EPP001

A randomised, single-blind, sham-controlled clinical trial on the effects of intermittent Theta-Burst Stimulation (iTBS) on depressive and cognitive symptoms in patients with Treatment-Resistant Depression

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Introduction

Major Depressive Disorder (MDD) is a severe psychiatric condition characterised by persistent low mood, anhedonia, cognitive impairment, and social cognition (S-Cog) deficits, all of which impair quality of life and functional recovery[1]. Up to 50% of patients develop Treatment-Resistant Depression (TRD), for which effective therapeutic options remain limited[2].

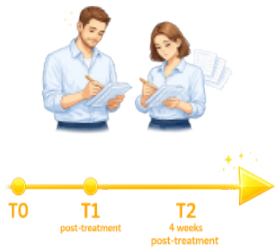
In recent years, growing attention has focused on social cognition alterations in patients with MDD. Social cognition includes the mental processes involved in perceiving, interpreting, and responding to social stimuli, such as emotion recognition, theory of mind, empathy, and interpersonal biases. Evidence suggests that, beyond classical affective and cognitive symptoms, patients with MDD also exhibit sociocognitive impairments that may contribute to both disorder maintenance and functional impairment[1]. In particular, performance on social cognitive tasks appears to be inversely associated with depression severity, while an increased propensity toward negative emotions may persist even during remission[3].

Transcranial magnetic stimulation (TMS) has emerged as a promising treatment for treatment-resistant depression (TRD). Among TMS protocols, intermittent theta-burst stimulation (iTBS) is of particular interest due to its capacity to enhance neuroplasticity and induce long-term potentiation–like effects, while significantly reducing session duration compared with conventional TMS paradigms, thereby improving clinical feasibility and tolerability[4].

This study aims to evaluate the efficacy of an iTBS protocol in improving depressive symptoms and S-Cog deficits in patients with TRD.

Table 1. Evaluated Domains and Assessment tools.

Evaluated Domains	Assessment tools
Depression	HDRS-21; BDI-II
Psychopatology	SCL-90
Functioning	WHODAS 2.0
Quality of Life	SF-36
Neurocognition	BAC-A
Social Cognition (S-Cog)	Reading the Mind in the Eyes Test; Ekman Test; Faux Pas Test



Methods

Forty patients with Treatment-Resistant Depression (TRD) will be recruited and randomised to receive either active intermittent Theta-Burst Stimulation (iTBS) targeting the left dorsolateral prefrontal cortex (lDLPFC) or sham stimulation. Patients will undergo comprehensive socio-demographic, clinical, neurocognitive and social-cognitive, and functioning assessments at baseline (T0), post-treatment (T1), and 4 weeks post-treatment (T2). Evaluated Domains and Assessment tools are presented in Table 1.

The neurostimulation protocol is consistent with FDA-approved guidelines for TRD. Specifically, patients with TRD will undergo 20 iTBS sessions over 4 weeks (5 days/week). The iTBS pattern will consist of bursts of three pulses at 50 Hz, repeated at 5 Hz, delivered in 2-second trains followed by 8-second inter-train intervals, for a total of 600 pulses per session [4].

Forty healthy controls (HC) will also be recruited and will complete clinical and cognitive/social-cognitive assessments at T0 only. Data from HC will be used as a benchmark to interpret the effects of active and sham iTBS in patients.

Primary outcome:
≥50% reduction in depressive symptoms and ≥30% improvement in social cognition (S-Cog), calculated as the percentage change in mean scores between T0 and T1 on validated measures of depression and S-Cog.

Secondary outcomes:
i) Maintenance of clinical and S-Cog improvements at T2.
ii) Changes from pre- to post-treatment in functioning, quality of life, and other cognitive domains.

Results

The study is currently in the recruitment phase. Ethical approval and protocol standardization have been completed.

Data will be analyzed to assess changes in clinical and functional outcomes.

Conclusions

- We expect an inverse association between depressive symptom severity and social cognition at baseline (T0).
- We hypothesise greater T0–T1 improvement in primary and secondary outcome measures in the active iTBS group compared with sham.

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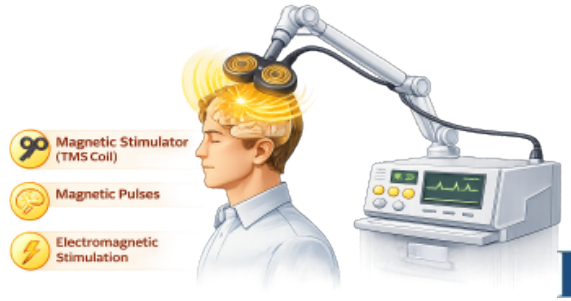
Transcranial Magnetic Stimulation (TMS)



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