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BRIEF COMMUNICATION

Intermittent theta-burst transcranial magnetic stimulation for autism spectrum disorder: an open-label pilot study

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Objective: Theta-burst stimulation (TBS) modulates synaptic plasticity more efficiently than standard repetitive transcranial magnetic stimulation delivery and may be a promising modality for neuropsychiatric disorders such as autism spectrum disorder (ASD). At present there are few effective interventions for prefrontal cortex dysfunction in ASD. We report on an open-label, pilot study of intermittent TBS (iTBS) to target executive function deficits and restricted, repetitive behaviors in male children and adolescents with ASD.
Methods: Ten right-handed, male participants, aged 9-17 years with ASD were enrolled in an open-label trial of iTBS treatment. Fifteen sessions of neuronavigated iTBS at 100% motor threshold targeting the right dorsolateral prefrontal cortex were delivered over 3 weeks.
Results: Parent report scores on the Repetitive Behavior Scale Revised and the Yale-Brown Obsessive Compulsive Scale demonstrated improvements with iTBS treatment. Participants demonstrated improvements in perseverative errors on the Wisconsin Card Sorting Test and total time for the Stroop test. The iTBS treatments were well tolerated with no serious adverse effects.
Conclusion: These preliminary results suggest that further controlled interventional studies of iTBS for ASD are warranted.

Keywords: Autism spectrum disorder; intermittent theta burst stimulation; noninvasive brain stimulation; theta-burst stimulation; repetitive transcranial magnetic stimulation

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with impairments in language acquisition, social functioning, motor skill abnormalities, restricted and repetitive behaviors, and executive functioning deficits. Despite considerable prior research efforts, there is a dearth of treatment options for the core features of ASD.[1] Studies with pharmacologic agents have had disappointing results and often demonstrate an unacceptable side effect burden with long-term use.[2] Effective, brain-based interventions for the core symptoms of ASD are lacking.[1]

Noninvasive brain stimulation interventions such as repetitive transcranial magnetic stimulation have increasingly been considered in the treatment of ASD.[3] Protocols with theta burst stimulation (TBS) exert a more rapid effect on neuroplasticity, compared to standard rTMS protocols. During TBS sessions, a series of three magnetic pulses are delivered at 50 Hz with 200 ms intervals (5 Hz). Intermittent TBS (iTBS) sessions deliver 2 second trains with 30 pulses every 10 seconds for 190 seconds for a total of 600 pulses. In general, iTBS is purported to facilitate cortical excitability and promote long-term potentiation-like effects.[4] Prior neurophysiological work suggests that adolescent and young adult patients with ASD have right hemispheric impairments in long-term potentiation-like plasticity.[5] Patients with ASD and obsessive-compulsive disorder often have shared clinical and neurophysiological features including deficits in cortical inhibition.[6,7] Herein we report on an open-label trial examining the feasibility, tolerability, and clinical effects of iTBS treatment in child and adolescent participants with ASD. A variety of rTMS and TBS treatment targets have been considered previously.[8] We elected to stimulate the right dorsolateral prefrontal cortex with the goal of targeting impairments in cortical inhibition and long-term potentiation-like plasticity.[5-7]

Methods

Study design

The ethics board at the Universidade de São Paulo, Brazil, approved the protocol and study procedures. During a screening visit, participants underwent a clinical assessment and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) was administered.[9] Diagnostic criteria for ASD were confirmed by three child and adolescent psychiatrists (CA, BBB, and HB). Age of language onset and psychotropic medication use were noted at this screening visit. During a baseline visit, participants completed a Wechsler Intelligence Scale for Children, 3rd ed. (WISC-III)[10] and underwent a brain magnetic resonance imaging (MRI) scan and an electroencephalography (EEG). Baseline parent report measures

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Table 1 Summary of outcome findings

	Baseline (n=10)	Posttreatment (n=10)	3-month follow-up (n=5)	Baseline and Posttreatment difference
RBS-R	27.40 (16.48)	13.30 (11.77)	12.20 (2.86)	t = 3.75, df = 9, p = 0.005, Cohen's d = 0.98
YBOCS	11.80 (6.07)	8.50 (5.38)	6.60 (6.84)	t = 2.70, df = 9, p = 0.02, Cohen's d = 0.54
WSCT	0.30 (0.19)	0.23 (0.21)	0.15 (0.12)	Wilcoxon signed rank test, p = 0.02, Cohen's d = 0.35
Stroop (seconds)	97.30 (26.53)	17.33 (12.25)	78.67 (26.41)	t = 4.47, df = 9, p = 0.002, Cohen's d = 0.72

Data presented as mean (standard deviation).
df = degrees of freedom; RBS-R = Repetitive Behavior Scale Revised; YBOCS = Yale Brown Obsessive Compulsive Scale, Compulsion Subscale. Perseverative Errors on the Wisconsin Card Sorting Test (WSCT) and the Stroop test (total time for completion).

included the Repetitive Behavior Scale Revised (RBS-R)[11] and the Yale-Brown Obsessive Compulsive Scale (YBOCS).[12] The Wisconsin Card Sorting Test (WSCT)[13] and the Stroop test[14] were administered on the first day of iTBS treatment immediately before the session. All outcome measures (RBS-R, YBOCS, WSCT, and Stroop test) were then repeated on the last day of iTBS treatment after the session and at a 3-month follow-up visit.

Participants

Ten male, right-handed, participants (ages 9-17) with ASD and impairing restricted and repetitive behaviors were recruited from the outpatient clinic at Instituto de Psiquiatria, Universidade de São Paulo. All participants had an intelligence quotient of 50 or greater on the WISC-III. Participants with any abnormalities on a brain MRI scan or EEG were excluded. Participants with unstable medical conditions or risk factors for seizure were also excluded.

iTBS intervention

Fifteen sessions of iTBS were delivered 5 days a week for 3 weeks. The right dorsolateral prefrontal cortex was located with neuronavigation (Vector Vision Brain LAB) on the first day of stimulation. Stimulations were performed with a Dantec MagPro2 stimulator (Medtronic, Minneapolis, MN, USA) and Neuro-MS Net Software (Neurosoft, Ivanovo, Russia). The iTBS sessions were delivered to the right dorsolateral prefrontal cortex over 300 seconds. Stimulation intensity was 100% of motor threshold with three pulses of 50 Hz bursts delivered at 5 Hz in 30 trains of 10 bursts with 8 seconds on and 2 seconds off.

Statistical analysis

The primary aims of the study were to examine clinical outcomes (RBS-R, YBOCS, WCST, Stroop test) after 15 sessions of iTBS and at a 3-month follow-up visit. Secondary aims considered feasibility based on participants' ability to adhere to the iTBS protocol and tolerability based on patient and family reports. Data were expressed as means and standard deviations. Distributions for each outcome measure were assessed for normality with the Shapiro-Wilk test. The RBS-R, YBOCS, and Stroop data demonstrated normal distributions and paired t-tests of outcomes were performed with SPSS. The WCST data did not have a normal distribution and a nonparametric (Wilcoxon signed rank) test was used.

Results

Outcome results are summarized in Table 1. Three-month follow-up data were available in five participants and are presented descriptively. Mean RBS-R scores demonstrated significant improvement from baseline to posttreatment (t = 3.75, degrees of freedom [df] = 9, p = 0.005, Cohen's d = 0.98). After iTBS treatments, the parent-report YBOCS revealed improvement in mean overall compulsion subscale scores (t = 2.70, df = 9, p = 0.02, Cohen's d = 0.54). Participants demonstrated enhanced performance on WCST with improvement in perseverative errors (Wilcoxon Signed Rank Test, p = 0.02, Cohen's d = 0.35) after iTBS treatment. Notably, there were no errors in Stroop test at baseline. However, total time for completion improved after treatment (t = 4.47, df = 9, p = 0.002, Cohen's d = 0.72). Participants tolerated the iTBS protocol with no significant side effects. There were no seizures during treatment sessions. All 10 participants completed the treatment protocol.

Discussion

This exploratory, open-label trial of iTBS in male children and adolescents with ASD examined clinical outcomes, feasibility, and tolerability of 15 sessions applied to the right dorsolateral prefrontal cortex with neuronavigated coil location. Treatment with iTBS appeared to improve restricted, repetitive behaviors, compulsions, and neurocognitive functioning. These preliminary findings suggest that iTBS may be a promising, brain-based intervention for the core symptoms of ASD. However, any interpretation must be placed in the context of substantial limitations. The study had an open-label design with a small sample size and did not examine neurophysiological correlates. Prior work suggests that interventional trials in ASD are particularly disposed to a large placebo response, thereby presenting challenges to interpretation of data in open-label studies and executing randomized, controlled trials with ASD samples.[15] This problem underscores the necessity of future objective, measurement-based approaches with target-engagement strategies. Feasibility and tolerability considerations are promising as our experience suggests that youth with ASD tolerated iTBS and were adherent to treatment. The present data will inform future biomarker-guided, controlled trials of iTBS for ASD.

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Disclosure

The authors report no conflicts of interest.

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