitalization was measured with the Clinical Global Impression-Improvement (CGI-I) scale (46), completed by a senior psychiatrist during the last week of the hospitalization. In this study, the CGI-I assessed the patient's overall symptom improvement during the hospitalization compared with his/her baseline state at admission, irrespective of the treatments provided (e.g., medication, structured psychotherapy, group interventions). We used the difference between the CGAS score at discharge and at admission, also labeled Δ-CGAS to track change in the level of functioning during the hospitalization. Unfortunately, information was not available for the Canadian sites.

2.4. Statistical analysis

Continuous variables (e.g., age) were described using mean and standard deviation; categorial variables (e.g., gender) using the number and percentage of occurrences. Three groups were compared: those in the WCWI group; those in the NPI group, those in the PI group. Analysis of variance (ANOVA) was used to compare means across the three groups. *Post hoc* Scheffe's tests were used for the comparisons between groups when ANOVA yielded a significant *F*-statistic. Chi-squared test was used to compare proportions across the three groups. The Kruskal–Wallis and the Fisher's exact tests were used as alternatives for non-normally distributed variables. No mathematical correction was made for multiple comparisons. The listwise deletion was used for missing values. Data were analyzed using R.

3. Results

3.1. Socio-demographic features and school functioning

There was no statistical difference in the three groups concerning mean age and gender (Table 1). Subjects in the PI and the NPI groups reported a higher rate of maltreatment compared to patients in the WCWI group (respectively, OR = 13.40, 95% CI [5.99–29.96] and OR = 6.40, 95% CI [3.41–12.01]). The likelihood of being exposed to sexual abuse was most important in the PI group, followed by those in the NPI, followed by the WCWI (PI vs. WCWI, OR = 14.77, 95% CI [6.10–35.79]).

Compared to patients in the WCWI group, adolescents with mood disorders in the PI group had on average higher rates of grade repetitions (OR = 3.24, 95% CI [1.50–7.01]), of special educational needs (OR = 3.21, 95% CI [1.60–6.44]), of school dropouts (OR = 4.94, 95% CI [2.41–10.12]) and referral to special educational facilities (OR = 7.25, 95% CI [2.17–24.19]). Differences between patients' characteristics in the PI and the NPI groups were only significant for school dropouts.

3.2. Aim 1: clinical features

The proportion of each subtype of depressive disorders differed across the three groups (Table 2). In the PI group, DMDD was the most frequent depressive subtype, followed by PDD and then MDD. In contrast, in the WCWI group, MDD was the most frequent depressive

TABLE 1 Sociodemographic features of youths with mood disorders in placement intervention vs. non-placement intervention vs. without child welfare intervention.

	Subjects without child welfare intervention ($n = 181$)	Subjects with child welfare intervention		*p* value
		Non-placement intervention ($n = 62$)	Placement intervention ($n = 41$)	
Demographic features				
Gender, female	76 (42%)	31(50%)	19 (43%)	0.528
Age (*y*) (mean ± SD)	14.61 ± 2.16	14.18 ± 2.41	14.22 ± 1.56	0.271
SES, good and middle, *n* (%)	164 (91%)^{a}	40 (65%)^{b}	18 (44%)^{c}	<0.001**
Psychosocial factors				
Maltreatment, all types, *n* (%)	34 (19%)^{a}	37 (60%)^{b}	31 (76%)^{b}	<0.001**
Sexual abuse, *n* (%)	10 (6%)^{a}	13 (21%)^{b}	19 (46%)^{c}	<0.001**
School performance				
Grade repetition, *n* (%)	25 (14%)^{a}	12 (20%)^{ab}	14 (36%)^{b}	0.006
Special educational needs, *n* (%)	48 (28%)^{a}	21 (36%)^{ab}	22 (58%)^{b}	<0.001**
School dropout (>3 months), *n* (%)	47 (26%)^{a}	23 (37%)^{a}	26 (65%)^{b}	<0.001**
Special educational facilities, *n* (%)	5 (3%)^{a}	10 (17%)^{b}	7 (17%)^{b}	<0.001**

*indicates $p < 0.05$ and **indicates $p < 0.01$. $^{a-c}$Means in a row without a common superscript letter differ ($p < 0.05$) in post hoc analyses. SES, socio-economic status.

TABLE 2 Clinical features of mood disorders among youths in placement intervention vs. non-placement intervention vs. without child welfare intervention.

	Subjects without child welfare intervention ($n = 181$)	Subjects with child welfare intervention		p value
		Non-placement intervention ($n = 62$)	Placement intervention ($n = 41$)	
Types of mood disorders, n (%)				
MDD	81 (45%)[a]	20 (32%)[a]	5 (12%)[b]	<0.001**
PDD	67 (37%)	24 (39%)	19 (46%)	0.542
DMDD	40 (22%)[a]	23 (37%)[b]	24 (59%)[c]	<0.001**
BD-I	12 (7%)	7 (11%)	5 (12%)	0.282
Clinical characteristics, n (%)				
SI	132 (73%)	45 (73%)	27 (66%)	0.654
SA	57 (32%)	23 (37%)	16 (39%)	0.540
NNSI	78 (43%)	22 (36%)	20 (49%)	0.375
Psychotic symptoms	21 (12%)	14 (23%)	8 (20%)	0.084
Chronic irritability	69 (38%)[a]	42 (68%)[b]	28 (68%)[b]	<0.001**
Repeated runaway	10 (9%)[a]	9 (24%)[b]	18 (51%)[c]	<0.001**
Substance misuse	13 (19%)[a]	5 (16%)[a]	13 (43%)[b]	0.015*
Clinical severity and functioning in inpatient adolescents (site 1 and 2)				
CGAS at admission (mean ± SD)	41.29 ± 11.3	39.21 ± 13.56	38.03 ± 13.96	0.378
CGI-S at admission (mean ± SD)	4.94 ± 0.96	4.95 ± 1.01	5.23 ± 0.97	0.295

*indicates $p < 0.05$ and **indicates $p < 0.01$. [a–c]Means in a row without a common superscript letter differ ($p < 0.05$). MDD, major depressive disorder; PDD, persistent depressive disorder; DMDD, disruptive mood dysregulation disorder; BD, bipolar disorder; SI, suicidal ideation; SA, suicidal attempt; NNSI, non-suicidal self-injury; CGAS, children-global assessment scale; CGI-S, clinical global impressions-severity.

subtype, followed by PDD and then DMDD. Youths in NPI had an intermediate profile. Youths in PI and in NPI groups were more likely to have chronic irritability compared to youths in the WCWI (respectively OR = 3.25, 95% CI [1.63–5.46]; OR = 3.41, 95% CI [1.85–6.28]). Youths in PI were more likely to have repeated runaway and substance misuse compared to the two other groups (vs. WCWI group, respectively, OR = 13.38, 95% CI [5.51–32.49]; vs. NPI OR = 6.00, 95% CI [2.52–14.27]). The likelihood of suicidal ideation, suicidal attempt, non-suicidal self-injury, and psychotic symptoms did not significantly differ across groups. The mean CGAS score and CGI-S score at admission were not statistically significant across groups in inpatient adolescents (sites 1 and 2).

The number of psychiatric diagnoses at discharge was more frequent in patients in the PI group (M = 2.44, SE = 1.05) and in the NPI group (M = 2.32, SE = 1.08) compared to those in the WCWI group (M = 1.88, SE = 1.00), $p = 0.001$; while the difference between the PI and the NPI did not reach statistical significance ($p = 0.572$) (Table 3). Compared to youths in the WCWI group, those in the PI group were more likely to have associated disruptive behavioral disorders (OR = 6.87, 95% CI [3.25–14.52]) and trauma-related disorders (OR = 3.78, 95% CI [1.6–8.94]) but were less likely to have anxiety disorders (OR = 0.44, 95% CI [0.18–1.05]). The comorbidity rate did not significantly differ between youths in the PI and NPI groups.

The number of neurodevelopmental disorders at discharge was more frequent in patients in the PI group (M = 1.03, SE = 1.21) and in the NPI group (M = 1.03, SE = 1.21) compared to those in the WCWI group (M = 0.41, SE = 0.71), $p = 0.001$; while the difference between the PI and the NPI did not reach statistical significance ($p = 0.904$). Compared to youths in the WCWI group, those in the PI were more likely to receive a diagnosis of associated neurodevelopmental disorder (53% vs. 31%, OR = 2.73, 95% CI [1.36–5.49], $p = 0.023$), without difference with the NPI group (51%). Youths in the PI were more likely to have a diagnosis of intellectual developmental disorder (OR = 10.23, 95% CI [1.80–58.03]), communication disorder (OR = 6.99, 95% CI [2.43–20.12]) or developmental coordination disorder (OR = 2.99, 95% CI [1.33–6.70]) compared to youths in the WCWI group. Greater delays in motor and language acquisitions existed in young people in PI compared to those in the WCWI group.

On average, patients in the PI group were the most likely to have prior hospitalization (any and repeated), an admission via the emergency room, and constraints during the stay (Table 4). The rate of prior contact with a psychologist, psychiatrist, and speech interventions did not differ across the three groups. Occupational therapy was more frequently observed in patients in the NPI group compared to the other two groups.

3.3. Aim 2: therapeutic outcomes in inpatients (sites 1 and 2)

Among adolescent inpatients (sites 1 and 2), the number of medications in patients in the PI group (M = 2.10, SE = 1.57) was overall not statistically different ($p = 0.96$) from patients in the NPI group (M = 1.59, SE = 1.12) or those in the WCWI group (M = 1.40,

TABLE 3 Associated psychiatric, developmental, and medical conditions in youths with mood disorders in placement intervention vs. non-placement intervention vs. without child welfare intervention.

	Subjects without child welfare intervention ($n = 181$)	Subjects with child welfare intervention		p value
		Non-placement intervention ($n = 62$)	Placement intervention ($n = 41$)	
Associated psychiatric disorders, *n* (%)				
Anxiety disorders	58 (32%)[a]	11 (18%)[ab]	7 (17%)[b]	0.027*
Trauma- & stressor-related disorders	16 (9%)[a]	9 (15%)[ab]	11 (27%)[b]	0.007*
Disruptive behavioral disorders	24 (13%)[a]	27 (45%)[b]	21 (51%)[b]	<0.001**
Psychotic disorders	3 (2%)	1 (2%)	1 (2%)	0.820
Eating disorders	14 (8%)	3 (5%)	1 (2%)	0.491
Associated neurodevelopmental disorders, *n* (%)				
Attention deficit disorder	23 (13%)[a]	18 (29%)[b]	6 (15%)[ab]	0.011*
Autism spectrum disorder	5 (4%)	1 (3%)	1 (3%)	0.999
Intellectual development disorder	2 (2%)[a]	5 (13%)[b]	4 (11%)[b]	0.006*
Communication disorder	7 (6%)[a]	9 (24%)[b]	9 (28%)[b]	<0.001**
Developmental coordination disorder	22 (20%)[a]	13 (35%)[b]	12 (39%)[b]	0.045*
Specific learning disabilities	10 (9%)[a]	10 (26%)[b]	6 (19%)[ab]	0.024*
Other developmental difficulties				
Pregnancy complications/fetal distress, *n* (%)	10 (9%)[a]	6 (17%)[ab]	10 (36%)[b]	0.003*
Speech acquisition delay, *n* (%)	14 (13%)[a]	13 (34%)[b]	13 (39%)[b]	0.001*
Motor acquisition delay, *n* (%)	21 (19%)[a]	15 (40%)[b]	15 (47%)[b]	0.003**
Medical conditions				
Chronic medical condition, *n* (%)	58 (32%)[a]	26 (42%)[ab]	22 (54%)[b]	0.027*
Overweight, *n* (%)	17 (15%)	12 (32%)	8 (23%)	0.073

*indicates $p < 0.05$ and **indicates $p < 0.01$. [a–c]Means in a row without a common superscript letter differ ($p < 0.05$) in post hoc analyses.

TABLE 4 Mental health service use of youths with mood disorders in placement intervention vs. non-placement intervention vs. without child welfare intervention.

	Subjects without child welfare intervention ($n = 181$)	Subjects with child welfare intervention		p value
		Non-placement intervention ($n = 62$)	Placement intervention ($n = 41$)	
Mental health service use, *n* (%)				
Prior hospitalization	59 (33%)[a]	25 (40%)[a]	32 (78%)[b]	<0.001**
Prior multiple hospitalizations	26 (14%)[a]	14 (23%)[a]	22 (54%)[b]	<0.001**
Admission via ER	59 (33%)[a]	20 (32%)[a]	27 (66%)[b]	<0.001**
Constraint measures during the stay	8 (7%)[a]	7 (18%)[b]	18 (51%)[c]	<0.001**
Speech therapy	19 (17%)	11 (29%)	9 (26%)	0.211
Occupational therapy	18 (16%)[a]	12 (32%)[b]	4 (11%)[a]	0.049*

*indicates $p < 0.05$ and **indicates $p < 0.01$. [a–c]Means in a row without a common superscript letter differ ($p < 0.05$).

SE = 1.35). Youths in the PI were more likely to receive an antipsychotic medication compared to youths in the WCWI groups (59% vs. 31%, OR = 3.15, 95% CI [1.57–6.32], $p = 0.009$), without significant difference with the NPI group (49%, $p = 0.188$). The rate of antidepressant treatment did not statistically differ between patients in the PI, NPI and WCWI groups (respectively, 31, 28 34%, $p = 0.799$) nor did the rate of mood stabilizers (respectively, 13, 13 12%, $p = 0.999$).

As shown in Figure 2, no significant difference was observed across the three groups concerning the CGI-I score at discharge and the Δ-CGAS score among inpatient adolescents (site 1 and 2). Based on the CGI-I score 56% of patients in the PI were found to be well or very well improved during the stay, vs. 46% among subjects in the NPI group and vs. 56% in the WCWI group ($p = 0.578$).

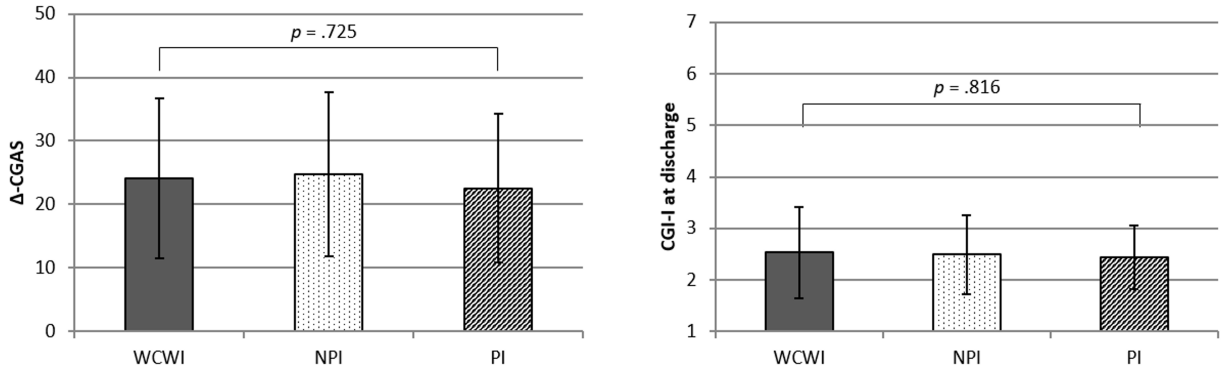

FIGURE 2
Comparisons between the average levels of patients' clinical and functioning improvement between the groups.

4. Discussion

4.1. Summary of the main results

This study aimed to describe the clinical features and the therapeutic outcomes of foster care youths with mood disorders compared to their counterparts without child welfare intervention. This research was motivated by the lack of information to guide care decisions for foster care youths, despite their frequent use of pediatric mental health care facilities in particular emergency services in most developed countries (7–9).

4.1.1. Clinical features

On average, patients in the PI group more frequently had chronic forms of depressive disorders, such as DMDD, and reported chronic irritability. These results are consistent with prior studies stressing a relation between ACEs and chronic irritability (48). The translational model of irritability developed by Brotman et al. (49) highlights the influence of parental roles in the development of the child's emotional regulation skills. In a context of foster care, dysfunctional early parent–child interactions, such as chaotic and unpredictable parental reactions to a child's emotional expression, could minimize the process of developing emotion regulation. Children raised by caregivers with poor parenting skills may have more difficulties to generalize adaptive coping behaviors based on with limited opportunity for trial-and-error instrumental learning and ill-adapted reinforcers. This is the first study that empirically confirms the high rate of DMDD in foster care youths who are often exposed to ACEs. Foster care youths with mood disorders also more frequently presented associated behavioral problems such as running away and substance abuse. These associations are likely due to an underlying impulsive trait (50); however, such hypotheses were not formally tested in this study. The rate of suicidal behavior and psychotic symptoms in foster care youths were not significantly different from the other groups of patients, contradicting previous findings reported in youths exposed to cumulative forms of ACEs (11, 13).

The current study confirms the high frequency of neurodevelopmental disorders in foster care youths with mood disorders compared to other patients. If previous studies put some emphasis on the high rate of ADHD in this population (1, 2), our findings found associations with intellectual development disorder, developmental coordination disorders, and communication disorders as reported earlier in the few studies that have searched for it (4). In our study, youths in the PI group were on average 2.6 times more at-risk of having a diagnosis of any neurodevelopmental disorder compared to those without child welfare intervention. These findings were consistent when comparing across the three groups the rate of perinatal risk factors, the delays in milestone psychomotor acquisition, and the difficulties in academic settings in the current research. A lack of awareness of neurodevelopmental disorders in foster care patients with mood disorders may represent a missed opportunity to provide remediation interventions, and finally to reach clinical remission and better school inclusion.

The mean level of functional impairment (based on CGAS score at admission) of inpatient youths with mood disorders living in foster care did not significantly differ from those in the NPI group and those in the WCWI group. This finding contradicts results from community-based and clinical samples (12, 14). It is possible that Berkson's bias explains that participants in the control groups (i.e., NPI, WCWI groups) who were recruited via university clinical research programs were principally composed of patients with severe and impairing forms of mood disorders.

4.1.2. Therapeutics

The higher rates of emergency care and hospitalization observed in foster care youths with mood disorders compared to other patients are consistent with the literature. As the patients' clinical severity (based on the CGI-S) were comparable across the three groups, the overuse of emergency services is likely to be linked to other risk factors, such as an impulsive trait or low level of adhesion to care (6, 51). An assumption which is indirectly supported by our data considering the higher rate of care under constraints reported in patients in the PI group compared to the two other groups (Table 4).

Access to occupational therapy was lower among patients in the PI group compared to those in the NPI group, while the rate of a developmental coordination disorder was comparable between these two groups. Giannitelli et al. (4) showed that inpatients in foster care had on average lower access to speech therapy compared to other inpatients. The co-occurrence of more frequent neurodevelopmental disorders and less access to rehabilitation care is particularly

concerning with regard to the academic difficulties faced by these patients reported here and in previous studies (36, 37).

No significant difference was found across the groups with regard to the use of antidepressants and mood stabilizers. In line with prior studies, (5, 6) the rate of antipsychotics prescription was higher in the PI group compared to the other groups. The low sample size prevents us to provide additional subgroup analyses to determine the influence of clinical indications on treatments choice. The lower proportions of "typical" forms of depression, i.e., MDD, reported in the PI group could in theory be associated with lower rates of antidepressant prescription, as no clear guidelines support the use of antidepressants in youths with PDD and DMDD, and no medication received an authorization by the national competent authorities in American or European countries for these indications (52).

Our study did not find any significant difference in the level of treatment response between the three groups, both at the clinical (i.e., CGI-I) and the functional level (i.e., change in CGAS score during the stay). These results should be interpreted with caution because these variables were collected only in settings 1 and 2, i.e., in patients referred for full-time hospitalization. It would be interesting to confirm these results in patients referred to intensive outpatient care. Although preliminary, these results support the hypothesis that the poorer response to treatment observed in foster care youths mainly involve environmental factors influencing the likelihood to access and/or to adhere to quality care treatment.

4.2. Strengths and limitations

These results must be considered in light of some methodological flaws that may limit their interpretation. The specific characteristics of inclusion sites should be considered when discussing the generalizability of these results. The outpatient and inpatient facilities involved mostly patients with severe treatment-refractory illness. For example, in site 1 a substantial proportion of youths could have been addressed from another hospital in a context of treatment-refractory psychiatric disorders, as the department became a specialized center for catatonic syndrome, bipolar disorder, and rare neurodevelopmental diseases with psychiatric manifestations. This secondary analysis of previous observational studies did not allow us the collection of information that may be pertinent for research purposes (e.g., patient's perceived alliance with the clinician, borderline personality traits) or to assess treatment efficacy under blind conditions. As noted above, a lack of statistical power due to a large number of potentially confounding variables and relatively small sample size complicated the interpretation of non-significant results. One could regret that the cross-sectional design of the study precluded us from examining how placement decision impacts the trajectory of emotional symptoms. The discussion about effect of family separation as a precipitating factor for mood disorders (35) should not overlook the fact that the placement decision is in most cases an opportunity to remove the child from severe stressors involving dysfunctional family interactions.

4.3. Clinical and research implications

Our current report invites clinicians to put specific emphasis on associated developmental impairments that may complicate diagnosis assessment in foster care youths with mood disorders. In addition to the patient's possible initial mistrust in mental health professionals due to trauma- and attachment-related factors, associated cognitive impairments such as attention, executive function, memory, language could complicate the assessment of mood symptoms. This may be particularly true for mood symptoms that refer to complex emotional states, such as anhedonia, guilt or shame. Of note, such cognitive impairments have been reported in young people exposed to repeated ACEs even in the absence of neurodevelopmental disorders (21, 53, 54). The assessment of perinatal risk factors influencing both neurodevelopmental and emotional disorders may be particularly hard in the context of family-separation with little reliable information about pregnancy and early childhood (5). Finally, clinicians could be prone to consider mood and neurodevelopmental disorders as differential rather than combined diagnoses (55). The identification of a combined form of mood and neurodevelopmental disorders in foster care youths is worth considering as it could represent an important therapeutic opportunity (5), such as specific remediation interventions for cognitive impairments (36).

Our results confirm data from studies conducted in the US, in particular the high rate of antipsychotic prescription (5, 6, 56, 57). We observed that foster care youths did not have a worse prognosis than other inpatients. This preliminary data supports the view that youths with mood disorders have comparable response rates to interventions provided during a hospitalization (i.e., in an environment where the youth's access and maintenance to the interventions is largely controlled, unlike ambulatory care). Said differently, it is likely that the negative effect of ACEs on the treatment response of pediatric mood disorders (26–29) is undermined by difficulties to access and to adhere to quality interventions rather than the effect of this intervention *per se* (which explains our title). Such an assumption could be empirically tested, for example, by comparing the response rate of antidepressants in youths exposed to ACEs in per protocol and in intent-to-treat analyses. The negative effect of ACEs on the treatment response of mood disorders noted in adults (14, 25) could be partly underpinned by the effect of persisting untreated mood symptoms due to life-long barriers to care. Chronic subsyndromal emotional disturbances in these patients could influence individual (e.g., cognitive distortions and biases) and social functioning (conjugal status, academic/professional achievement) which are also identified as moderators of the effectiveness of treatments provided for mood disorders (58). Following this, emphasis must therefore be placed on the influence of individual and environmental factors influencing all steps of the care pathway of the foster care youths leading to access and to adhere to quality interventions.

5. Conclusion

A higher rate of chronic forms of depression, with predominant irritability, was observed in youths with mood disorders in foster care compared to other patients. We also found a high rate of associated neurodevelopmental disorders in this population, more frequent prescriptions of antipsychotics and use of emergency care. If many factors could influence the access and the adhesion to mental health

interventions in foster care youths with mood disorders, we did not find any significant difference in the response to the therapeutic care provided during hospitalization. This finding is worth noting considering the usual therapeutic "defeatism" among clinicians caring for foster care youths, an assumption probably maintained by a lack of empirical evidence (16).

Data availability statement

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

Ethics statement

The studies involving humans were approved by Autorisation CNIL MR004 N°2208336v0. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the data analyzed were exclusively based on information collected during usual care.

Author contributions

XB, J-MG, DC, and RL: study concept, design, and drafting the manuscript. J-MG, RL, XB, and HL: acquisition of data. XB, J-MG, DC, RL, HP, JW, and FE-K: interpretation of data. PG, JW, and FE-K: critical revision of the manuscript for important intellectual content. XB, HL, HP, AC, DC, RL, JR, PG, FE-K, JW, and J-MG: final draft. 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.

Publisher's note

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Trends in prescription therapy for adolescents with depression in nine major areas of China during 2017–2021

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Objective: To date, no national-scale drug usage survey for adolescents with depression has been conducted in China, and the purpose of this study was to examine the national trends in prescriptions in Chinese adolescent depression patients from 2017 to 2021.

Methods: Prescribing data were extracted from the Hospital Prescription Analysis Cooperative Project. The average number of patients per year, the cost of treatment, and the prescription patterns (monotherapy vs. combination therapy) were analyzed, and subgroup analyses were conducted depending on age, sex, and drug class.

Results: The study included 674,099 patients from 136 hospitals located in nine major areas of China. Of all patients, the proportion of adolescents increased from 1.63% in 2017 to 6.75% in 2021. Visits by adolescent depression patients increased from 1,973 in 2017 to 9,751 in 2021, and the corresponding cost increased from 607,598 Chinese Yuan in 2017 to 2,228,884 Chinese Yuan in 2021. The incidence of adolescent depression among female individuals was far beyond that among male individuals. Combination therapy was more frequent than monotherapy, and the most commonly prescribed drugs were antidepressants, antipsychotics, antiepileptics, and antianxietics. Despite the use of sertraline decreasing from 47.90 to 43.39%, it was the most frequently used drug.

Conclusion: In summary, the prescriptions and cost of treatment for adolescent depression patients both increased rapidly. The widespread use of those drugs with weak clinical evidence reflects the current state of China, which should arouse our attention. The study can provide references for clinical treatment decisions and a basis for more efficient allocation of healthcare resources by the government.

KEYWORDS

adolescent depression, antidepressant, antipsychotic, sertraline, prescription

Introduction

Depression is one of the most common mental disorders that seriously affects the patients' psychosocial functions and quality of life. Adolescence is a key life period characterized by rapid social and emotional development, so it is a vulnerable time for depression (1). Despite all age groups experiencing an increase in depression prevalence, the rate of increase among adolescents

was significantly more rapid relative to adults (2). In adolescents aged 13–18 years in the United States, the lifetime and 12-month prevalence of major depressive disorder (MDD) were 11.0 and 7.5%, respectively (3), according to the "China National Mental Health Development Report (2019–2020)" released by the Institute of Psychology of the Chinese Academy of Sciences. Detection rate is the detection rate of depressive symptoms. The survey was conducted using a self-rating scale. According to the score, there is no, mild, or severe depression. The results of the scale can only reflect the severity of depression at a certain time but not a diagnosis. The detection rate of depression among Chinese adolescents was 24.6%, and the rate of MDD was 7.4%. Adolescents with depression have an elevated risk of other psychopathology (4), physical health outcomes (5, 6) and recurrence in later life (7); meanwhile, the increase in suicide attempts, nicotine abuse, alcoholism, and drug abuse have been found to be associated with adolescent depression (8, 9).

Except for psychotherapy, drug therapy is one of the main treatment methods for depression in adolescents, and various factors influence the choice of drug, including the depression type, severity of the symptom, patient age, guidelines, prescribing doctor's experience, cost, and so on. Therefore, understanding the current situation of adolescent depression drug usage is crucial for improving depression treatment. For now, there is little information available about the use of drugs for adolescent depression in China. Therefore, to assess the time trends and patterns of prescriptions for adolescents with depression, we conducted a cross-sectional study in nine major areas in China from 2017 to 2021.

Methods

Ethics

Ethics approval was obtained from the First Affiliated Hospital of Zhejiang Chinese Medical University for this study. This study was retrospective, so informed consent was not required.

Data source

A database from the Hospital Prescription Analysis Cooperative Project was used to extract the data, and this approach has been used widely in Chinese pharmacoepidemiology studies and has been validated (10, 11). Participating hospitals provided prescription information for the database on sampling days. During the year, there were 40 randomized sampling days, not a full year of data; that is, the data were sampled randomly. The prescription data included the code, sex, age of patients, date, location, diagnosis, generic drug name, dose, and cost. This study included outpatient prescriptions meeting the following criteria: (1) prescriptions for patients aged 12–17 years; (2) those for the diagnosis of depression, without restrictions on the diagnostic criteria and severity of disease; (3) those issued from hospitals in Beijing, Shanghai, Guangzhou, Hangzhou, Chengdu, Zhengzhou, Shenyang, Tianjin, and Heilongjiang that participated in the program continuously from 2017 to 2021. Data were obtained from hospitals located in the east, west, south, and north of China, which covered a substantial geographical area and represented the entirety of the country.

Analysis

Trends in proportions will be tested by the Cochran–Armitage trend test. Other trends will be analyzed by the Mann–Kendall trend test. The statistical analysis was conducted using R Version 4.2.1[1] software.

Results

Total trends in visits and expenditure

A total of 674,099 patients issued from 2017 to 2021 were identified in this study. As Table 1 and Figure 1 indicate, during the study period, there was no significant trend in patients with depression ($p = 0.462$), while the proportion of adolescents increased from 1.63% in 2017 to 6.75% in 2021 ($p < 0.001$). The adolescence visits increased from 1,973 in 2017 to 9,751 in 2021 ($p = 0.027$), and the total expenditure increased dramatically from 607,598 Chinese Yuan (CNY) in 2017 to 2,228,884 CNY in 2021 ($p = 0.027$).

Trends stratified by sex

A stratified analysis of the trends in depression among adolescents by sex is shown in Table 2, the proportion of females (67.56–76.68%) was generally higher than male patients (23.32–32.44%), and the proportion of females showed a significant increase trend, while the trend of males decreased obviously (both $p < 0.001$).

Trends in treatment patterns

Figure 2 shows the trends in treatment patterns. Combination therapy was the predominant pattern of treatment, monotherapy

1 http://www.R-project.org

TABLE 1 Age structure of included patients, 2017–2021.

Age	Number of patients (%)					P_1	P_2
	2017	2018	2019	2020	2021		
12–17	1973 (1.63)	3,020 (2.21)	5,588 (3.85)	7,484 (5.91)	9,751 (6.75)	0.027	<0.001
≥18	119,346 (98.37)	133,780 (97.79)	139,449 (96.15)	119,066 (94.09)	134,642 (93.25)	0.807	<0.001
Total	121,319	136,800	145,037	126,550	144,393	0.462	

P_1, p-value for trend in the number of patients, assessed by the Mann–Kendall trend test; P_2, p-value for trend in the proportion of patients, assessed by the Cochran-Armitage trend analysis.

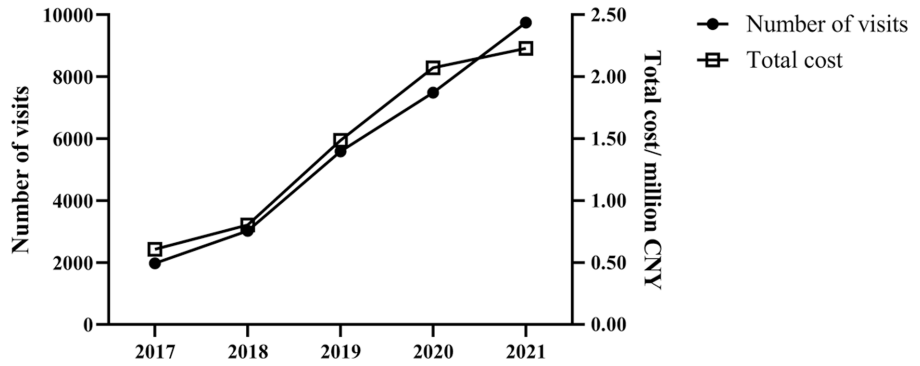

FIGURE 1
Trends in visits and cost of adolescents with depression in 136 hospitals located in nine major areas of China from 2017 to 2021.

TABLE 2 Gender distribution of adolescent depressive patients, 2017–2021.

Sex	Number of patients (%)					P_1	P_2
	2017	2018	2019	2020	2021		
Male	640 (32.44)	957 (31.69)	1,447 (25.89)	1745 (23.32)	2,358 (24.18)	0.027	<0.001
Female	1,333 (67.56)	2063 (68.31)	4,141 (74.11)	5,739 (76.68)	7,393 (75.82)	0.027	<0.001

P_1, *p*-value for trend in the number of patients, assessed by the Mann–Kendall trend test; P_2, *p*-value for trend in the proportion of patients, assessed by the Cochran–Armitage trend analysis.

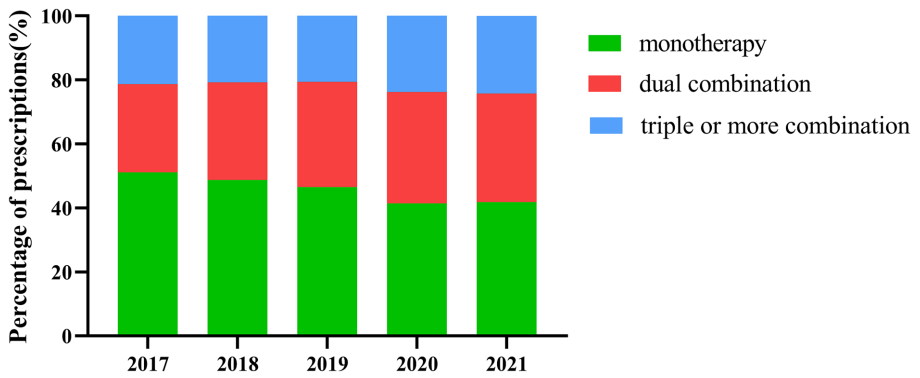

FIGURE 2
Trends in patterns of adolescent depression treatment.

showed a decreasing trend over time ($p < 0.001$), while the proportion of dual combination therapy and triple or more combination therapy kept on increasing during the 5-year period (both $p < 0.001$).

Trends by drug class

Figure 3 and Table 3 show annual prescriptions of drug classes and specific drugs. The most commonly prescribed drug classes were antidepressants, antipsychotics, antiepileptics, and antianxietics. Antidepressants remained in the leading position of the prescriptions (49.52–55.99%) though the percentage showed a decreasing trend ($p < 0.001$). The use of antipsychotics (20.55–25.89%), and anxiolytics (9.56–13.86%) increased over the period; however, the percentage of antiepileptics decreased from 10.86% in 2017 to 8.14% in 2021 (all $p < 0.001$). Nearly half of the patients were prescribed sertraline, the most commonly prescribed drug, but its use rate among visits continued to decrease ($p < 0.001$). At the end of the study, quetiapine and fluoxetine were the second and third most commonly prescribed drugs, respectively, and both showed an increasing trend (both $p < 0.001$).

Discussion

In China, there is limited research being conducted on prescription patterns for adolescents with depression. As far as we know, this study is the most comprehensive evaluation of drug use and trends among this patient group in China because the data were drawn from 136 hospitals located in nine major areas of China, and the results are nationally representative. Adolescents with depression are often accompanied by other complications. There are more than

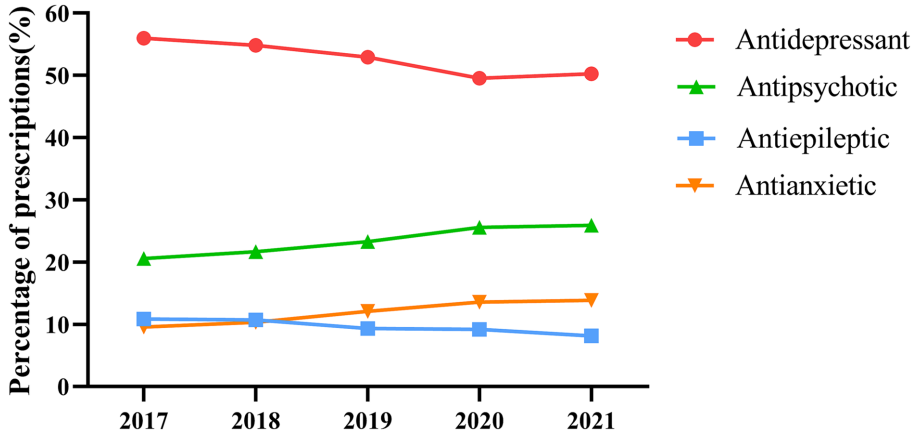

FIGURE 3
Prescription trends by drug class.

TABLE 3 Prescription visits by drug and drug class, 2017–2021.

Drug class	Drug	Number of visits (%)					P_1	P_2
		2017	2018	2019	2020	2021		
Antidepressant	Sertraline	945 (47.90)	1,521 (50.36)	2,829 (50.63)	3,483 (46.55)	4,231 (43.39)	0.027	<0.001
	Fluoxetine	139 (7.05)	289 (9.57)	581 (10.40)	851 (11.37)	1,076 (11.03)	0.027	<0.001
	Fluvoxamine	163 (8.26)	213 (7.05)	423 (7.57)	659 (8.81)	867 (8.89)	0.027	<0.001
	Escitalopram	176 (8.92)	202 (6.69)	295 (5.28)	370 (4.94)	728 (7.47)	0.027	0.971
	Venlafaxine	118 (5.98)	126 (4.17)	158 (2.83)	158 (2.11)	223 (2.29)	0.043	<0.001
	Duloxetine	45 (2.28)	60 (1.99)	127 (2.27)	176 (2.35)	190 (1.95)	0.027	0.570
	Mirtazapine	59 (2.28)	79 (2.62)	124 (2.22)	158 (2.11)	185 (1.90)	0.027	0.016
	Agomelatine	4 (0.20)	25 (0.83)	111 (1.99)	206 (2.75)	433 (4.44)	0.027	<0.001
	Trazodone	32 (1.62)	42 (1.39)	124 (2.22)	174 (2.32)	287 (2.94)	0.027	<0.001
Antipsychotic	Olanzapine	203 (10.29)	303 (10.03)	563 (10.08)	737 (9.85)	851 (8.73)	0.027	0.036
	Quetiapine	161 (8.16)	325 (10.76)	724 (12.96)	1,155 (15.43)	1,593 (16.34)	0.027	<0.001
	Aripiprazole	125 (6.34)	166 (5.50)	338 (6.05)	488 (6.52)	685 (7.02)	0.027	0.047
	Lithium carbonate	68 (3.45)	145 (4.80)	305 (5.46)	608 (8.12)	704 (7.22)	0.027	<0.001
	Risperidone	60 (3.04)	70 (2.32)	170 (3.04)	235 (3.14)	404 (4.14)	0.027	<0.001
Antiepileptic	Sodium valproate	164 (8.31)	272 (9.01)	424 (7.59)	517 (6.91)	554 (5.68)	0.027	<0.001
	Magnesium valproate	77 (3.90)	84 (2.78)	150 (2.68)	206 (2.75)	289 (2.96)	0.027	0.492
	Lamotrigine	53 (2.69)	83 (2.75)	195 (3.49)	261 (3.49)	334 (3.43)	0.027	0.166
	Oxcarbazepine	32 (1.62)	59 (1.95)	69 (1.23)	173 (2.31)	155 (1.59)	0.086	0.822
Antianxietic	Alprazolam	135 (6.84)	223 (7.38)	439 (7.86)	805 (10.76)	844 (8.66)	0.027	0.004
	Lorazepam	75 (3.80)	151 (5.00)	252 (4.51)	479 (6.40)	648 (6.65)	0.027	<0.001
	Tandospirone	52 (2.64)	44 (1.46)	194 (3.47)	272 (3.63)	420 (4.31)	0.086	<0.001
	Oxazepam	25 (1.27)	62 (2.05)	206 (3.69)	154 (2.06)	356 (3.65)	0.086	<0.001

P_1, *p*-value for trend in the number of patients, assessed by the Mann–Kendall trend test; P_2, *p*-value for trend in the proportion of patients, assessed by the Cochran–Armitage trend analysis.

70 diagnoses including depression in China. The objective of this study was to understand the prescribing patterns of adolescent patients diagnosed with depression in China.

As we know, the prevalence of depression increased significantly in China and around the world (2, 12). However, in this study, over the course of the study period, there were no significant trends among patients with depression. When the data from the last 2 years were excluded, it showed a significant increasing trend. The abnormal fluctuations in 2020 and 2021 may be due to COVID-19, which has spread quickly around the world since December 2019. Many studies

have confirmed that outpatient and inpatient volume in healthcare facilities at all levels in China declined significantly during pandemics (13–15). It is important to note that adolescent visits have risen sharply over time, especially in female subjects, and female visits were twice as common as male visits in 2017, while the ratio jumped to 3.1 in 2021, according to several epidemiological studies (16–18), approximately twice as many females suffer from depression as males; however, the factors causing this difference to remain unclear, and biological (19, 20) and social stress (21) mechanisms might account for the gender gap.

Guidelines (22, 23) in many countries suggest a stepwise approach for the treatment of depression in adolescents. For mild depression, the National Institute for Health and Clinical Excellence (NICE) and the American Psychological Association (APA) recommend that psychotherapy and cognitive-behavioral therapy might be sufficient interventions, and antidepressant medication should not be used in the initial stage of treatment. For adolescents with moderate-to-severe depression, NICE recommends combined therapy (fluoxetine and psychological therapy) if adolescents fail to respond to a specific psychological therapy after four to six sessions, and suggests that sertraline or citalopram is the second-line treatment when fluoxetine does not work or is not tolerated due to side effects. Fluoxetine was approved by the US Food and Drug Administration (US FDA) to treat depression in children aged 8 years or older, and escitalopram was approved in adolescents aged 12–17 years. In China, none of the antidepressants was approved for treating depression in adolescents until 31 May 2021; from that day on, fluoxetine was approved by the China Food and Drug Administration (C FDA) for the treatment of moderate-to-severe depression in children aged 8 years or older. In our study, the most commonly prescribed drugs for treating adolescent depression were antidepressants. More than half of the prescriptions and more than 80% of visits used it. Selective serotonin reuptake inhibitors (SSRIs) were the predominant antidepressants in China. Among the antidepressants, sertraline occupies the most prominent position. Although its use rate continued to decrease, those that ranked second to fourth were fluoxetine, fluvoxamine, and escitalopram in 2021, whose proportions were 11.03, 8.89, and 7.47%, respectively. The substantial use of sertraline for adolescents was also reported in other countries (24–27), which may be owing to its effectiveness and well tolerated with mild adverse reactions (28, 29). Fluoxetine was the first drug approved by the US FDA for the treatment of adolescent depression, and according to previous meta-analyses (30, 31), fluoxetine (alone or in combination with cognitive-behavioral therapy) was the most effective treatment for acute moderate-to-severe depressive disorder in adolescents. While only one in ten visits used it in China, the usage of fluoxetine showed a significant increasing trend over the study period, and the latter trend is worth paying attention to. Fluvoxamine was approved for obsessive-compulsive disorder (OCD) and has a good therapeutic effect for depression with psychotic symptoms, anxiety, fear, impulse motion, suicidal behavior, and obsessive thinking. In Japan (27), fluvoxamine was the third-choice agent (selected by 13% of physicians) for adolescents with depression because of the long history of clinical use and safety profile known. Similar results were achieved in our study as the ranked third antidepressant, prescription of fluvoxamine increased progressively and the proportion maintained at approximately 8% for years. Escitalopram, the S-enantiomer of racemic citalopram, was recommended for patients older than 12 years by the US FDA, and a small amount of evidence showed that escitalopram was effective for depression in adolescents (32); however, there was just a small proportion of prescriptions for escitalopram in our study, and the high cost may restrict its use. A significant increase in suicidal behavior was observed in young people taking venlafaxine (31), and NICE guidelines (22) recommend against its usage. A downward trend of venlafaxine has been observed in this study, which is encouraging.

Depressive episodes were not only the core of depressive disorder (unipolar depression) but also the main clinical phase of bipolar disorders (BDs). BDs are psychiatric disorders with both depressive and manic episodes, which include bipolar I disorder and bipolar II disorder (33). By the end of this study, the percentage of patients receiving monotherapy was less than half and showed a significant decreasing trend over time, which suggests that the standard therapeutic approach failed to achieve satisfactory results on a majority of occasions. For adolescents with BD, augmenting the treatment strategy with antipsychotics or mood stabilizers should be considered. Lithium carbonate is classified as an antipsychotic drug in China's current medical insurance list; therefore, in this study, we analyzed it together with other antipsychotics. Lithium carbonate as the first-generation mood stabilizer was approved by the US FDA for the treatment of manic or mixed episodes in adolescents. Atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone) as second-generation mood stabilizers were also approved, while valproate (first-generation mood stabilizer) has not been approved up to now. In China, the use of sodium valproate coincides with US-FDA approval which showed a significant downward trend. Unfortunately, due to the fragmented evidence of psychotropic agents in adolescents, there was still no consensus on the efficacy of the drug on BD. For instance, Renk et al. (34) found that atypical antipsychotics were more effective than lithium in the treatment of manic and mixed episodes; however, McIntyre et al. (33) regarded lithium as the gold standard mood stabilizer. When it comes to treating a depressive episode of BD, the US FDA recommends a combination of olanzapine and fluoxetine, while according to experts in China, quetiapine, olanzapine, and a combination of lithium and lamotrigine were recommended as Class A (bipolar I disorder), and quetiapine was recommended as Class A (bipolar II disorder). In our study, quetiapine has replaced olanzapine as the most prescribed antipsychotic since 2018, which was consistent with the Chinese guidelines, and although prescriptions of lithium accounted for a small proportion of visits, its growth rate was the fastest and more than doubled in the 5 years. In addition to the efficacy, the safety of psychotropic agents needs to be considered. A high risk of weight gain was found for olanzapine and quetiapine. Risperidone and olanzapine showed significantly higher prolactin increase (35).

Antianxietic is a type of medication used to relieve anxiety and tension. Throughout the study period, the top four most used antianxietics were alprazolam, lorazepam, oxazepam, and tandospirone; the first three drugs belong to the benzodiazepines (BZDs) and tandospirone is a 5-hydroxytryptamine (5-HT) 1A receptor agonist. For the treatment of anxiety in adolescents, guidelines recommend SSRIs as first-line pharmacotherapy and serotonin-norepinephrine reuptake inhibitors (SNRIs) as the second-line pharmacotherapy (36–38). Studies of BZDs in adolescents with

anxiety were limited, and some controlled trials have not shown efficacy. Simeon et al. (39) found that alprazolam and placebo did not differ statistically in terms of clinical global rating. Similarly, in another study of alprazolam (40), there were no significant differences among the alprazolam, imipramine, and placebo groups on change in anxiety scales. In this regard, the rapid rise of BZD prescriptions in China needs attention. Clinicians should use BZDs more cautiously not only because of their low efficiency but also because of the possibility of substance dependence, substance abuse, and side effects (36). Compared with the BZDs, tandospirone has a significantly lower abuse potential (41). In a study of adolescents with anxiety disorder (42), tandospirone has shown safety and efficacy that was not inferior to sertraline; however, larger and longer clinical trials are needed.

This study had some limitations. First, the cohort was not stratified by complication or severity. There are no data on how the prescription pattern differs between patients with depression alone and depressed patients with comorbidities. They require a more detailed investigation. Second, the included hospitals were all located in major cities, which may have caused sampling bias.

Conclusion

In summary, the prescriptions and cost of treatment for adolescent depression patients both increased rapidly. The widespread use of those drugs with weak clinical evidence reflects the current state of China, which should arouse our attention. The study can provide references for clinical treatment decisions and a basis for more efficient allocation of health care resources by the government.

Data availability statement

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

Author contributions

LW and FW: conceptualization. LZ, YZ, and JY: data curation. LW, LZ, YZ, JY, NB, WF, and FW: formal analysis. FW: funding acquisition and resources. WF and FW: investigation. LZ, YZ, JY, and NB: methodology. WF and FW: validation. 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.

Publisher's note

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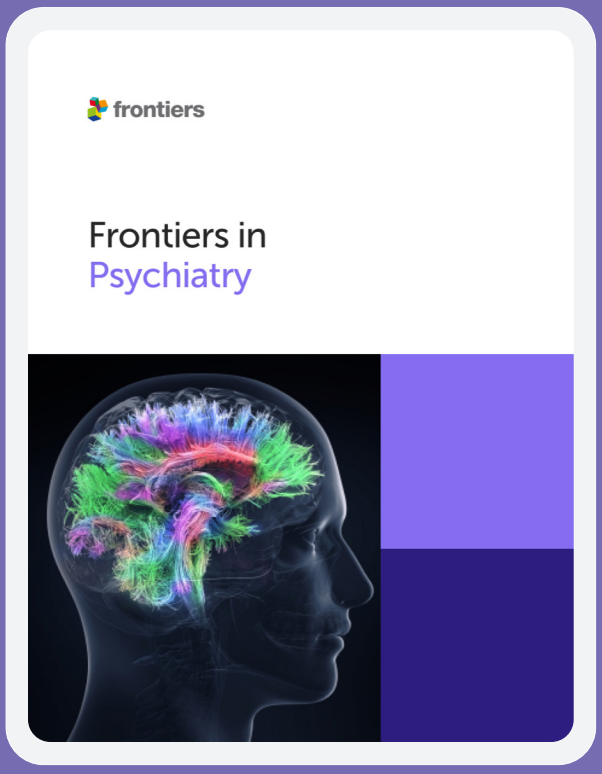

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