STOP-TIC: Strengthening Tourette Treatment Options using TMS to Improve CBIT

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Introduction
TS symptoms persist in 20% of adults and can significantly impact the quality-of-life. Pharmacologic therapies have side effects, and surgical treatments are invasive. CBIT is an effective therapy for TS; however, it may only result in a 40% tic reduction in adult patients. Therefore, there is a critical need to develop more effective treatments for TS.

Hyperactivity of the SMA has been implicated in the pathophysiology of TS. Previous studies have shown successful tic reduction with low-frequency rTMS targeted to the SMA, inhibiting cortical excitability. Recent studies involving stroke and Parkinson's disease indicated that priming of brain networks with rTMS could augment motor and cognitive learning. We, therefore, propose to use rTMS with SMA and then employ CBIT in patients with adult TS to increase the net benefits. The central hypothesis is that low frequency (LF)- rTMS will augment the effects of CBIT through favorable priming of the SMA network.

Study Design
Adult patients diagnosed with TS who are on stable concurrent medication regimens will be randomly assigned to active or sham stimulation. The neuromodulation protocol will comprise 1 Hz rTMS targeted to the SMA at 110% of the resting motor threshold. Each session will consist of 6 trains lasting 5 minutes each with an intertrain interval of 1 minute for a total duration of 35 minutes (1800 pulses). Participants will receive four sessions in a row over four consecutive days for a total of 16 sessions. Following rTMS, patients will undergo eight 1-hour CBIT sessions over ten weeks via telemedicine. IRB approval has been obtained and we are currently open for enrollment.

Primary Outcome: Yale Global Tic Severity Scale (YGTSS)
Secondary Outcomes:
- modified Brown Obsessive-Compulsive Inventory (mBOC)
- Beck Depression Inventory (BDI)
- Yale Anxiety Inventory (YAI)
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)
- Adult ADHD Self-Report Scale (ASRS)
- Gilles de la Tourette Syndrome – Quality of Life scale (GTS-QOL)

Neurophysiological Outcomes:
- Motor Evoked Potential
- Cortical Silent Period
- Short Interval Intracortical Inhibition
- High-Density EEG
- Functional MRI

Discussion
The novelty of our protocol is three-fold. First, we will be using rTMS to prime CBIT therapy. Small studies have shown rTMS to reduce tics; however, using rTMS in conjunction with CBIT effectively is an innovative treatment approach that may benefit patients with TS even further than either treatment alone. Second, we have been very thoughtful about the logistical constraints that rTMS and CBIT may generate, especially during a pandemic. Accelerated rTMS protocols that condense multiple weeks of treatments into a few consecutive days are safe and well-tolerated in other patient populations but have not yet been studied in patients with TS. We have adapted an LF-rTMS protocol delivered over three weeks that successfully reduced tics to be completed within four consecutive days. Given the similar efficacy of tele-CBIT to in-person CBIT, we will employ ten weeks of tele-CBIT. Both of these innovative approaches should improve feasibility and retention. Third, our outcome measures investigate both clinical changes as well as corresponding physiological changes. The benefit of measuring outcomes at three timepoints allows us to directly compare active and sham neurostimulation alone and compare the cumulative effects of active and sham stimulation followed by CBIT therapy.

References
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