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Effect of novel accelerated intermittent theta burst stimulation on suicidal ideation in adolescent patients with major depressive episode: a randomised clinical trial

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To the editor:

Affective disorders, including major depressive disorder (MDD) and bipolar disorder, have emerged as the primary cause of adolescent suicide. Moreover, suicide mostly occurs in the major depressive episode (MDE) of affective disorders. Suicidal ideation (SI) has been identified as an immediate precursor to suicide, such that reducing its severity is conducive to suicide prevention in adolescents. Currently, there is a lack of effective interventions to address SI in adolescents with MDE. The antisuicidal effect was transient even with ketamine treatment in adolescents with MDD.[1] A previous study has shown the effectiveness of accelerated intermittent theta burst stimulation (aiTBS) on SI.[2] Additionally, aiTBS delivered at 20 Hz appears to be more effective than aiTBS delivered at 50 Hz for treating refractory depression.[3] Furthermore, aiTBS with a 60-minute intersession interval may achieve greater efficacy than that with an 8–15 min interval.[4] In recent years, cerebellar stimulation has received particular attention. Therefore, the present study designed a randomised and sham-controlled protocol to explore the effects of aiTBS delivered at 20 Hz targeting the cerebellum on SI in adolescent patients in the MDE.

Between March 2023 and September 2023, patients diagnosed with MDD or bipolar disorder, all with current MDE according to the Diagnostic and Statistical Manual for Mental Disorders—Fifth Edition criteria, were recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Jinan University, Guangzhou, China. Inclusion criteria were as follows: (1) aged between 12 and 17 years; (2) 24-item Hamilton Depression Rating Scale (HDRS-24) >20; (3) Young Mania Rating Scale <7; (4) Beck Scale for Suicide Ideation (SSI) ≥12. All subjects had no severe somatic disorder, other major psychiatric disorder, contraindication to aiTBS or history of electroconvulsive therapy.

The present study was registered at the Chinese Clinical Trial Registry (ChiCTR2300068954). All participants signed informed assent forms, and their legal guardians signed informed consent forms.

The SSI, HDRS-24 and Beck Hopelessness Scale (BHS) were measures of current SI intensity, depression severity and hopelessness, respectively. The Young Mania Rating Scale was used to monitor for manic/hypomanic switching. All assessments were performed at baseline (T0), on each day during the intervention (T1, T2, T3, T4) and after 1 week of therapy (T5). Adverse events were recorded.

Stimulation was carried out using a 70 mm figure-of-eight coil and a Magstim Rapid magnetic biphasic stimulator (Magstim Company). The aiTBS therapy was carried out over 4 days with five sessions daily for a total of 20 sessions, targeting the left dorsolateral prefrontal cortex (DLPFC) and left lateral cerebellum (LC). An interval of 60 min was taken between sessions. The parameters of an aiTBS session are as follows: triplet 20 Hz bursts repeated at 5 Hz, 2 s on and 8 s off, 600 pulses in total, at 80% resting motor threshold. Patients were randomly assigned at 1:1 to receive either active or sham aiTBS. Simple randomisation was performed by an independent research assistant using a computerised random number generator.

The active group received real stimulation to both the left DLPFC and the left LC. The sham group received real stimulation of the left DLPFC and sham stimulation of the left LC. The sham stimulation was administered with the coil rotated 90°. Medication remained constant during the aiTBS-stimulation period.

SPSS (IBM V.25, Chicago, Illinois, USA) was used for all statistical analysis. Significance was set at p<0.05 (two-tailed). Shapiro-Wilk test was used for normality. Linear mixed-effects models were conducted to analyse the primary and secondary outcomes, with the patient as a random factor, group (active vs sham) and time (T0 to T5) as fixed factors. Post hoc analysis was Bonferroni corrected for multiple comparisons. To further investigate whether the main effect on SI was attributed to improvements in depression, we performed linear mixed-effects models on the SSI score, including time and HDRS responder (at T5) as factors. HDRS responder was defined as a 50% or greater reduction in HDRS score. We also conducted a mediation analysis using the aiTBS treatment, HDRS score and SSI score as an independent variable, mediator variable and dependent variable, respectively.

16 were randomised to the active group and 16 to the sham group, with no drop-out. No significant difference in demographic and baseline clinical characteristics was observed between groups (online supplemental table S1). Response and remission (defined as a score of zero on both item 4 and item 5 of the SSI) rates on SI at T4 were 50.00% and 25.00% in the active group and 31.30 and 12.50% in the sham group, with no significant differences between groups.

The results from the linear mixed-effects models indicated a statistically significant decrease in SSI scores for both groups after intervention (F=16.60, p<0.001), with no significant group effect (F=1.98, p=0.170) or interaction (F=1.21, p=0.307). The SSI score fell markedly at T1 and reached a stable level at T2 with active aiTBS treatment, whereas it decreased significantly until T3 with sham aiTBS treatment. Similarly, both HDRS and BHS scores presented a main effect of time (HDRS: F=36.30, p<0.001; BHS: F=6.57, p<0.001), but no statistically significant main effect of group or group-by-time interaction effect (all p>0.05). Both groups showed a steady decrease in HDRS score from T1 through to T5. For the BHS score, the active group experienced a decline at T2 that lasted until T5, whereas the sham group showed no significant change throughout the study (figure 1). The results of these linear mixed-effects models remained unchanged after adjustment for diagnosis, sex, age of onset and medication (online supplemental table S2).

When divided into HDRS responders and non-responders, the linear mixed-effects showed a significant time effect (F=15.19, p<0.001) and interaction (F=6.62, p<0.001), but no significant effect of the factor 'HDRS responders at T5' (F=2.19, p=0.150). Post hoc analyses revealed a significant trend of SSI score reduction (t=5.45, p<0.001) from T1 to T5 in HDRS responders but not in non-responders (t=−0.66, p=0.524). Moreover, HDRS responders had lower SSI score than non-responders at T5 (t=3.18, p=0.003) (figure 2). The mediation analyses suggested that HDRS score mediated the association between aiTBS treatment and SSI score, with significant indirect effects (β=−1.68, 95% confidence interval (CI): −2.45 to −0.99) and non-significant direct effects (β=0.05, 95 % CI: −0.74 to 0.83), indicating a full mediation effect (online supplemental figure S1).

Over the course of treatment, no instances of manic/hypomanic switches, suicide attempts, seizures or severe adverse events were observed. A few participants reported localised discomfort or pain at the stimulation site during therapy, as well as dizziness during or after the session; however, these symptoms remitted spontaneously within half an hour or less. Specifically, in the active group, three participants reported headache at the left DLPFC stimulation site, seven reported headache at the left LC stimulation site and two reported dizziness during or after the left LC session; in the sham group, eight participants reported headache at the left DLPFC stimulation site, and no one reported headache or dizziness during or after sham stimulation of the left LC. Notably, no participant withdrew due to intolerance.

To our best knowledge, this is the first randomised controlled study to investigate the effects of 20 Hz aiTBS on suicidal risk in adolescents and to explore the antisuicidal effect of the cerebellum as a potential stimulation site. The principal findings of our study were as follows:

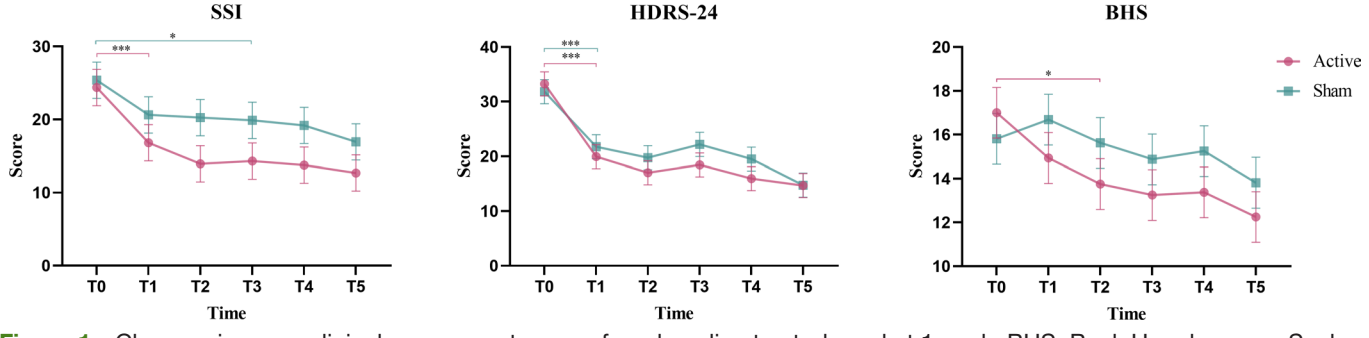

Figure 1 Changes in mean clinical assessment scores from baseline to study end at 1 week. BHS, Beck Hopelessness Scale; HDRS-24, 24-item Hamilton Depression Rating Scale; SSI, Beck Scale for Suicide Ideation. T0, baseline; T1–T4, each day during the intervention; T5, study end at 1 week. Error bars denote standard error of the mean.*p<0.05, **p<0.01, ***p<0.001.

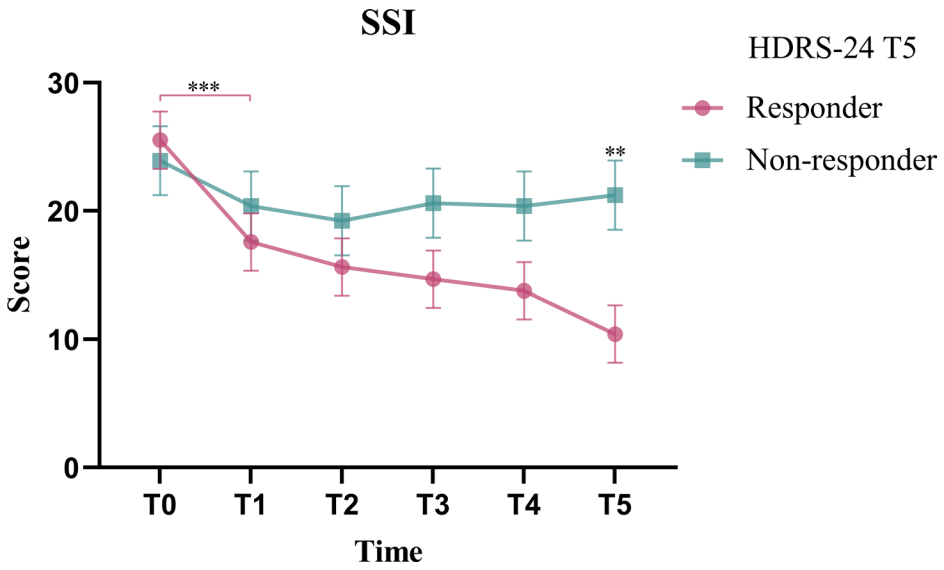

Figure 2 Changes in SSI mean scores over time in HDRS responders and non-responders. HDRS-24, 24-item Hamilton Depression Rating Scale; SSI, Beck Scale for Suicide Ideation. T0, baseline; T1–T4, each day during the intervention; T5, study end at 1 week. HDRS responder was defined as a 50% or greater reduction in HDRS-24 score at T5. Error bars denote standard error of the mean. *p<0.05, **p<0.01, ***p<0.001.

(1) both groups achieved an overall improvement in SI, but the active group had a faster onset of therapeutic response than the sham group; (2) the antisuicidal effect of the novel 20 Hz aiTBS appeared to be related to its antidepressant effect; (3) in the active group, but not in the sham group, hopelessness was significantly alleviated. The present study provides a scientific basis for expanding the use of this novel aiTBS to the prevention and treatment of adolescent suicide.

To date, there are only two publications on the novel 20 Hz iTBS, both supporting its superior antidepressant efficacy and safety compared with bilateral neuronavigated iTBS delivered at 50 Hz. Initially, Stubbeman *et al* proceeded to administer 20 Hz iTBS therapy to patients with refractory depression who did not respond to 50 Hz iTBS therapy, resulting in notable alleviation of depressive symptoms.[5] Subsequently, they devised an open-label investigation to validate the effectiveness of 20 Hz iTBS therapy in adult patients with treatment-resistant depression, documenting a response rate of 83% and a remission rate of 72%.[3] On this basis, the present randomised controlled trial further investigated the antisuicidal and antidepressant effects of 20 Hz aiTBS in adolescent patients with depression. Similar results have been observed in our study, where 20 Hz aiTBS therapy improved SI, depressive symptoms and hopelessness, with no serious adverse events. These results indicate that 20 Hz aiTBS has promising antisuicidal and antidepressant efficacy in adolescents. A recent study examining 50 Hz iTBS in 10 sessions over two consecutive weeks reported improvement in SI and depressive symptoms in adolescent depression, aligning with our findings and highlighting iTBS as a potential therapy for depressed adolescents.[6] There has also been evidence that 50 Hz aiTBS can effectively attenuate SI in adults, independent of depressive symptoms.[2] However, we found that the antisuicidal effect of 20 Hz aiTBS appeared to be related to its antidepressant effect in adolescents. This may be explained by the stronger link between suicide and depression among adolescents.[7] Furthermore, a recent study also noted an alleviation of depressive symptoms with 50 Hz aiTBS, accompanied by a significant reduction in SI.[8] Taken together, aiTBS may be an effective intervention for adolescent suicide. As this study did not include 50 Hz aiTBS as an additional control, it remains unclear whether there are significant differences between aiTBS at 20 Hz and 50 Hz for the treatment of SI. Future studies should address this aspect.

The current study found that both intervention groups had improvement in SI and depressive symptoms, with the active group demonstrating a faster therapeutic effect on SI. Furthermore, the active group achieved improvement in hopelessness, while the sham group did not. These findings imply that 20 Hz aiTBS over the dual sites of the left DLPFC and LC may serve as a promising and innovative therapeutic approach to address depressive symptoms, SI and hopelessness in adolescent depression. In recent years, neurostimulation of the cerebellum using repetitive transcranial magnetic stimulation (rTMS) has become increasingly popular. Cerebellar stimulation not only tunes cerebellar excitability but also modulates cerebro-cerebellar circuits that drive cognitive and affective operations.[9] For example, rTMS/iTBS targeting the cerebellum can safely attenuate depressive symptoms and restore DLPFC–cerebellum network connectivity in schizophrenia.[10] Nevertheless, aberrant functional connectivity of the cerebellum has been shown in adolescents with depression and suicide attempts.[11] Furthermore, increased cerebellar connectivity with the DLPFC predicted the antidepressant effect of rTMS in patients

with depression.[12] Therefore, the antisuicidal and antidepressant effects of 20 Hz aiTBS with combined left DLPFC–LC stimulation in patients with depression may be explained by restoring cerebellar structure and function as well as modulating the cerebello-cortical pathways. However, the utilisation of cerebellar stimulation using aiTBS in mental disorders, particularly affective disorders, remains in the exploratory phase of research. Further validation of its anti-suicidal effectiveness and investigation of the precise neurobiological mechanism underlying its effects are necessary.

Currently, no consensus exists on the intersession interval of aiTBS. Previous studies usually employed a short intersession interval, such as 15 min, with most of the studies demonstrating significant antisuicidal and antidepressant placebo effects. It cannot be ruled out that these placebo effects are possibly attributable to the short intervals. Preclinical studies have shown that intervals of 8–15 min can induce homeostatic effects of metaplasticity, while intervals of 60 min can induce additive effects.[4 13] Similar findings were reported in the clinical trial, with long intervals (45–60 min) recommended.[14] One possible reason is that an iTBS session can boost cortical excitability for up to 60 min.[15] A short intersession interval of 8–15 min may promote homeostatic rather than additive metaplastic effects that preserve network stability. Consequently, there is an overall absence of changes in excitability following these accelerated regimens. However, repeating the iTBS regimen every 60 min may have additive effects of metaplasticity. Based on preclinical and preliminary clinical studies, a 60-minute interval may enhance therapeutic efficacy. On the other hand, a longer interval may prolong the total duration of treatment, increase treatment costs and decrease treatment compliance. As a result, further investigation is needed to determine the optimal intersession interval, with both advantages and disadvantages taken into consideration. As the comparison between the short and long intervals was not addressed in the present study, it remains unclear whether there were any differences in therapeutic efficacy between these two groups. Further research on this topic is planned.

The present study has several limitations. First, the small sample sizes may reduce statistical power; hence, a larger sample size is needed to validate the current findings. Second, a sham dual-site left DLPFC–LC stimulation group was not included as a control. Third, aiTBS was administered in combination with medication because patients with severe SI were recruited in this trial and the suicide risk should be taken into account. To minimise the influence of medication on experimental results, medication remained unchanged during the treatment period. Finally, subgroup analyses based on diagnosis were not performed given the small sample size. Further research efforts are needed in this regard.

In summary, the 20 Hz aiTBS protocol used in this study demonstrates potential as a viable and safe intervention for adolescent patients with depression and SI. The implemented protocol displayed a sustained reduction in SI lasting for 1 week. This effect was observed irrespective of the presence of active or sham stimulation but appeared to be correlated with improvement in depressive symptoms. Nonetheless, additional cerebellar stimulation accelerated SI reduction and showed superior efficacy in reducing hopelessness. Further investigation is warranted to assess the efficacy of 20 Hz aiTBS as an acute intervention for suicide risk in unipolar and bipolar depression in sham-controlled trials with large sample sizes.

Contributors DH: conceptualisation, validation, investigation, methodology, formal analysis, writing—original draft, visualisation. SZ: conceptualisation, validation, methodology, supervision, formal analysis, writing—review and editing. XS and RZ: investigation and methodology. SL: methodology, writing—review and editing. YJ: conceptualisation, supervision, methodology, writing—review and editing, funding acquisition.

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Competing interests None declared.

Patient consent for publication Not applicable.

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