Antidepressant and Anti-anxiosomatic Effect of Prolonged Intermittent Theta-Burst Stimulation Monotherapy for Medication and Conventional TMS-Resistant Major Depression: A Three-Arm, Randomized, Double-Blind, Sham-controlled Study

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Background
A growing evidence supported that dorsomedial prefrontal cortex (DMPFC) plays a pivotal role not only in depression but anxiosomatic symptoms modulation. Until now, there was no study to investigate the antidepressant and anti-anxiosomatic effect of prolonged intermittent theta-burst stimulation (piTBS) over bilateral DMPFC. In addition, head-to-head comparison between standard iTBS and piTBS for clinical efficacy remains elusive.

Aims & Objectives
To investigate the antidepressant and anti-anxiosomatic efficacy of piTBS over bilateral DMPFC.

Methods
This double-blind, randomized, sham-controlled trial recruited 34 patients with highly treatment-resistant depression(TRD) unresponsive to antidepressants and standard repetitive transcranial magnetic stimulation(rTMS). They were randomly assigned to one of three monotherapy groups (standard iTBS, piTBS and sham) to receive twice-daily bilateral DMPFC stimulation for three weeks. Sham coil was used in this trial. Hamilton Depression Rating Scale (HDRS-17), Depression and Somatic Symptoms Scale (DSSS), and anxiosomatic cluster symptoms derived by HDRS-17 were evaluated at a baseline, week-1, week-2 and week-3. Multivariable generalized estimating equations analysis was performed.

Results
PiTBS group demonstrated better antidepressant efficacy rated by subjective DSSS scales than standard-iTBS and sham (post-hoc, piTBS v.s. standard iTBS, p=0.002; piTBS v.s. sham, p=0.038). PiTBS also exhibited more decreases in anxiosomatic symptoms rated by HDRS-17 than standard iTBS (p=0.001), but no difference of overall HDRS-17 score changes compared with standard iTBS. Mild suicidality could have better antidepressant efficacy than moderate to severe suicidality.

Discussion & Conclusion
This first randomized, double-blind sham-controlled trial for piTBS over bilateral DMPFC demonstrated a pilot evidence of anti-anxiosomatic and antidepressant efficacy in highly refractory depressed patients. This circuit-based neuromodulation may be more suitable for those depressed patients with highly anxiosomatic symptoms.