Different but Shared Molecular Mechanisms Underlying 10-Hz Repetitive Transcranial Magnetic Stimulation and Intermittent Theta Burst Stimulation over Left Prefrontal Cortex for Treatment-Resistant Depression: A Randomized Sham-Controlled Trial

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Background
10-Hz repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex (DLPFC) and intermittent theta burst stimulation (iTBS) over left DLPFC are effective antidepressant options for treatment-resistant depresion. However, the exact molecular mechanisms remain elusive.

Aims & Objectives
We aimed to investigate molecular mechanisms underlying rTMS and iTBS over left DLPFC by combining prefrontal TMS-evoked potentials (TMS-EEG) and whole-brain glucose metabolisms by 18F-FDG PET.

Methods
Cortical TMS-evoked potential markers from left DLPFC were measured at baseline and repeated immediately after 1st session of left PFC 10-Hz rTMS (n=18; 120% resting MT, 3000 pulses), iTBS (16; 80% active MT, 1800 pulses), and sham (14; rTMS or iTBSrandomly assigned, using a sham coil). Whole-brain glucose metabolisms were measured at baseline (n=40). The entire treatment was 20 sessions.

Results
A single session of rTMS simultaneously modulated P60 [mainly glutamate receptor (GluR)-mediated excitation] and N100 [mainly GABA-b receptor (GbR)-mediated inhibition] at left DLPFC. Repeated-measure ANCOVA analysis revealed a significant group effect (G) on LICI ($p<0.05$; post-hoc: iTBS<rTMS<sham), indicating a lower LICI in the iTBS group. Correlation tests showed that N100 decreases to a single session of iTBS at baseline significantly correlated with antidepressant effects after 20 sessions of iTBS ($r=-0.622$, $p=0.008$), and a trend finding was also found for rTMS. Antidepressant effects of active brain stimulation, especially iTBS, correlated with baseline N100 changes to a single session of brain stimulation. Correlations between certain neurophysiological markers (i.e., left DLPFC N100, P60, and N45) and metabolisms of the default mode network (DMN, the main finding was posterior cingulate cortex) were noted (FWE-corrected $p<0.001$).

Discussion & Conclusion
The first study showed different but shared molecular mechanisms underlying iTBS and rTMS. A single session of rTMS modulated glutamate receptor-mediated excitation (P60) and GABA-b receptor-mediated inhibition (N100), but only the N100 changes slightly correlated with final antidepressant effects of an adequate rTMS trial. By contrast, iTBS seems to modulate LICI and the suppression of GABA-b receptor-related N100 at baseline. The shared mechanisms of left PFC rTMS/iTBS may converge on modulating GABA-B function in the DMN.