Modulation of Neuroplasticity and Cortical Excitability in Patients with Treatment Resistant Depression

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Methodological Question Being Addressed: Cortical inhibitory mechanisms, especially associated with the dysregulation of the gamma amino butyric acid (GABA)-ergic system, has been purported to play a role in the pathophysiology of major depressive disorder (MDD). This study aimed at assessing cortical excitability and plasticity associated with treatment resistant depression (TRD), using transcranial magnetic stimulation (TMS) combined with motor evoked potential (MEP) and electroencephalographic (EEG) recordings.

Introduction: TMS is a noninvasive tool for investigating cortical inhibitory mechanisms associated with GABAergic neurotransmission. Using the paired-pulse TMS paradigm, short interval intracortical inhibition (SICI, a $GABA_A$-dependent process) and intracortical facilitation (ICF, a glutamate dependent process) can be assessed. Studies investigating SICI and ICF suggest that there is a decreased SICI for MDD patients compared to healthy subjects, while no difference in ICF was observed. Little is known about cortical excitability and plasticity in treatment resistant depression.

Methods: The study was approved by the Duke University School of Medicine Institutional Review Board. Ten depressed patients (7 female) and nine age-matched healthy volunteers (5 female) enrolled. Depressed patients must meet Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition diagnostic criteria for MDD, without psychotic features, and must have had an inadequate response to at least two antidepressants, one of which is in the current episode of depression. Subjects must have an Inventory of Depressive Symptomatology 30-item Clinician-rated (IDS-C30) total score ≥ 34. The cortical excitability and plasticity assessment battery consists of: 1) Determination of resting motor threshold (RMT), defined as the lowest TMS intensity required to produce MEPs of >50 μV in at least 5 out of 10 consecutive stimuli using a figure-of-eight coil over the optimal hotspot in the left primary motor cortex; 2) Resting-state EEG recording with eyes open for 5 minutes; 3) Somatosensory evoked potential (SEP), in which EEG was recorded while subject receives electrical stimulation of the right median nerve an intensity of three times sensory threshold; 4) Paired-pulse TMS, in which a conditioning subthreshold stimulus (90% RMT) was delivered followed by a test suprathreshold stimulus (130% RMT) as interstimulus intervals (ISI) of 2, 3, 15, and 25 ms; 5) simultaneous TMS-EEG, in which TMS was delivered to the dorsal lateral prefrontal cortex (F3).

Results: Resting EEG showed a significant suppression of alpha band power for the TRD group relative to controls at the parietal and occipital sites ($p < .05$), but not as the frontal cortex. The SEP recorded at CP3 (referenced to CP4) showed a suppression of the P30 component for TRD

relative to healthy controls ($p < .05$). For paired-pulse TMS, there was a significant group-by-ISI interaction effect ($p < .05$); of interest, at 25 ms ISI, there was a significant reduction in MEP amplitude for the TRD group compared to controls ($p < .05$), which indicates a lack of ICF. The TMS-evoked potentials recorded at FCz (average reference) showed an elevation of the P30 component for TRD relative to controls ($p < .05$). Finally, no difference in motor threshold was observed between TRD and controls.

Conclusions:
Overall, TRD patients showed a general downregulation of cortical excitability in our battery of assessments. Although the direct neuronal underpinnings behind this phenomenon are unknown, it is likely that the suppression of response seen in TRD patients is related to deficiencies in plasticity mechanisms.

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