

Research Progress on the Application of Accelerated Transcranial Magnetic Stimulation in Major Depressive Disorder with Suicidal Ideation

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Abstract

Major depressive disorder (MDD) comorbid with suicidal ideation (SI) is a critical risk factor for suicidal behavior. Conventional antidepressant treatments have a slow onset of action and fail to meet the clinical need for rapid reduction of suicide risk. Accelerated transcranial magnetic stimulation (aTMS), by shortening treatment cycles and accelerating symptom relief, offers a novel interventional strategy for this patient population. This article systematically reviews the application of accelerated TMS in MDD with suicidal ideation, focusing on its efficacy, underlying mechanisms, targeting challenges, and safety profile, aiming to inform rapid and safe intervention strategies for this group.

Keywords

Accelerated Transcranial Magnetic Stimulation, Repetitive Transcranial Magnetic Stimulation, Suicidal Ideation, Major Depressive Disorder

1. Introduction

Major depressive disorder is a mood disorder characterized primarily by significant and persistent depressed mood. It is associated with high morbidity and elevated suicide risk (Monroe & Harkness, 2022). MDD with suicidal ideation represents one of the most challenging clinical scenarios in psychiatry. A recent meta-

analysis indicates that the prevalence of suicidal ideation among Chinese MDD patients is as high as 48.18%, and approximately 30% of patients continue to experience suicidal ideation even after remission of depressive symptoms (Zhang, 2022). Among current mainstream treatments, antidepressant medications typically take several weeks to exert their effects (Le et al., 2025). While effective, electroconvulsive therapy is associated with significant cognitive side effects (Argyelan et al., 2021), limiting its widespread use as a first-line rapid intervention. Thus, there is an urgent clinical need for novel interventions that offer faster onset, higher safety, and greater feasibility. In recent years, non-invasive brain stimulation techniques have shown broad application prospects and high acceptance as non-pharmacological interventions for various psychiatric disorders (Siddiqi & Fox, 2024), becoming a research hot spot. Repetitive transcranial magnetic stimulation (rTMS) has been approved by the FDA for treating depression, but its conventional protocol (one session per day for 4 - 6 weeks) is lengthy (Miron et al., 2021), and cannot meet the clinical need for rapid treatment. Studies have shown that aTMS, by administering multiple sessions daily, can accumulate a pulse dose comparable to or even higher than conventional protocols within a few days, thereby significantly shortening the time to onset (Chen et al., 2023a). Additionally, aTMS has demonstrated unique advantages in rapidly alleviating suicidal ideation in patients with depression. This article systematically reviews the efficacy, potential mechanisms, targeting challenges, and safety of aTMS in the treatment of MDD with suicidal ideation, and discusses future directions, aiming to provide a reference for clinical practice.

2. Neurobiological Basis and Potential Mechanisms of Accelerated TMS for MDD with Suicidal Ideation

Studies have shown that aTMS can reduce suicidal ideation in a short period, and the possible mechanism lies in the cumulative effect of heterosynaptic plasticity—i.e., the ability of neurons to adjust their response to subsequent stimulation (long-term potentiation, LTP, or long-term depression, LTD) based on prior activity history, thereby maintaining the stability and dynamic balance of neural networks (Thomson & Sack, 2020). A key parameter in TMS treatment for depression is the inter-train interval: too short an interval tends to trigger homeostatic regulation (upregulation of response threshold) and weaken the therapeutic effect, whereas an appropriately longer interval (e.g., the commonly used 50 min) facilitates the accumulation of plasticity (Jin et al., 2023). Clinical studies provide empirical support for this: the Stanford team used an accelerated iTBS protocol with 10 sessions per day and a 50-min inter-train interval (the SAINT protocol) and achieved a remission rate of 65.1% in treatment-resistant depression within 5 days, with a mean time to onset of only 2.3 days (Cole et al., 2022).

Patients with suicidality show abnormal functional connectivity in the suicide-related damaged network (SRDN), and aTMS can reduce this abnormality, with such changes correlating with treatment response (Wang et al., 2025). A systematic review points out that the neurobiological mechanisms associated with

suicidal behavior include altered function and connectivity of the dorsolateral prefrontal cortex (DLPFC), which is involved in impulse control and emotional regulation. TMS targets the DLPFC to modulate the connectivity between the prefrontal cortex and limbic system, thereby ameliorating suicidal ideation (Virto-Farfan & Tafet, 2025). At the level of specific mechanisms underlying the rapid reduction of suicidal ideation, aTMS involves multi-level synergistic actions. aTMS not only affects local cortical excitability but may also alter the global regulatory network through connections between the prefrontal cortex and limbic regions (such as the amygdala, hippocampus, and nucleus accumbens), improving impulsivity and emotion dysregulation, both of which are important neural underpinnings of suicidal ideation. At the target and brain network level, the left DLPFC is a core regulatory target. Through projections to subgenual anterior cingulate cortex (sgACC), insula, hippocampus, and other emotion- and interoception-related regions, it modulates the function of the prefrontal-limbic circuit (Virto-Farfan & Tafet, 2025). Further studies revealed that the anti-suicidal effect of aTMS is associated with functional connectivity changes in the insula-hippocampus pathway, whereas its antidepressant effect is associated with the sgACC circuit, suggesting that the two effects may involve different neural pathways (Li et al., 2024). At the systemic level, aTMS can rapidly regulate hypothalamic-pituitary-adrenal axis function, promote monoamine neurotransmitter turnover, and inhibit neuroinflammatory responses rTMS (Zhao et al., 2018). A comparative study showed that for depressed patients with moderate-to-severe suicidal ideation, both accelerated theta-burst stimulation and continuous theta-burst stimulation improved depressive symptoms, but the improvement in suicidal ideation differed (right DLPFC continuous theta-burst stimulation performed better in early reduction of suicidal ideation) (Zhao et al., 2024).

In summary, aTMS reduces suicidal ideation in a short period through triple mechanisms: heterosynaptic plasticity enhancement, brain network functional reshaping, and neuroendocrine-immune regulation.

3. Clinical Application Regimens of aTMS in MDD with Suicidal Ideation

3.1. Accelerated High-Frequency rTMS Protocols

Accelerated high-frequency rTMS protocols have been explored early and are now a common option in clinical practice. Theleritis et al. (2017) compared twice-daily versus once-daily 10 Hz rTMS in treatment-resistant depressed patients with SI and found that the accelerated protocol produced greater improvement on the suicide item score. George et al. (2014) employed a more intensive protocol (10 Hz rTMS, three times daily for three consecutive days) and observed a rapid decrease in total scores on suicide ideation scales, indicating that short-duration, high-density stimulation has favorable rapid-onset properties. Zhu et al. (2019) applied high-intensity 5 Hz left DLPFC stimulation three to four times daily for three consecutive days and found that, compared with the conventional once-

daily protocol, the accelerated protocol rapidly reduced suicidal ideation and improved clinical symptoms within one week. Overall, existing evidence suggests that accelerated high-frequency rTMS has rapid intervention potential for MDD patients with suicidal ideation. However, limitations include small sample sizes, lack of sham control, inconsistent parameters, and short follow-up periods in most studies.

3.2. Accelerated Intermittent Theta Burst Stimulation (aiTBS) Protocol

The accelerated intermittent theta burst stimulation (aiTBS) protocol is currently a hotspot in clinical application and research. Baeken et al. (2019) treated 45 MDD patients with accelerated iTBS over the left DLPFC and found significant reductions in both suicidal ideation and depression severity, suggesting the potential of aiTBS to reduce suicidal ideation. (Zhao et al., 2024) compared accelerated cTBS and accelerated iTBS in treatment-resistant depressed patients with suicidal ideation, and found that accelerated iTBS was superior to accelerated cTBS in improving suicidal ideation at week 1, providing preliminary evidence for the rapid anti-suicidal effect of iTBS. Wilkening et al. (2022) used a protocol of four daily iTBS sessions (1800 pulses each) with 50-minute intervals for five consecutive days, resulting in a 34.61% reduction in suicide ideation scale scores. Collectively, the above studies have demonstrated the potential of aiTBS in clinical application. The most landmark progress, however, pertains to the SAINT protocol. It uses 10 daily sessions of aiTBS for five consecutive days, combined with individual functional magnetic resonance imaging to precisely target the left DLPFC spot showing the most negative functional connectivity with the sgACC. Preliminary studies showed that SAINT rapidly reduced suicidal ideation within 5 days, with an effective rate of 86.67% (Cole et al., 2022). Despite the SAINT protocol's practical challenges—including demanding equipment, high cost, and complex operation—the aiTBS protocol has undeniably shown considerable potential in intervening for patients with major depressive disorder accompanied by suicidal ideation.

4. Target Selection and Localization Methods for aTMS

4.1. Target Selection

Precise target localization is a core prerequisite for ensuring the efficacy of aTMS on depressive symptoms and suicidal ideation. Traditional rTMS mostly uses the left DLPFC as the standard intervention target, following the classic “left high/right low” paradigm (Kong, 2021)—i.e., high-frequency stimulation of the left DLPFC or low-frequency stimulation of the right DLPFC, with both protocols having similar efficacy and tolerability. With the development of neuroimaging and aTMS techniques, stimulation targets have expanded from a single DLPFC to key brain regions of the emotion and interoception circuitry, such as sgACC, insula, and hippocampus (Cheng et al., 2021). Among these, sgACC, as a hub of the pathological brain network in depression, has stable functional connectivity with

the DLPFC; individual associated targets can be selected based on brain imaging features, which is more suitable for patients with treatment-resistant depression and high suicide risk (Cash & Zalesky, 2024). The prefrontal-limbic circuit and insula-hippocampus pathway have been confirmed as specific neural circuits regulating depressive mood and suicidal ideation; precise intervention targeting these networks can significantly improve hopelessness, negative cognition, and somatic symptoms (Virto-Farfan & Tafet, 2025). Current clinical target selection has gradually shifted from fixed anatomical localization to circuit-oriented and individualized precise targeting based on brain functional connectivity, allowing flexible protocol formulation according to illness severity and presence of suicide risk, thereby effectively improving the targeting and clinical efficacy of aTMS (Chen et al., 2023b).

4.2. Localization Methods

Current commonly used TMS target localization methods include scalp-distance surface localization, structural MRI localization, resting-state fMRI localization, and task-state fMRI localization (Bai et al., 2026).

Scalp-distance surface localization mainly includes the 5-cm rule, the Beam F3 system, and the international 10 - 20 electrode system. The advantages are simple operation and no need for imaging equipment, making it suitable for promotion in primary medical institutions; however, it is a fixed, unified calibration pattern that ignores individual differences in skull morphology, cortical anatomy, and brain functional connectivity (Wang, 2024). Clinical data show that when using the traditional 5-cm rule to define the treatment target, 30% - 70% of patients do not have their actual stimulation site precisely targeting the intended brain region (Perera et al., 2016).

Individualized structural MRI localization can achieve brain anatomical visualization through three-dimensional structural imaging and diffusion tensor imaging, precisely delineating the boundaries of DLPFC subregions (Brodmann areas 46 and 9), and predicting treatment response by analyzing the structural connectivity characteristics between DLPFC and sgACC (Fox et al., 2013). However, this method is limited to the anatomical level and cannot reflect the pathological nature of brain network dysfunction in MDD patients with suicidal ideation.

Resting-state fMRI functional connectivity localization is a recent research hotspot and the core foundation of the SAINT protocol. By selecting individual targets based on functional connectivity characteristics between DLPFC and sgACC, it can significantly improve clinical remission rates (Wang et al., 2024). However, this technique has limitations such as insufficient routine scan duration, poor stability of functional connectivity, interference of data preprocessing with target determination and sgACC being susceptible to magnetic susceptibility artifacts, resulting in low signal-to-noise ratio in core brain regions and limited target reliability. Real-time TMS-fMRI simultaneous monitoring also faces issues such as magnetic field artifacts, expensive equipment, and complex operation, making

it difficult to popularize in routine clinical practice (Liu, 2025). New techniques such as task-state fMRI and multimodal imaging fusion, although theoretically advantageous, suffer from non-uniform experimental standards, cumbersome procedures, and high data heterogeneity, and are still in the stage of scientific exploration without widespread clinical adoption (Xia, 2022). In summary, aTMS target localization has entered an image-guided individualized precision phase, but problems such as anatomical localization deviation, insufficient functional stability, high technical barriers, and lack of industry standards remain. There is an urgent need to establish standardized and easily disseminable systems for target selection and clinical application.

5. Safety of Accelerated aTMS

A large body of research has shown that accelerated TMS has a generally favorable safety profile, with common adverse effects including headache and tinnitus, most of which are mild and self-limiting. One study involving 10 elderly patients who received five daily sessions of 20 Hz rTMS showed good tolerability (Dardenne et al., 2018). Additionally, large-sample studies of twice-daily 20 Hz rTMS and three-times-daily 10 Hz rTMS reported no serious adverse events (Fitzgerald et al., 2018; Virto-Farfan & Tafet, 2025).

However, there have been case reports of serious adverse events. Geerts et al. (2015) reported a case of severe depersonalization symptoms in a patient receiving five daily sessions of 20 Hz accelerated stimulation. The symptoms emerged on the third treatment day and were observed only during the active accelerated phase, with no abnormalities during the sham phase. The researchers speculated that the accelerated stimulation may have triggered the symptoms, but the patient had underlying subclinical depersonalization symptoms at baseline that may have been missed, and the accelerated high-frequency stimulation might have merely reinforced pre-existing symptoms. Kallel & Brunelin (2020) reported a case of an 18-year-old patient who experienced a generalized seizure lasting 65 seconds (self-terminating) during the third session of the second day of accelerated left DLPFC treatment (five daily sessions). In summary, although serious events are rare, a history of epilepsy and other risk factors should be strictly ruled out before administering aTMS, and protocols should be individualized based on the patient's specific condition.

6. Discussion

This review systematically summarizes the progress in the application of aTMS in MDD with suicidal ideation. Overall, aTMS (especially the SAINT protocol) is effective in rapidly reducing suicidality and depressive symptoms, and its short-term safety is good. However, several aspects deserve in-depth discussion.

6.1. Clinical Heterogeneity of Stimulation Parameters in aTMS

The rapid-onset advantage of aTMS has been validated in multiple studies. For

example, the SAINT protocol achieved a remission rate of 65.1% in treatment-resistant depression within 5 days, with a mean time to onset of only 2.3 days, demonstrating a time-efficacy superiority far beyond traditional rTMS (Cole et al., 2022; Zhao et al., 2024). Nevertheless, existing studies show considerable heterogeneity in stimulation parameters, including number of sessions per day (2 - 10/day), inter-train interval (e.g., 50 min vs. shorter intervals), total number of pulses, and treatment duration (3 - 5 days). This heterogeneity, on the one hand, reflects the flexibility and broad exploratory space of aTMS protocols; on the other hand, it limits cross-study comparisons and clinical translation. Although the SAINT protocol has superior efficacy, its reliance on high-precision equipment and individual functional MRI makes it difficult to implement in resource-limited clinical settings. Relatively simplified high-frequency rTMS protocols (e.g., 2 - 3 sessions/day) can also rapidly reduce suicidal ideation, but with lower remission rates. This difference suggests that the dose-response relationship and the heterosynaptic plasticity effects dependent on inter-train intervals have not been fully optimized (Thomson & Sack, 2020), and most studies lack sham control and long-term follow-up, limiting conclusions on durability of efficacy and placebo effects.

6.2. Separation of Neural Pathways for Anti-Suicidal and Antidepressant Effects

Recent evidence suggests that the neural pathways through which aTMS reduces suicidal ideation may differ from those underlying its antidepressant effect. Li et al. (2024) reported that the anti-suicidal effect is associated with functional connectivity changes in the insula-hippocampus pathway, whereas the antidepressant effect is associated with the sgACC circuit. This separation indicates that the two effects are mechanistically distinguishable—the anti-suicidal effect is mainly mediated by the insula-hippocampus pathway (interoception and emotional integration), while the antidepressant effect primarily relies on the prefrontal-limbic sgACC circuit. This separation has important clinical implications: targeting only the left DLPFC-sgACC network (as most protocols do) may not be the optimal strategy for intervening in suicidal ideation. Future mechanistic studies should combine multimodal neuroimaging (e.g., simultaneous TMS-fMRI, PET) to parse the above pathways and identify optimal targets specific to suicidal ideation. Monitoring electroencephalogram (EEG) at baseline and after treatment as an important predictor of treatment response suggests, at multiple levels (frequency domain features, hemispheric asymmetry, functional connectivity, and microstates), that EEG analysis holds promise for providing objective information for suicide risk assessment. Studies have indicated that neurochemical and neurophysiological changes during depression treatment often precede subjective symptom improvement (Zhao et al., 2025). By comparing EEG characteristics before and after intervention in depressed patients, potential neurophysiological indicators related to treatment response and symptom improvement can be identified, offering important clues for exploring objective biomarkers of

depression. Therefore, future mechanistic research should integrate multimodal brain imaging and electrophysiological techniques to deeply dissect the differential neural circuits underlying anti-suicidal and antidepressant effects and to identify the optimal regulatory targets for suicidal ideation.

6.3. Evolution of Target Localization Techniques

Current target localization methods range from scalp landmarks to fMRI functional connectivity. Traditional rTMS mostly uses fixed anatomical localization of the left DLPFC (e.g., the 5-cm rule or Beam F3 system), which is simple to operate and easy to popularize, but 30% - 70% of patients do not have their actual stimulation site precisely targeting the intended brain region. With the development of imaging techniques, individual functional connectivity localization based on resting-state fMRI (such as the negative functional connectivity between DLPFC and sgACC in the SAINT protocol) has significantly improved clinical remission rates, representing a major advance from “anatomical standard” to “functional network” targeting. However, this technique still faces multiple challenges: limited stability of resting-state fMRI, low signal-to-noise ratio of sgACC due to magnetic susceptibility artifacts, and considerable variability in data preprocessing pipelines across studies, which may lead to inconsistent efficacy across centers. Although task-state fMRI and multimodal image fusion have theoretical advantages, they are complicated to operate, lack standardized protocols, and remain at the stage of scientific exploration. Therefore, there is an urgent need to develop standardized, reproducible, and cost-effective targeted workflows that balance precision with clinical feasibility.

6.4. Evidence Gaps in Safety Considerations

Based on existing literature, aTMS is generally well-tolerated, with common adverse reactions being mild headache and tinnitus that are mostly self-limiting. Multiple large-sample studies and studies in elderly patients have reported no serious adverse events, providing preliminary safety evidence for clinical dissemination of aTMS. However, rare serious adverse events (one generalized seizure and one severe depersonalization) (Geerts et al., 2015; Kallel & Brunelin, 2020) remind us that strict pre-screening (e.g., excluding history of epilepsy) and individualized protocol selection are crucial. More importantly, current safety data are mainly derived from adult populations; evidence in adolescents, the elderly, pregnant women, and patients with comorbid neurological diseases is extremely limited. The neuroplasticity, tolerability, and adverse reaction profiles of these special populations may differ from those of adults. Future studies should systematically evaluate the safety of aTMS across different ages and disease conditions and establish corresponding clinical guidelines.

6.5. Methodological Limitations

Overall, current research in the aTMS field provides important preliminary evidence

for MDD with suicidal ideation, particularly showing unique advantages in rapid onset. However, several methodological limitations still constrain the level of evidence: small sample sizes, lack of sham control, short follow-up periods (mostly ≤ 4 weeks), and lack of maintenance treatment protocols. No studies have directly compared the long-term efficacy of aTMS with electroconvulsive therapy or ketamine (the current gold standard for rapidly reducing suicide risk), and there are few pragmatic trials with long follow-up (≥ 6 months) or head-to-head comparisons.

7. Conclusion and Future Perspectives

aTMS has considerable potential for rapidly reducing suicide risk in MDD patients with suicidal ideation, with the SAINT protocol showing particularly outstanding efficacy. However, this field is still in the exploratory stage and faces the following key issues: 1) The neural mechanisms underlying the rapid reduction of suicidal ideation by aTMS have not been fully elucidated; 2) Optimal accelerated parameters (daily frequency, inter-train interval, total pulses, course duration) have not been unified, and large-sample, multi-center, randomized sham-controlled trials are urgently needed; 3) Evidence for aTMS application in special populations such as adolescents, the elderly, and pregnant women is extremely limited; 4) Most current studies use only scale-based assessments, which carry some subjectivity. Future research can combine scale-based assessments with objective assessment methods such as EEG for multi-level and multi-dimensional evaluation. Therefore, future studies should focus on large-scale multi-center randomized controlled trials, integrate electrophysiology and brain imaging modalities, deeply dissect the differential mechanisms of anti-suicidal and antidepressant effects at the neural circuit level, and explore individualized rapid intervention clinical pathways based on precision assessment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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