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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

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Author contributions

Drs. Croarkin, Nakonezny, Deng, Doruk Camsari, and Lewis conceptualized and designed the study. Drs. Croarkin and Lewis acquired the data. Drs. Croarkin, Nakonenzy, Deng, and Lewis analyzed and interpreted the data. Drs. Croarkin, Nakonezny, Deng, Romanowicz, Vande Voort, Doruk Camari, Schak, Port, and Lewis drafted the manuscript, provided critical revisions, and rewrote the manuscript.

Trial registration

ClinicalTrials.gov identifier: NCT00587639

An Evaluation of Safety and Feasibility Using Repetitive Transcranial Magnetic Stimulation (rTMS) in Adolescents with Depression

https://clinicaltrials.gov/ct2/show/NCT00587639

ClinicalTrials.gov identifier: NCT01502033

Study of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed Teens

https://clinicaltrials.gov/ct2/show/NCT01502033

ClinicalTrials.gov identifier: NCT01804270

rTMS for Depressed Teens: A Sham-Controlled Trial, Part 1

https://clinicaltrials.gov/ct2/show/NCT01804270

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.

Keywords

Adolescent; Brain Stimulation; Depression; Suicidality; Suicidal Ideation; Transcranial magnetic stimulation

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 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 ideation for those aged 11 years and older

in community, clinical, and research settings (Brent et al., 2009; Posner et al., 2011). The present study utilized what is referred to as the C-SSRS "Intensity of Ideation" subscale (hereafter referred to as "C-SSRS"), in which 5 items (frequency of ideation, duration of ideation, controllability of ideation, deterrents, and reason for ideation) are each rated on 5-point ordinal scales and totaled (for a range of 0-25) (Posner et al., 2011). A score of 0 indicates that the participant did not endorse suicidal ideation in the rated period, and higher subscale scores reflect a greater intensity of suicidal ideation. The CDRS-R Item 13 and C-SSRS were evaluated at baseline and at two week intervals (weeks 2, 4, and 6) across the six weeks of acute TMS treatment. Both scales rated suicidal ideation occurring during the two weeks prior to each evaluation.

2.4 Covariates

Covariates were selected *a priori*. Age, sex, and illness severity have been identified as been idenfied as risk factors of suicidal behaviors in adolescents (Brent et al., 1994; Brent et al., 2009; Cash and Bridge, 2009; Asarnow et al., 2011); thus, these variables were included as covariates in the models to bolster precision in the evaluation of the change in suicidal ideation over the 6 weeks of acute TMS treatment. Depression severity was assessed using the total score of the clinician-rated CDRS-R, and illness (depression) severity was assessed using the clinician-rated Clinical Global Impression-Severity (CGI-S) scale, which consists of a 7-point ordinal scale ranging from 1 = normal, not at all ill to 7 = among the most extremely ill patients (Guy, 1976). The CDRS-R total and CGI-S scores were time-varying covariates measured at baseline and then at each subsequent TMS visit (weeks 2, 4, and 6) across the six-week acute study period.

2.5 Statistical analysis

Demographic and clinical characteristics of the 19 adolescents in the current study were described using the sample mean ± SD for continuous variables and frequency (percentage) for categorical variables. To examine the change in suicidal ideation (via CDRS-R Item 13) over the 6 weeks of acute TMS treatment, we evaluated three separate within-subjects models. First, an ordinal logistic (cumulative logit) regression model via a Generalized Estimating Equation (GEE) analysis of repeated measures was used to estimate the change in suicidal ideation over the 6 weeks of acute TMS treatment without adjusting for the change in illness (depression) severity (CGI-S) over the TMS treatment period. Second, a linear regression model via a GEE analysis of repeated measures was used to estimate the change in illness (depression) severity (CGI-S and CDRS-R total score) over the 6 weeks of acute TMS treatment. Finally, and third, an ordinal logistic regression model within a GEE framework was used to estimate the change in suicidal ideation over the 6 weeks of acute TMS treatment while adjusting for the change in illness (depression) severity (via CGI-S score as a time-varying covariate). Sex and age were included as covariates in each of the three models, and each model also contained a fixed effects term for time. For the ordinal logistic regression, the cumulative probabilities were modeled over the higher-ordered suicidal ideation scale scores (more suicidal ideation). The 95% Wald confidence interval was calculated for each odds ratio (OR). Maximum likelihood estimation and robust standard errors (Sandwich/Empirical Estimator) along with Type 3 tests of fixed effects were used with the Wald Chi-Square statistic. The sandwich (robust covariance matrix) estimator

was applied to the compound symmetry covariance structure. A weight statement was also included in each of the GEE models to account for the varied number of TMS sessions completed by each of the participants (the weight was calculated as the number of TMS sessions completed divided by the total number of possible sessions [$n = 30$]). All youth were included in the weighted analysis, but weighted in proportion to the number of TMS sessions they attended (e.g., 30/30, 29/30, 17/30, and 5/30). Thus, as a measure of precision, the weighted analysis gives more weight to estimates that included a greater number of TMS sessions attended and less weight to estimates that included a smaller number of TMS sessions attended.

2.6 Sensitivity analysis

The change in suicidal ideation over the 6 weeks of acute TMS treatment was also examined in a sensitivity analysis, but with C-SSRS used as the outcome measure of suicidal ideation. Because of the small sample size ($n = 19$) and exclusionary criteria, we observed a frequency distribution of the ordinal-scaled C-SSRS scores that ranged from 0 to 11, with sparseness observed in each of the categories from 1 to 11. Thus, for this sensitivity analysis, the C-SSRS was operationalized as a binary outcome (coded "No," if scored 0—no endorsement of suicidal ideation and coded "Yes," if scored either 1, 2, 3,…,11—any endorsement of suicidal ideation). We used a generalized binary logistic mixed model analysis of repeated measures, similar to the framework described above, to examine the change in suicidal ideation over the 6 weeks of acute TMS treatment. For this analysis, CDRS-R total was the time-varying covariate of depression severity. We modeled the probability of suicidal ideation (coded "Yes").

Statistical analyses were carried out using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). The procedures of PROC GENMOD and PROC GLIMMIX in SAS software were used to conduct the analysis. The level of significance was set at $\alpha = 0.05$ (two-tailed) and, because of the exploratory nature of this study, *p*-values were not adjusted for multiple testing.

3. Results

3.1 Participant characteristics

Demographic and clinical characteristics of the 19 adolescents in the current study are shown in Table 1. Of the 19 youth, 68.42% were female, and the mean age was 16.00 ± 1.29 years (age range = 13-19 years). Mean CDRS-R total scores were 65.58 ± 7.91 at baseline and 41.21 ± 14.57 at week 6. Mean CGI-S scores were 5.10 ± 0.73 at baseline and 3.00 ± 1.59 at week 6. Of the 19 youth, 42.11% (8/19) reported a lifetime history of at least one suicide attempt.

One participant withdrew from the study after 17 treatment sessions for reasons unrelated to suicidal ideation or behavior (concerns about academic expectations). Another participant experienced worsening suicidal ideation after 5 TMS treatments and was admitted for inpatient psychiatric care, resulting in withdrawal from the study. No participants attempted or completed suicide during study participation. The mean number of TMS sessions

completed was 27.94 ± 6.30 (range = 5-30); 16 patients completed all 30 sessions, and 1 patient each completed 29, 17, and 5 sessions, respectively.

According to the CDRS-R Item 13, 36.84% (7/19) reported having no suicidal ideation at baseline, and 83.33% (15/18) reported having no suicidal ideation at post-treatment/study exit. Of the 18 youth who were assessed on the CDRS-R at both time points, 55.56% (10/18) showed improvement on Item 13 (suicidal ideation) between baseline and post-treatment, while 38.89% (7/18) had minimum scores of 1 at baseline and showed no change at post-treatment. One participant (5.56%) showed a worsening (baseline score of 3 to a study exit score of 5; this participant was hospitalized).

According to the C-SSRS, 21.05% (4/19) reported having no suicidal ideation at baseline, and 70.59% (12/17) reported having no suicidal ideation at post-treatment. Of the 17 youth who were assessed on the C-SSRS at both time points, 58.82% (10/17) showed improvement on the Intensity of Ideation score (C-SSRS) between baseline and post-treatment. No change was observed in 35.29% (6/17), of whom 4 had minimum scores of 0 (i.e., no suicidal ideation) at both time points, and 5.88% (1/17) showed a worsening (baseline score of 3 to an exit score of 8).

3.2 Suicidal ideation and IMS treatment

As shown in Table 2, the linear model GEE analysis of repeated measures revealed that depression severity measured via the CDRS-R total score ($\hat{b} = -8.6939$, SE = 1.0209, 95% CI = −10.6948 to −6.6930, $p = 0.0001$; Table 2) and illness (depression) severity measured via the CGI-S ($\hat{b} = -0.7840$, SE = 0.0906, 95% CI = −0.9616 to −0.6063, $p = 0.0001$) both significantly decreased over the six-week acute TMS treatment period, while controlling for sex and age. The ordinal logistic regression revealed that, without adjusting for the change in illness (depression) severity (CGI-S), the predicted odds of suicidal ideation (CDRS-R Item 13) significantly decreased over the six weeks of acute TMS treatment (OR = 0.4074, 95% CI = 0.2656 to 0.6247, $p = 0.0001$; Table 3, Model 1a; Figure 1), while controlling for sex and age. However, as shown in Table 3 from Model 2a, after we adjusted for the change in illness (depression) severity (CGI-S) as a time-varying covariate in the ordinal logistic regression model, the magnitude of the decrease (or predicted odds) in suicidal ideation (CDRS-R Item 13) over the six weeks of acute TMS treatment (from visit-to-visit) was attenuated and rendered non-significant (OR = 0.6681, 95% CI = 0.3697 to 1.2074, $p = 0.1817$; Table 3, Model 2a; Figure 1), while also controlling for sex and age. The mosaic plot (Figure 2a), which shows the observed cumulative frequency distribution for the ordinal-scaled suicidal ideation outcome (CDRS-R Item 13) by TMS visit week, is consistent with the pattern of findings from the ordinal logistic regression.

3.3 Sensitivity analysis: Suicidal ideation and TMS treatment

The binary logistic regression revealed that, without adjusting for the change in depression severity (CDRS-R total score), the predicted odds of suicidal ideation (C-SSRS) significantly decreased over the six-week acute TMS treatment period (OR = 0.4622, 95% CI = 0.2938 to 0.7270, $p = 0.0012$; Table 4, Model 1b; Figure 1), while controlling for sex and age. However, as shown in Table 4 from Model 2b, after we adjusted for the change in

depression severity (CDRS-R total score) as a time-varying covariate in the binary logistic regression model, the magnitude of the decrease (or predicted odds) in suicidal ideation (C-SSRS) over the six weeks of acute TMS treatment (from visit-to-visit) was attenuated and rendered non-significant (OR = 0.8319, 95% CI = 0.4086 to 1.6923, $p = 0.6045$; Table 4, Model 2b; Figure 1), while also controlling for sex and age. The mosaic plot (Figure 2b), which shows the observed cumulative frequency distribution for the binary suicidal ideation outcome (C-SSRS) by TMS visit week, is consistent with the pattern of findings from the binary logistic regression.

4. Discussion

This exploratory study sought to evaluate the impact of an acute course of high-frequency TMS on suicidal ideation in adolescents with treatment-resistant depression. Treatment with TMS was safe and feasible in this sample of adolescents. Findings suggest that suicidal ideation improved over the course of TMS treatment, but this was likely mediated by improvement in depressive symptom severity. This conclusion must be considered preliminary but is encouraging in the context of the recognized knowledge gaps regarding TMS treatment in adolescents (Donaldson et al., 2014).

To our knowledge, this is one of the first studies to specifically examine outcome measures of suicidal ideation in an adolescent sample receiving an investigational brain stimulation treatment. A prior study by Bloch et al. (2008) examined nine adolescents (aged 16-18 years) with treatment-resistant depression who underwent 20 sessions of 10 Hz TMS at 80% motor threshold, with 2-second trains and 58-second intertrain intervals, for 20 minutes per session, applied to the L-DLPFC. Bloch et al. assessed pretreatment (mean = 100, SD = 46.9) and posttreatment (mean = 88, SD = 54.6) suicidal ideation via the Suicide Ideation Questionnaire (Reynolds, 1991), revealing a nonsignificant decrease in suicidal ideation after TMS treatment. This study included participants with greater depressive symptom severity and comorbidity compared to our sample and also utilized less aggressive TMS dosing (Bloch et al., 2008).

Unfortunately, the pressing need for intervention development for adolescents with suicidality is hampered by a myriad of ethical, regulatory, and pragmatic challenges (C. A. King et al., 2017). First, institutional review boards and the FDA often mandate the exclusion of participants with severe suicidality and recent suicide attempts. This has resulted in a substantial dearth of evidence regarding the efficacy and safety of many psychiatric interventions in this particularly vulnerable population who desperately need effective treatments. Second, determining an adolescent's capacity to assent to investigational interventions in the context of emotional dysregulation, historically suboptimal decisions, and recent suicide attempts is a complex process. Acute suicidal ideation also often improves with the structure of an intensive outpatient or inpatient treatment program, but the impact of such treatment programs on long-term prognosis is uncertain (Vitiello et al., 2009). Investigators also have the important task of clarifying unrealistic assumptions, as participants and their parents may believe that research interventions will cure a participant's suicidality or address longstanding psychological distress (C. A. King et al., 2017). Finally, research interventions targeting suicidality in

adolescence must contend with a heterogeneous population, as these youth often have trauma histories, substance use, psychosocial stressors, and multiple comorbidities (Brent et al., 1994; Brent et al., 2009; Vitiello et al., 2009; J. D. King et al., 2017). Nevertheless, the existing lack of effective, evidence-based neurobiological treatments for suicidal adolescents is unacceptable, and these various obstacles do not excuse our field from the ethical mandate to pursue further work in this area.

There are a number of limitations of the current study to consider. The present sample size was small, and the TMS treatment was adjunctive with no sham control. Definitive conclusions related to the impact of TMS on adolescent suicidality would necessitate a larger sample with a sham-controlled group. Additionally, adolescent participants were taking a variety of antidepressant medications concurrently. This was an exploratory study based on pooled data from protocols that were not designed to study suicidality as a primary outcome. Given the inherent difficulties of studying interventions for adolescents with suicidal ideation, larger samples and additional outcome measures, such as the Beck Scale for Suicidal Ideation (Beck et al., 1979), will be necessary. Moreover, measures of suicidal ideation in our study were based on interviews with adolescents and parents and thus were subject to reporting bias and participants' willingness to disclose suicidal ideation. Future studies that employ behavioral tasks assessing cognitive processes central to suicidality may offer more robust and comprehensive outcome measures pertaining to suicide risk. The sample was also limited in terms of severity of suicidality, as patients who had recently attempted suicide were excluded, and participants were outpatients who could be safely maintained in the study protocol. Our study examined the impact of TMS treatment on suicidal ideation, and it is worth noting that suicidal ideation is a relatively poor predictor of subsequent suicide attempt or death by suicide (Franklin et al., 2017; Glenn et al., 2017). Neural representations of suicide attempters also might differ from those of suicidal ideators who never attempt suicide (Just et al., 2017). Additionally, modulation of prefrontal cortical activity via neurostimulation techniques could impact other cognitive and affective processes, including externalizing vs. internalizing behaviors, which have been shown to be associated with different suicidal behaviors (Verona et al., 2004). Thus, our preliminary findings on the impact of TMS on suicidal ideation should not be extrapolated to outcomes of suicidal behavior, particularly attempted or completed suicide.

Finally, future efforts with target engagement biomarkers for suicidal ideation would enhance study rigor and our understanding of the neurobiology of adolescent suicidality (Guyer et al., 2016; Lichenstein et al., 2016). Recent evidence indicates altered cortical inhibition in depressed adolescents with histories of suicidal behavior (Lewis et al., 2018). Given the putative mechanism of TMS in restoring the excitatory-inhibitory balance of cortical networks, TMS holds promise as a rational, brain-based treatment approach for addressing cortical physiologic deficits in this population. Future TMS treatment studies should include relevant neurophysiologic and neurochemical measures in order to elucidate the mechanistic effects of TMS in suicidal adolescents.

In summary, adolescents with treatment-resistant depression who underwent high-frequency TMS to the L-DLPFC appeared to have improvement in suicidal ideation across 30 sessions associated with improvement in depressive symptom severity. This study will inform future

efforts focused on targeting suicidality in adolescents with TMS treatment. Larger analyses with sham-controlled data are necessary and forthcoming (Neuronetics, 2018). Future efforts will also consider pragmatic and neurodevelopmental contexts and target engagement biomarkers for individualized dosing. Theta burst (Li et al., 2014; Opie et al., 2017) and accelerated protocols (George et al., 2014; Baeken et al., 2017; Williams et al., 2018) may have particular utility for this population due to their feasibility for intensive treatment scheduling and potential for reducing time-to-response. However, these will require systematic evaluation for safety in the context of adolescent neurodevelopment. Effective, tolerable, and targeted brain-based interventions such as TMS for suicidality in adolescents would have a prominent impact on morbidity, mortality, and clinical practice (Baeken et al., 2017; Williams et al., 2018).

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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 an 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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HIGHLIGHTS

- Suicide is a leading cause of death in adolescents worldwide
- Direct treatments for suicidality in adolescents are lacking
- Transcranial magnetic stimulation (TMS) may be an intervention for suicidality
- TMS improved suicidal ideation and depressive symptoms

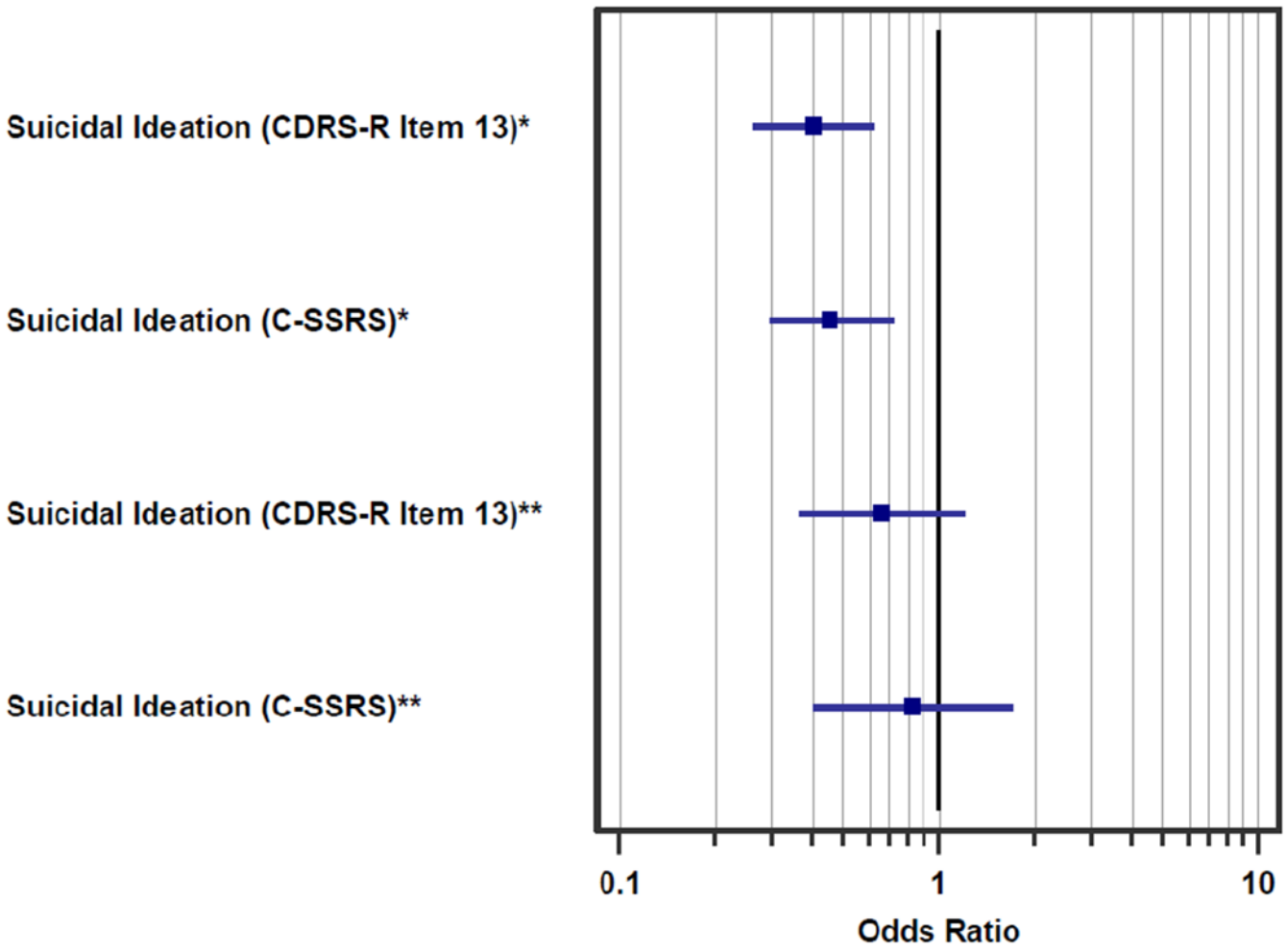

Figure 1.

Forest plot, from the ordinal logistic regression (CDRS-R Item 13) and binary logistic regression (C-SSRS), showing the change (or decrease) in the predicted odds of suicidal ideation over the 6 weeks of acute TMS treatment with/without adjusting for the change in illness (depression) severity as a time-varying covariate. The cumulative probabilities were modeled over the higher-ordered suicidal ideation scale score (more suicidal ideation) in the ordinal logistic model for CDRS-R Item 13 and the probability of suicidal ideation was modeled in the binary logistic model for C-SSRS. An estimated Odds Ratio < 1 indicated lower predicted odds of suicidal ideation over the 6 weeks of acute TMS treatment.
0.1110Odds RatioSuicidal Ideation (CDRS-R Item 13)*Suicidal Ideation (C-SSRS)*Suicidal Ideation (CDRS-R Item 13)**Suicidal Ideation (C-SSRS)**
*Not adjusted for the change in illness (depression) severity over the TMS treatment period.
**Adjusted for the change in illness (depression) severity as a time-varying covariate over the TMS treatment period.

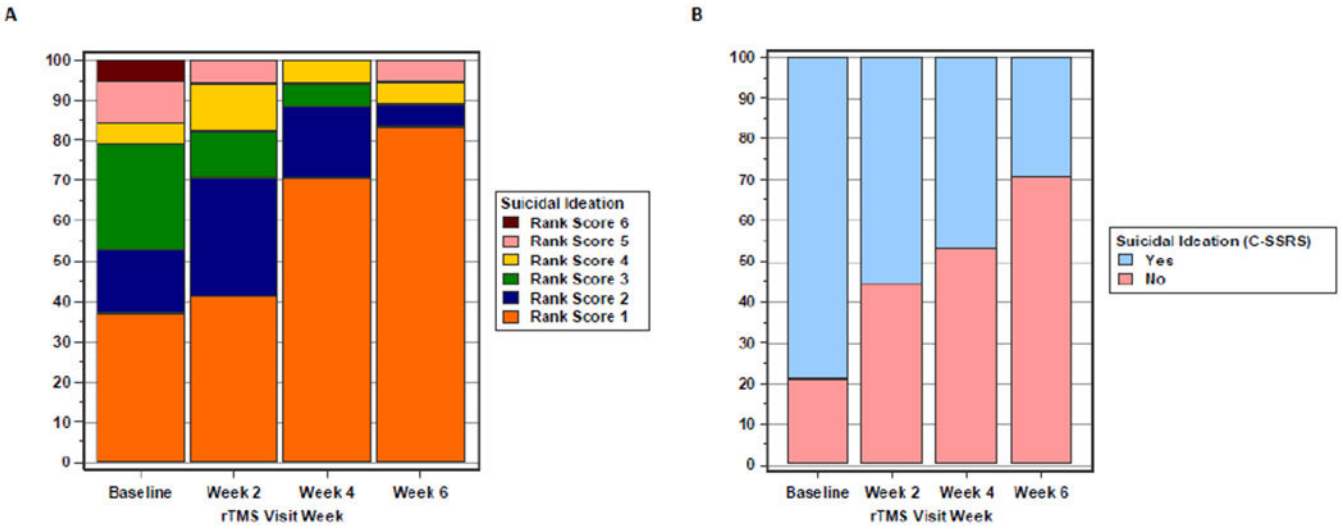

Figure 2.

Mosaic plots of the observed cumulative frequency distribution for measures of suicidal ideation by TMS visit week. A) The ordinal-scaled suicidal ideation (CDRS-R Item 13) outcome (Rank 1=no suicidal ideation, Rank 6=recurrent thoughts of suicide). B) The binary suicidal ideation outcome (C-SSRS).

Table 1

Demographic and clinical characteristics of the adolescent sample

Participant Characteristic	Overall Study Sample (*n* = 19)
Demographic Characteristics	
Age in years (observed range: 13-19 years), mean ± SD	16.00 ± 1.29
Female, *n* (%)	13 (68.42%)
Race, *n* (%)	
White, Non-Hispanic	18 (94.74%)
Clinical Characteristics	
Responded to TMS treatment, *n* (%)	9 (47.37%)
Duration of MDD episode in weeks, mean ± SD	100.63 ± 73.43
Number of TMS sessions (up to 30 sessions), mean ± SD	27.94 ± 6.30
CDRS-R total score (observed range: 49-82) at baseline, mean ± SD	65.58 ± 7.91
CDRS-R total score (observed range: 21-68) at post-treatment (week 6), mean ± SD	41.21 ± 14.57
CGI-S (observed range: 4-6) at baseline, mean ± SD	5.10 ± 0.73
CGI-S (observed range: 1-6) at post-treatment (week 6), mean ± SD	3.00 ± 1.59
CGI-S (observed range: 4-6) at baseline, median (IQR, 25th-75th Pctl)	5 (5-6 Pctl)
CGI-S (observed range: 1-6) at post-treatment (week 6), median (IQR, 25th-75th Pctl)	3 (2-4 Pctl)
Suicidal Ideation and Behavior	
CDRS-R Item 13 (observed range: 1-6) at baseline, mean ± SD	2.52 ± 1.57
CDRS-R Item 13 (observed range: 1-5) at post-treatment (week 6), mean ± SD	1.44 ± 1.15 *
CDRS-R Item 13 at baseline, median (IQR, 25th-75th Pctl)	2 (1-3 Pctl)
CDRS-R Item 13 at post-treatment (week 6), median (IQR, 25th-75th Pctl)	1 (1-1 Pctl) *
C-SSRS Intensity of Ideation (observed range: 0-10) at baseline, mean ± SD	4.26 ± 3.31
C-SSRS Intensity of Ideation (observed range: 0-9) at post-treatment (week 6), mean	1.76 ± 3.07 **
C-SSRS Intensity of Ideation at baseline, median (IQR, 25th-75th Pctl)	4 (2.25-6.75 Pctl)
C-SSRS Intensity of Ideation at post-treatment (week 6), median (IQR, 25th-75th Pctl)	0 (0-3.5 Pctl) **
No suicidal ideation (CDRS-R Item 13) at baseline, *n* (%)	7 (36.84%)
No suicidal ideation (CDRS-R Item 13) at post-treatment (week 6), *n* (%)	15 (83.33%) *
No suicidal ideation (C-SSRS) at baseline, *n* (%)	4 (21.05%)
No suicidal ideation (C-SSRS) at post-treatment (week 6), *n* (%)	12 (70.59%) **
Lifetime history of non-suicidal self-injury, *n* (%)	12 (63.16%)
Lifetime history of at least one suicide attempt, *n* (%)	8 (42.11%)
Number of lifetime suicide attempts, mean ± SD	0.63 ± 0.83
Total lifetime suicide attempts, *n* (%)	
Zero	11 (57.89%)
One	4 (21.05%)
Two	4 (21.05%)

* Missing 1 observation.

** Missing 2 observations.

Abbreviations: CDRS-R, Children's Depression Rating Scale, Revised; C-SSRS, Columbia Suicide Severity Rating Scale; IQR, interquartile range; MDD, major depressive disorder; Pctl, percentile; TMS, transcranial magnetic stimulation.

Table 2

Illness and depression severity across the 6-week acute TMS treatment period (n = 19)

Model Outcome and Variable	Parameter Estimate	Std Error	*p*-value	95% CI for Parameter Estimate	
Illness Severity (CGI-S)					
Intercept	4.5299	2.6234	0.0842	−0.6118	9.6716
Age	0.0347	0.1642	0.8326	−0.2871	0.3565
Sex (female vs. male)	0.0589	0.4719	0.9006	−0.8660	0.9839
Time effect (TMS visit week)	−0.7840	0.0906	0.0001	−0.9616	−0.6063
Depression Severity (CDRS-R Total)					
Intercept	43.3876	17.0466	0.0109	9.9769	76.7984
Age	1.0247	1.0290	0.3193	−0.9920	3.0415
Sex (female vs. male)	5.8612	4.4215	0.1850	−2.8048	14.5272
Time effect (TMS visit week)	−8.6939	1.0209	0.0001	−10.6948	−6.6930

Note: Time = TMS visit week. Std Error = Robust/empirical standard error estimate. A separate linear regression model via a GEE analysis of repeated measures (with a Gaussian distribution) was used to estimate the change in illness severity (measured via the CGI-S) and depression severity (measured via the CDRS-R total score) over the 6 weeks of acute TMS treatment, while adjusting for age and sex.

Table 3

Suicidal ideation (CDRS-R Item 13) across the 6-week acute TMS treatment period ($n = 19$).

Model 1a Outcome and Variable	Parameter Estimate	Std Error	*p*-value	Odds Ratio	95% CI for Odds Ratio	
Suicidal Ideation (CDRS-R Item 13)						
Age	−0.2863	0.2001	0.1522	0.7510	0.5074	1.1114
Sex (female vs. male)	−1.2529	0.8432	0.1373	0.2856	0.0547	1.4913
Time effect (TMS visit week)	−0.8979	0.2182	0.0001	0.4074	0.2656	0.6247
Model 2a Outcome and Variable						
Suicidal Ideation (CDRS-R Item 13)						
Age	−0.3234	0.2242	0.1491	0.7236	0.4663	1.1228
Sex (female vs. male)	−1.3407	0.7934	0.0911	0.2616	0.0552	1.2389
CGI-S (time-varying[a])	0.6478	0.3149	0.0397	1.9113	1.0311	3.5427
Time effect (TMS visit week)	−0.4032	0.3019	0.1817	0.6681	0.3697	1.2074

Note: Time = TMS visit week. Std Error = Robust/empirical standard error estimate. A separate ordinal logistic regression model via a GEE analysis of repeated measures was used to estimate the change in suicidal ideation (measured via CDRS-R Item 13) over the 6 weeks of acute TMS treatment with/without adjusting for the change in illness (depression) severity (CGI-S) as a time-varying covariate. The cumulative probabilities were modeled over the higher-ordered suicidal ideation scale score (more suicidal ideation).

An estimated Odds Ratio < 1 for time effect indicated lower predicted odds of suicidal ideation over the 6 weeks of acute TMS treatment.

[a]CGI-S Score was a time-varying covariate across the 6-week acute TMS treatment period (TMS visit weeks 0, 2, 4, and 6).

Table 4

Suicidal ideation (C-SSRS) across the 6-week acute TMS treatment period (n = 19).

Model 1b Outcome and Variable	Parameter Estimate	Std Error	*p*-value	Odds Ratio	95% CI for Odds Ratio	
Suicidal Ideation (C-SSRS)						
Age	−0.7264	0.4895	0.1573	0.4836	0.1713	1.3653
Sex (female vs. male)	0.7846	1.0862	0.4805	2.1915	0.2191	21.9178
Time effect (TMS visit week)	−0.7717	0.2256	0.0012	0.4622	0.2938	0.7270
Model 2b Outcome and Variable						
Suicidal Ideation (C-SSRS)						
Age	−0.8869	0.5713	0.1401	0.4119	0.1227	1.3829
Sex (female vs. male)	0.3149	1.2086	0.7978	1.3701	0.1056	17.7609
CDRS-R total (time-varying[a])	0.0814	0.0271	0.0041	1.0848	1.0274	1.1455
Time effect (TMS visit week)	−0.1844	0.3538	0.6045	0.8319	0.4086	1.6923

Note: Time = TMS visit week. Std Error = Robust/empirical standard error estimate. A separate binary logistic mixed model repeated measures analysis (with a binary distribution) was used to estimate the change in suicidal ideation (measured via C-SSRS) over the 6 weeks of acute TMS treatment with/without adjusting for the change in depression severity (CDRS-R total score) as a time-varying covariate. CSSR-S was operationalized as a binary outcome (coded “No,” if scored 0—no endorsement of suicidal ideation and coded “Yes,” if scored either 1, 2, 3,…,11—any endorsement of suicidal ideation).

An estimated Odds Ratio < 1 for time effect indicated lower predicted odds of suicidal ideation over the 6 weeks of acute TMS treatment.

[a]CDRS-R total score was a time-varying covariate across the 6-week acute TMS treatment period (TMS visit weeks 0, 2, 4, and 6).