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Research paper

High-frequency repetitive TMS for suicidal ideation in adolescents with depression

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ABSTRACT

Background: This exploratory study sought to examine the effect of an acute course of high-frequency repetitive TMS on suicidal ideation in adolescents.

Methods: Data were pooled from 3 prior protocols providing a 30-session course of open-label TMS treatment for adolescents with treatment-resistant depression. All participants (n = 19) were outpatients taking antidepressant medication, with TMS provided as adjunctive treatment. Suicidality was assessed at baseline, after 10 treatments, after 20 treatments, and after 30 treatments. Outcome measures of suicidal ideation included the Columbia Suicide Severity Rating Scale (C-SSRS) "Intensity of Ideation" subscale and Item 13 "Suicidality" on the Children's Depression Rating Scale, Revised (CDRS-R).

Results: The predicted odds of suicidal ideation (CDRS-R Item 13 and C-SSRS Intensity of Ideation subscale) significantly decreased over 6 weeks of acute TMS treatment without adjustments for illness (depression) severity. However, the magnitude of the decrease in the predicted odds of suicidal ideation across 6 weeks of treatment was attenuated and rendered non-significant in subsequent analyses that adjusted for illness (depression) severity.

Limitations: This was an exploratory study with a small sample size and no sham control. Regulatory and ethical barriers constrained enrollment of adolescents with severe suicidality.

***Conclusions*:** The present findings suggest that open-label TMS mitigated suicidal ideation in adolescents through the treatment and improvement of depressive symptom severity. Although caution is warranted in the interpretation of these results, the findings can inform the design and execution of future interventional trials targeting suicidal ideation in adolescents.

1. Introduction

Suicide is a leading cause of death in adolescents worldwide (Kessler et al., 2005; World Health Organization, 2014; National Center for Health Statistics, 2017). Epidemiologic studies suggest that nearly 20% of adolescents in the U.S. consider suicide, 15% have formulated plans for suicide, and nearly 10% attempt suicide annually (Cash and Bridge, 2009; Kann et al., 2016). Despite vigorous research efforts and the outlay of considerable resources, the rate of suicide attempts and completion continues to rise in the U.S. (National Center for Health Statistics, 2017; Olfson et al., 2017). Early life suicidality also envisages similar behaviors in adulthood (Cash and Bridge, 2009; Cox Lippard

ABBREVIATIONS: ATHF, Antidepressant treatment history form; CDRS-R, Children's depression rating scale, revised; CGI-S, Clinical global impression-severity scale; C-SSRS, Columbia suicide severity rating scale; DSM-IV-TR, *Diagnostic and statistical manual of mental disorders, fourth edition, text revision*; FDA, Food and drug administration; GEE, Generalized estimating equation; IQR, Interquartile range; K-SADS-PL, Schedule for affective disorders and Schizophrenia for school-age children-present and lifetime version; L-DLPFC, Left dorsolateral prefrontal cortex; MDD, Major depressive disorder; PCTL, percentile; TMS, Transcranial magnetic stimulation

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et al., 2014; Copeland et al., 2017). Adolescence is a period characterized by rapid brain changes with pruning of excitatory synapses and increased myelination throughout the frontal, temporal, and parietal regions to facilitate emotional regulation, impulse control, and executive functioning (Cox Lippard et al., 2014; Guyer et al., 2016; Lichenstein et al., 2016; Johnston et al., 2017). This neurodevelopmental window, defined as ages 12–21 years by the U.S. Food and Drug Administration (2003), is a period of great risk and opportunity (C. A. King et al., 2017).

Beyond prevention programs, risk assessments, crisis intervention, and psychotherapeutic treatments, there are essentially no standard, brain-based interventions for acute suicidal crises or chronic suicidality in adolescents (Brent et al., 2009; Zalsman et al., 2016; C. A. King et al., 2017; J. D. King et al., 2017). There is much interest in the potential anti-suicidal effects of electroconvulsive therapy (Fink et al., 2014), lithium (Roberts et al., 2017; Smith and Cipriani, 2017), clozapine (Bastiampillai et al., 2017), and ketamine (Grunebaum et al., 2017) in adult populations, but there are substantial knowledge gaps with respect to adolescents (Al Jurdi et al., 2015; Zalsman et al., 2016). These knowledge deficits highlight the challenges of studying adolescents with suicide attempts or ideation. Typically, adolescents who have recently attempted suicide are excluded from research protocols, which in turn circumscribes recruitment. Adequate sample sizes are challenging to recruit, and suicidal patients are frequently hospitalized, thereby creating confounds (King and Kramer, 2008; C. A. King et al., 2017). Antidepressant medications, while not a direct treatment for suicidality, are often part of a treatment plan for suicidal adolescents, as these are beneficial for related major depressive disorder (MDD). However, there is uncertainty regarding how antidepressant medications impact suicidal thinking and behaviors at the level of the individual patient (Cipriani et al., 2016). These challenges leave clinicians with few options to directly address suicidality in adolescent patients.

Recently, there has been interest in examining neuromodulation interventions such repetitive transcranial magnetic stimulation (TMS) for suicidal thinking in adults (George et al., 2014; Sun et al., 2016). Daily, repetitive, left prefrontal, high-frequency TMS is a standard, FDA-cleared treatment for MDD in adult patients (22 years of age or older; U.S. Food and Drug Administration, 2003) who have failed to improve with prior antidepressant treatment (O'Reardon et al., 2007; George et al., 2010). Treatment with TMS addresses corticolimbic inhibitory-excitatory imbalances related to depression. Suicidal thinking also likely involves disrupted emotional regulation and executive functions in corticolimbic circuitry (Lefaucheur et al., 2014). Within this context, researchers have recently examined the impact of accelerated high-frequency TMS (Baeken et al., 2014; George et al., 2014; Baeken et al., 2015; McGirr et al., 2015; Baeken et al., 2017) and novel TMS protocols such as theta burst stimulation (Williams et al., 2018) on treatment-resistant depression and suicidal ideation in adults. Accelerated protocols provide high-dose TMS, with multiple sessions per day over three to five days as opposed to daily treatments over four to six weeks (George et al., 2014; Baeken et al., 2017; Williams et al., 2018). Such approaches hold promise for severely ill patients needing more aggressive interventions with the potential for rapid improvement, such as those with high suicide risk.

Initial pilot studies suggest that daily, left prefrontal, high-frequency TMS may be a safe and effective intervention for treatment-resistant depression in adolescents (Bloch et al., 2008; Wall et al., 2011; Donaldson et al., 2014; Krishnan et al., 2015; Wall et al., 2016). A randomized, sham-controlled trial for MDD in adolescents is currently underway (Neuronetics, 2018). It is unknown if TMS treatment directly impacts suicidal thoughts in adolescents. Preliminary study could inform evolving research protocols and future clinical practice. This study aimed to examine changes in suicidality among adolescents undergoing an acute course of high-frequency TMS for the treatment of depression.

2. Methods

2.1. Participants

Data were pooled from 3 prior protocols providing 6 weeks of open-label TMS treatment for adolescents with treatment-resistant depression (Wall et al., 2011; Wall et al., 2016). All three studies were approved by the Mayo Clinic institutional review board and had approved FDA investigational device exemptions. Participants had all failed at least one prior trial of antidepressant medication based on Antidepressant Treatment History Form (ATHF) criteria (Sackeim, 2001). All participants (n = 19) were outpatients and were taking an antidepressant medication (either a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor) at a fixed and minimally effective dose as defined by ATHF criteria. Participants did not take antipsychotics, mood stabilizers, benzodiazepines, stimulants, tricyclic antidepressants, or bupropion during TMS treatment. Participants in psychotherapy had no change in the frequency of appointments or focus of therapy sessions in the 4 weeks preceding TMS or during the study. All participants had urine drug screens prior to TMS treatment. Female participants had urine pregnancy tests. Participants underwent a clinical interview and research assessment with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Co-occurring attention-deficit/hyperactivity, persistent depressive, and anxiety disorders were not exclusionary. Substance use, psychotic, bipolar, eating, somatic symptom, pervasive developmental, posttraumatic, and obsessive-compulsive disorders were exclusionary. Intellectual disabilities were also exclusionary. Notably, a suicide attempt in the preceding 6 months was an exclusion criterion. Investigational TMS was provided as adjunctive treatment to antidepressant medication.

2.2. Procedures

All participants underwent TMS treatment using the NeuroStar® Therapy System (Neuronetics, Inc., Malvern, PA, USA). The TMS sessions consisted of 10 Hz, 120% motor threshold treatment delivered to the left dorsolateral prefrontal cortex (L-DLPFC) in 4-second stimulus trains separated by 26-second intertrain intervals, with 3,000 magnetic pulses per session. Participants received 30 sessions over 6–8 weeks. Suicidality and depressive symptom severity were assessed at baseline, after 10 treatments, after 20 treatments, and after 30 treatments. In study 1 (n = 7) the TMS coil was moved 5 cm anterior to the area of motor cortex producing maximal *abductor pollicis brevis* contraction for treatment localization in the L-DLPFC (Wall et al., 2011). Studies 2 and 3 (n = 12) employed neuroanatomical magnetic resonance imaging guided coil targeting of the L-DLPFC for TMS treatment (Wall et al., 2016).

2.3. Outcome variables

We examined suicidal ideation as an outcome distinct from depression severity in view of both the clinical significance of suicidality and the fact that adolescents with a wide range of depression severity may experience suicidal thoughts. The primary outcome was suicidal ideation, which was measured over the six-week acute TMS treatment period using the single suicidal ideation item (Item 13) on the clinician-rated Children's Depression Rating Scale, Revised (CDRS-R; Poznanski et al., 1984). Clinicians rated participants' suicidal ideation at each visit using the CDRS-R Item 13, which is an ordinal scale ranging from 1 ("understands the word suicide but does not apply the term to himself/herself") to 7 ("has made a suicide attempt within the last month or is actively suicidal"). The Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) was used as a secondary outcome measure of suicidal ideation. The C-SSRS is a semi-structured clinician-rated interview created to assess severity of suicidal behavior and