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Transcranial Magnetic Stimulation for Adolescent Depression (TMSAD)

INTRODUCTION

Treatment options for major depressive disorder (MDD) in youth are limited, with concerns over efficacy (Carvalho et al., 2007) and safety (Adegbite-Adeniyi et al., 2012; Menke et al., 2012; Cipriani et al., 2016). Evidence suggests 30-50% of adolescents and young adults with MDD are treatment-resistant, leading to lifelong consequences (Fava, 2003). Consequently, new interventions for treatment-resistant MDD in youth are needed (Souery et al., 2011). One potential treatment is repetitive transcranial magnetic stimulation (rTMS)(MacMaster et al., 2016). Prior research demonstrates that rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) in adults is well-tolerated, safe, and effective for MDD (George, 2010; Lefaucheur et al., 2014; Leggett et al., 2015; Milev et al., 2016; McClintock et al., 2017). Prior studies (case series and reports) of rTMS in MDD patients below the age of 22 are limited but encouraging, but substantial knowledge gaps remain (Donaldson et al., 2014).

OBJECTIVE

With this in mind, we conducted a trial of LDLPFC rTMS in youth with treatment resistant MDD. We hypothesized that rTMS would reduce depressive symptom severity in youth with MDD.

DESIGN

Open label trial of TMS.

METHODS

This study was approved by the Conjoint Health Research Ethics Board (CHREB) for the University of Calgary.

Participants

Participants were recruited from the community and clinics in our area. Inclusion criteria were: (1) age 12-22 years, (2) diagnosis of MDD, based on an interview with the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL)(Kaufman et al., 1997) with a symptom severity of 40 or greater on the Children's Depression Rating Scale Revised (CDRS-R)(Poznanski et al., 1985), (3) history of failing to respond to at least one selective serotonin reuptake inhibitors (SSRI) trial (minimum 8-week treatment at an adequate dose; retrospectively determined on interview), and (4) ability to provide informed consent. Psychotropic medications were allowed if the dose has been stable for six weeks with adequate compliance, and with a commitment to not change

medication/dosage during the trial period, unless deemed medically necessary. Exclusion criteria included: (1) previous seizures or epilepsy, (2) hypertension, (3) previous neurological or psychiatric diagnoses (specifically - bipolar disorder or psychosis) (4) pregnancy, (5) implanted metal or medical device, or (6) left-handedness.

Assessments

Participants were assessed at baseline, weekly during rTMS, and at the completion of treatment. Core clinical assessments were designed to confirm diagnosis (baseline), define symptoms, and assess treatment response. The K-SADS-PL (Kaufman et al., 1997), was used to assess both present and lifetime psychiatric symptomatology. The CDRS-R (Poznanski et al., 1985) was administered at baseline and treatment completion to quantify moderate to severe depressive symptom severity in participants. The Hamilton Depression Rating Scale (Ham-D)(Hamilton, 1967) and Beck Depression Inventory (BDI)(Beck et al., 1997), were used to assess depressive symptoms at baseline, the end of each week for safety monitoring, and after treatment completion. The Hamilton Anxiety Rating Scale (Ham-A)(Hamilton, 1959), to assess anxiety levels, was also administered at baseline and after treatment completion. We endeavored to complete assessments within two weeks of initiation and termination of rTMS.

The primary outcome measure of treatment response was defined as a greater than 50% reduction in Ham-D scores from baseline to end-point. A secondary exploratory measure of clinically meaningful response was also preset at 30% based on American College of Neuropsychopharmacology (ACNP) recommendations (Rush et al., 2006). We also examined predefined criteria for remission (Ham-D score ≤ 7 post-rTMS) and partial remission (Ham-D score ≤ 10 post-rTMS and a $\geq 50\%$ reduction in Ham-D score).

rTMS

TMS was performed at the Alberta Children's Hospital. The TMS intervention utilized a Magstim SuperRapid2, air-cooled 90mm figure-of-8-coil (Magstim, Wales UK). Using a neuronavigation system (Brainsight2, Rogue Research, Montreal), the TMS coil was monitored in real time and co-registered with the individual's structural MRI. Imaging was performed on a 3T GE MR750w scanner using a 24-channel head coil. Anatomical scan parameters were: Axial T1-w 3D BRAVO with TR = 8204 milliseconds, TE = 3.168 milliseconds, flip angle = 10 degrees, 226 slices with 0.8 mm thickness, 300 x 300 matrix.

On the first day, motor evoked potentials (MEP) were recorded to determine the resting motor threshold (RMT) in the standard manner (Kirton et al., 2010). To initially locate the DLPFC target site, the 5-cm rule was applied, in which the scalp position 5cm anterior to the hotspot along a line to the nasion was marked (George et al., 1995; George et al., 1996; Herwig et al., 2001; Herwig et al., 2003). Neuronavigation confirmed accurate DLPFC (adjusted if needed) targeting. The TMS coil was subsequently placed tangential to the scalp, and angled at 45 degrees to the midline and fixed over the target using a mechanical arm. The target was marked on the neuronavigation system, allowing real time targeting and accurate session to session reliability.

rTMS was applied at 10 Hz. Each train consisted of 40 suprathreshold (120% RMT) pulses over 4 seconds with an inter-train interval of 26 seconds. Treatment sessions lasted 37.5 minutes (75 trains/3000 pulses), and occurred at the same time of day on every weekday for a period of three weeks (15 days total). During TMS, only passive activities were allowed (i.e., watching movies or TV, listening to music). Three weeks of treatment was selected based on existing rTMS evidence in adult MDD and our rTMS experience in pediatric stroke (Kirton et al., 2008; Davis, 2014). Participants were monitored for adverse events and tolerability using a Pediatric TMS Safety and Tolerability Measure (Garvey, 2005) on days 1, 6, and 11. Items were self-rated.

STATISTICAL CONSIDERATIONS

For the primary outcome, we hypothesized that rTMS would result in a significant reduction in depression symptom severity as measured by the Ham-D. We used a paired t-test comparing baseline to post-rTMS with $p < 0.005$. We increased the threshold in keeping with recommendations designed to improve reproducibility (Benjamin et al., 2017). For exploratory measures (i.e., CDRS, BDI, Ham-A) we used a paired t-test comparing baseline to post-rTMS with $p < 0.01$ to correct for multiple comparisons (Bonferroni). Analyses were performed with IBM SPSS (version 24; New York, USA).

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