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Research paper

Feasibility and clinical effects of theta burst stimulation in youth with major depressive disorders: An open-label trial

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ABSTRACT

Background: Conventional treatments for youth depression, such as antidepressants, have modest efficacy, side effects, and ongoing controversies regarding safety. Repetitive transcranial magnetic stimulation (rTMS), specifically theta burst stimulation (TBS), applied to the dorsolateral prefrontal cortex (DLPFC) has demonstrated efficacy for the treatment of depression in adults. However, the feasibility and clinical response to TBS for youth depression has yet to be explored.

Methods: Twenty participants between the ages of 16 to 24 years old with MDD were recruited. The intervention consisted of 10 treatment sessions over the course of two weeks, in which participants received intermittent TBS and continuous TBS stimulation to the left and right DLPFC, respectively. Change in the Hamilton Rating Scale for Depression (HRSD-17) score was the primary outcome. Clinical assessments occurred at baseline, after the fifth treatment session, and within a week after treatment completion.

Results: Of the twenty participants, eighteen received all TBS sessions, and seventeen completed all clinical assessments. There was a significant reduction in depressive symptoms following treatment completion ($p < 0.001$). Four of the twenty patients had more than 50% reduction in their depressive symptoms, two of whom achieved remission. All participants received and tolerated at least six daily TBS treatments with no major adverse events.

Limitations: Study was an uncontrolled, open-label design.

Conclusion: Ten sessions of TBS was feasible, well tolerated, and appeared to have clinical effects for the treatment of depressed youth. Future sham-controlled randomized trials are warranted to validate these findings in a larger cohort of youth depression.

1. Introduction

The lifetime prevalence of major depressive disorder (MDD) is estimated to be 11.0% in adolescents and young people aged 15–24 (youth) (Avenevoli et al., 2015), with this rate steadily increasing over the last decade (Mojtabai et al., 2016). The initial treatment of MDD in youth often involves antidepressants (e.g. selective serotonin reuptake inhibitors (SSRIs)), cognitive-behavioral therapy (CBT), or their combination (March et al., 2007). However, an estimated 30% to 50% of youth have treatment-resistant depression (TRD) as their symptoms do not respond to first line treatments (Fava, 2003). Even when conventional therapies yield remission in youth with MDD, it is common for residual depressive symptoms to remain (Kennard et al., 2006). Additionally, there are concerns and controversies regarding the safety and efficacy of antidepressant medications in youth MDD (Bridge et al., 2007; Hetrick et al., 2012). In particular, antidepressant medications have been associated with side effects including suicidal thoughts and behaviors in those 24 years of age and younger (Hetrick et al., 2012;

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Stone et al., 2009). Furthermore, several placebo-controlled clinical trials have shown no benefits of antidepressant medications compared to placebo (Cheung et al., 2005) and a meta-analysis of clinical trials in this population has revealed only modest antidepressant efficacy (Bridge et al., 2007). Although randomized controlled trials and practice guidelines support the use of CBT alone and CBT with pharmacotherapy for youth depression, many adolescents do not respond to either treatment approach (Birmaher et al., 2007; Brent et al., 2008; Cheung et al., 2007; "Depression in children and young people: identification and management | Guidance and guidelines | NICE," 2005; Melvin et al., 2006). For example, results of a large-scale randomized controlled trial of adolescents with depression illustrated that antidepressants in combination with CBT treatment was superior to either treatment alone, but relapse rates were 40% at one-year follow-up (Reinecke et al., 2009; The Treatment for Adolescents With Depression Study (TADS) Team et al., 2009). Collectively, the relatively low rate of antidepressants response (alone or in combination with CBT) underscores the need for novel interventions in youth depression.

Repetitive TMS (rTMS) applied to the dorsolateral prefrontal cortex (DLPFC) is approved by the FDA in adults 18 and older with depression and is known to be safe and efficacious in improving depressive symptoms in adult TRD. Meta-analyses have reported rTMS response rates (i.e., change in symptom ≥ 50%) of about 30% (Berlim et al., 2014; Gaynes et al., 2014), compared to 17% in placebo control groups, offering hope for treatment-resistant patients (Rush et al., 2006). More specifically, the application of high frequency (i.e., > 1 Hz) rTMS (HF-rTMS) to the left DLPFC and/or low frequency (i.e. < = 1 Hz) rTMS (LF-rTMS) to the right DLPFC have been shown to be efficacious in the treatment of depression (Fitzgerald et al., 2006).

However, among the shortcomings of HF- and/or LF- rTMS is the lengthy duration (19 min or 37.5 min (unilateral) to 40 min (bilateral)), and relatively high intensity of stimulation (120% resting motor threshold (MT)) that can induce scalp discomfort (McGirr et al., 2015). In comparison, theta burst stimulation (TBS) is a shorter and more biologically potent rTMS protocol which may more effectively engage brain circuitry (Huang et al., 2005; Li et al., 2014). TBS is similar to the endogenous theta rhythms of the brain and is thought to more effectively modify cortical activity through induction of long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity (Huang et al., 2005). TBS involves application of 3 bursts of 50 Hz rTMS repeated every 200 ms at 80% active MT, either continuously (cTBS), for a total of 40 s for 600 pulses, or intermittently (iTBS) (every 8 s) for a total of 3 min for 600 pulses. Importantly, despite the relatively short duration of TBS compared to conventional rTMS, the alteration of LTP and LTD by TBS can last for approximately 70 min after treatment - more than twice as long as the duration of the after effects reported through conventional rTMS (Thut and Pascual-Leone, 2010). This feature also enables bilateral treatment with the addition of only a few seconds of stimulation. A sham-controlled clinical trial revealed that a combination of iTBS and cTBS applied to the left and right DLPFC, respectively, provides superior antidepressant effect to unilateral or sham in adult patients with refractory depression (Li et al., 2014). Furthermore, a recent study in adult TRD found iTBS to be non-inferior when compared to the conventional 10 Hz rTMS for the treatment of depressive symptoms, all while requiring a fraction of the treatment time (Blumberger et al., 2018). Thus, the current evidence supports TBS as both a feasible and efficacious treatment of MDD in adult populations.

In the context of youth MDD, more than six open label trials to date have examined rTMS as a treatment for adolescents with depression (reviewed in Donaldson et al. (2014) . These results suggest rTMS to be associated with clinical response and well-tolerated, even in some adolescents who did not respond to antidepressants, CBT or ECT. Treatment with rTMS during adolescence may also have long-lasting effects on depressive symptoms. Mayer et al. (2012a), for instance, found both sustained treatment response and a significant improvement in planning abilities and reaction time compared to baseline at three year-followup (Mayer et al., 2012a). Furthermore, a recent study found that compared to adults, youth had a greater response to rTMS when used for the treatment of depression (Zhang et al., 2018), suggesting that rTMS may be an effective option in this population. Finally, adverse events related to TBS were recently compared to that of single/paired pulse studies in 165 pediatric population (6–18 years of age) (Hong et al., 2015). No severe adverse events or seizures were reported for TBS. Adverse events were rated minimal/mild and comparable to adverse events reported for single/paired pulse TMS. Together, the evidence for modest efficacy of traditional treatments and the support for efficacy and tolerability of rTMS when other treatments have failed, strongly support the rationale for the use of rTMS for depression in youth - and particularly for youth TRD.

The evidence suggests that TBS holds great potential as a novel rTMS dosing paradigm in the treatment of depressive symptoms in youth. Treatment with TBS appears to have similar efficacy to conventional rTMS paradigms with a comparatively shorter treatment time (Blumberger et al., 2018; Li et al., 2014). The few studies that have been conducted to date also suggest that rTMS may be both a tolerable and efficacious treatment for youth MDD. However, these prior studies have been limited to the application of either high or low frequency rTMS (Donaldson et al., 2014). Therefore, to our knowledge, the application and clinical impact of TBS in youth MDD remains unexplored. Finally, both the left and right DLPFC have been implicated in youth MDD; this includes youth MDD exhibiting lesser structural asymmetry between the left and right DLPFC(Liu et al., 2016), as well altered DLPFC functional connectivity with subcortical structures (Connolly et al., 2017; Singh et al., 2018). Bilateral TBS has been shown to have superior efficacy compared to unilateral TBS in decreasing depressive symptoms in adult TRD (Li et al., 2014). Therefore, this study was designed to examine the feasibility and potential clinical impact of bilateral TBS in youth MDD.

2. Methods

2.1. Design

The clinical trial was designed as an open label two-week treatment trial, described in detail below. The trial began recruitment in 2015 and completed recruitment in 2017. The study was registered (https://clinicaltrials.gov/ct2/show/NCT02472470).

2.2. Patients

Patients aged 16–24 with a diagnosis of depression were recruited for this study (**Fig. 1**). Patients were eligible for enrollment if they had not gone through any changes in their treatments (psychotherapeutic and medication) for at least four weeks prior to the study. Participants were recruited from the community by advertisements posted on web-based media, at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada, at other hospitals or colleges and universities in the Greater Toronto Area, and at youth wellness centres. The inclusion and exclusion criteria for the study included:

Inclusion: (1) outpatients; (2) between the ages of 16 and 24; (3) with the capacity to assent or consent to study participation; (4) Mini-International Neuropsychiatric Interview (MINI) confirmed diagnosis of MDD single or recurrent; (5) no change in treatment (psychotherapy or medication) for at least four weeks prior to participation in the study; (6) Hamilton Rating Scale for Depression (HRSD-17) score of 20 and higher; (7) at least one failed/refused/intolerant antidepressant trial in the current episode as determined by Antidepressant Treatment History Form (ATHF) and (8) no safety concerns endorsed on TMS Screening and Information Form.

Exclusion: (1) lifetime MINI diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, delusional disorder, current

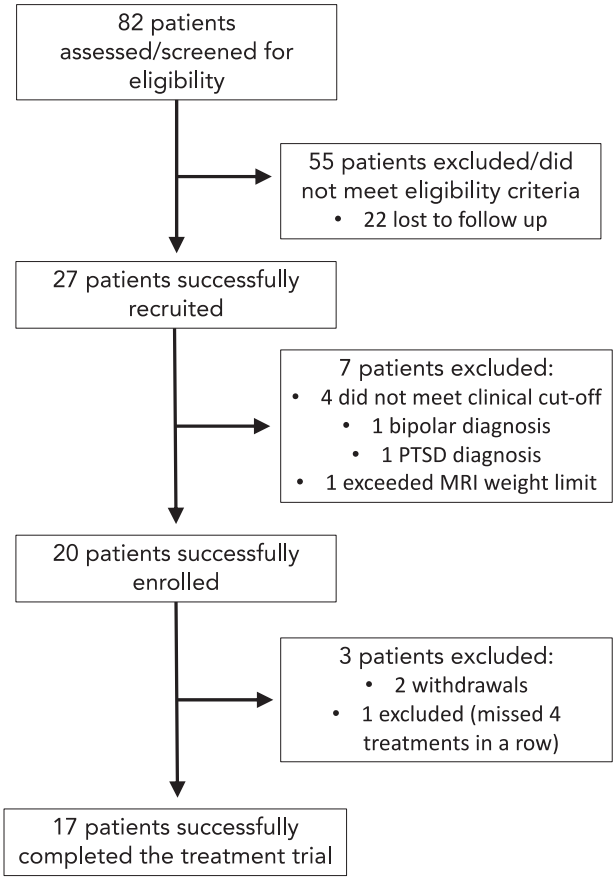

Fig. 1. Trial profile. PTSD: Post-traumatic stress disorder; MRI: Magnetic resonance imaging.

psychotic symptoms, post-traumatic stress disorder, obsessive compulsive disorder, autism spectrum disorder, a history of epilepsy or any other major neurological disorder; (2) history of substance use disorders (moderate to severe) within the last 3 months as determined by MINI; (3) concomitant major unstable medical illness; (4) acutely suicidal or high risk for suicide as assessed by a study psychiatrist; (5) ineligible to receive TMS or MRI as indicated by TMS Screening and Information Form and; (6) a change in treatment status during the study trial that was considered to be a confound to the study. This included change in medication or CBT, each reviewed case by case by the study psychiatrists; (7) patients on medications that were considered a confound to the study including benzodiazepines, antipsychotics, mood stabilizers, stimulants and anticonvulsants; and (8) having failed brain stimulation (rTMS, electroconvulsive therapy, or transcranial current stimulation) in the past.

2.3. Screening evaluation

Patients were first screened over the phone using the TMS Screening and Information Form, which included assessment of medical history and any potential contraindications to magnetic exposure. Then on the baseline visit (i.e. within a week before the start of the trial), assessments administered included the MINI for confirmation of diagnosis of MDD, Demographic and Medical Information Form, ATHF, and the Columbia-Suicide Severity Scale (C-SSRS) (Posner et al., 2011).

2.4. Clinical assessments

The HRSD-17 (Hamilton, 1967) was the primary outcome measure which was obtained at baseline, after five treatment sessions, and within a week after completing the ten treatment sessions. Secondary outcome measures were also assessed at these three time points (baseline, after five treatment sessions, within a week after all treatment sessions) and included: The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996; Rush et al., 2006); The Children's Depression Rating Scale, revised-version (CDRS-R) for patients under the age of 18 (Poznanski et al., 1984); and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993). In addition, anhedonia was assessed using the Dimensional Anhedonia Rating Scale (DARS) (Rizvi et al., 2015) at baseline and within a week after all treatment sessions. Finally, the following descriptive assessments were conducted at baseline to characterize the population for comparison with other studies: impulsivity was measured using the short form of the Barratt Impulsiveness Scale (BIS) (Patton et al., 1995); and personality with the Brief Five-Factor Personality Inventory (NEO-FFI3) (Gosling et al., 2003).

2.5. Imaging for treatment target

The imaging protocol consisted of an 8-minute high-resolution T1 anatomical sequence which was obtained to guide TMS coil positioning during visits for each individual patient. Neuro-navigation was used based on it being reported to enhance the response to rTMS treatment in those with depression, due to more precise targeting of the DLPFC (Fitzgerald et al., 2009). Coordinates used (in Talairach) were $x = -35$, $y = 45$, and $z = 35$ for the left DLPFC, and $x = 34$, $y = 46$, and $z = 35$ for the right DLPFC.

2.6. Intervention

The study involved ten treatment sessions (i.e., five days a week for two weeks or up to 2.5 week if patients missed treatment sessions). Due to a lack of prior data on the safety of TBS in youth, a shorter treatment protocol was selected to establish safety and feasibility of TBS in youth. A prior clinical trial had demonstrated clinical efficacy of this protocol (i.e. ten TBS treatment sessions) in adult depression (Li et al., 2014). Subjects received rTMS sessions (1800 iTBS pulses to left DLPFC, 1800 cTBS pulse to right DLPFC, randomized for order of administration) once daily on weekdays for two weeks (Li et al., 2014). The DLPFC target location was identified through cortical co-registration using each individual's anatomical MRI, and DLPFC coordinates were chosen to target the same brain area as previously published methods (Fox et al., 2012). Prior to the first treatment, each subject's resting MT and active MT (AMT) were determined. Treatment was conducted at 80% of AMT throughout the trial.

2.7. Safety and monitoring procedure

To ensure patient safety, we monitored all participants closely using the following procedure: 1) Every patient underwent a detailed clinical consult with the study psychiatrists (YK/DC/JL) in order to determine their suitability and safety to participate in the protocol. The clinical interview served to determine if TBS was safe and rule out symptoms requiring immediate attention, such as acute suicidal risk. 2) In addition to the initial assessment, the C-SSRS was conducted at least every three days during the treatment visits to ascertain clinical risks. Finally, a urine drug screen was carried out during the baseline visit for assessment of drug use. 3) If at any point during the study it was determined that the patient was unstable, the participant exited the study. Additionally, a participant would exit the study if they missed more than 20% of the treatment sessions consecutively (i.e., 2 sessions in a row) or 40% (i.e., 4 sessions) within two weeks. An adverse events form was administered before and after every daily treatment session (i.e., 20 times throughout the treatment trial) to document any adverse event as reported by the patient. The adverse event form recorded information such as: the relation of the adverse event to the study (1 = not related, 2 = probably not related, 3 = possibly related, 4 = most probably

related), the severity grade of the adverse event (1 = mild, 2 = moderate, 3 = severe), action followed (1 = no treatment, 2 = treatment with medication, 3 = treatment other, 4 = hospitalization, 5 = CPR, 6 = other), and the outcome (1 = resolved, 2 = resolving, 3 = not resolved, 4 = resolved with sequelae, 5 = fatal, 6 = unknown).

2.8. Data analysis

Repeated measures ANOVA were conducted to examine the clinical changes associated with TBS intervention measured by HSRD-17 across assessment periods. For post-hoc *t*-tests, Bonferroni correction were used. We used an intent-to-treat analysis approach, using data collected from all participants who enrolled in the study ($n = 20$). A secondary repeated measures ANOVA was conducted with only those who completed the study protocol ($n = 17$). We also assessed whether any clinical features at baseline were associated with changes in depressive symptoms. For this, we examined the association between depressive symptoms, impulsivity, and anhedonia, as measured by the HRSD-17, BIS and DARS respectively at baseline, to the extent of change in depressive symptoms following TBS therapy.

3. Results

3.1. Clinical and behavioral characteristics

All patients had a primary diagnosis of MDD, with a mean number of ATHF trials score of 3.0 ± 2.2 based on the current episode. As defined by the MINI, all 20 participants had a current episode of MDD, and only one participant met the criteria for recurrent MDD. 13 of the 20 participants exhibited treatment resistance, defined as a score of equal to or greater than 3 on the ATHF for two or more treatment trials (Sackeim, 2001). The remaining 7 did not meet criteria for treatment resistance (mean number of ATHF trials score of 1.7 ± 1.1). 14 of the 20 participants were on medication at the time of testing (see **Supplementary Table 1** for antidepressant medication history of each participant). Comorbid diagnoses included Generalized Anxiety Disorder ($n = 6$), Attention Deficit Hyperactivity Disorder ($n = 3$), Panic Disorder ($n = 1$), Dysthymia ($n = 1$), and Seasonal Affective Disorder ($n = 1$) (**Table 1** for further demographic information). Presence of personality disorder was assessed using the Diagnostic Interview for DSM-IV Personality Disorder; 6 participants exhibited presence of a personality disorder, which included avoidant ($n = 5$), obsessive-compulsive ($n = 2$), borderline ($n = 1$), and narcistic ($n = 1$). Baseline DARS and BIS scores were 40.6 ± 19.1 and 64.7 ± 8.5 respectively, representing medium anhedonia, a value similar to MDD groups in other studies in which the DARS was used (Rizvi et al., 2015), and normal impulsiveness, a value similar to healthy individuals (Stanford et al., 2009). Mean *t* scores for each personality trait as measured through NEO-FF1 were: 69 ± 5 for neuroticism, 34 ± 8 for extraversion, 55 ± 12 for openness to experience, 50 ± 11 for agreeableness, and 36 ± 8 for conscientiousness, reflecting the sample was characterized by high level of neuroticism, low extraversion, average openness and agreeableness, and lower than average conscientiousness.

Table 1
Demographic information of participants.

Demographic variable	
Number of participants	20
Age range (mean ± SD)	16–24 (20.9 ± 2.6)
Sex (M/F)	10/10
Years of education ± SD	14.2 ± 2.2
Receiving psychotherapy (yes/no)	10/10
Handedness (left/right/both)	3/16/1
Employed (yes/no)	7/13

3.2. Feasibility of TBS

All participants received and tolerated at least six daily TBS treatments with no major adverse events. Eighteen participants (90% of sample) received all ten treatments, and seventeen subjects (85%) completed the study. Of the three non-completers: one missed four treatments in a row and was excluded; one voluntarily withdrew after the eighth treatment, and one completed all treatments but did not return for post clinical assessments. Two out of three non-completers exhibited a decrease in depressive symptoms following five treatments. All completers had a decrease in their depressive symptoms following the ten TBS treatment sessions.

3.3. Clinical changes with TBS

In the intent-to-treat sample, there was a signficiant reduction in HRSD-17 scores from baseline (22.4 ± 2.9) to post-treatment session #5 (17.1 ± 5.73) ($p < 0.001$; Cohen's $d = 1.178$) and post-treatment session #10 (13.5 ± 5.00) ($p < 0.0001$; Cohen's $d = 1.862$). By the end of treatment #10, four patients were responders (i.e., at least 50% reduction), and two of these patients achieved remission (HRSD ≤ 7) (**Fig. 2**, **Table 2**). Moreover, completers exhibited a significant improvement in depressive symptoms between baseline and post treatment # 5 ($p < 0.001$), and post-treatment #5 and post-treatment #10 ($p < 0.05$). For secondary outcome measures, when comparing baseline to post all treatment sessions, we found a decrease in BDI-II scores by 32.0% ± 31.1%, a decrease in CDRS-R scores by 37.8% ± 21.1%, and an increase in Q-LES-Q scores by 30.0% ± 38.1% (**Table 2**).

Moreover, a significant positive correlation was found between reduction in HRSD-17 and a higher baseline DARS (i.e., less anhedonia; $r = 0.616$, $p = 0.008$) (**Fig. 3**). No correlation was found between reduction in HRSD-17 and baseline HRSD-17 ($r = -0.09$, $p = 0.7$) or BIS ($r = -0.002$, $p = 1.0$).

We also investigated for potential differences between those with TRD and those who did not meet criteria for TRD. Neither HRSD-17 scores at baseline nor the reduction in HRSD-17 scores following TBS were significantly different between the two groups ($p = 0.491$ and $p = 0.373$, respectively). Effect sizes with respect to reduction in HRSD-17 scores following TBS for each group were: Cohen's $d = 1.871$ for the TRD group, and Cohen's $d = 1.827$ for the non-TRD group.

With respect to HRSD-17 scores, one participant exhibited higher depressive symptoms after five treatments (HRSD-17 = 31) compared to baseline (HRSD-17 = 28). This patient was eventually excluded due to non-compliance and thus did not finish the treatment trial. The clinical and demographic characteristics of this participant were as follows: 21 years old, had a primary diagnosis of MDD and Generalized Anxiety Disorder, along with Ehlers-Danlos syndrome, and had the highest HRSD-17 score at baseline amongst participants, with a score of 28.

3.4. Safety and adverse events

Suicidal ideation was reported in 17 of the 20 patients at baseline as measured by C-SSRS, with a mean intensity of 3.11 ± 1.45 (i.e. medium severity) and frequency of 2.64 ± 0.86. Upon completion of the study, 9 of the 17 patients who completed the treatment course reported some form of suicidal ideation, with a mean intensity of 2.11 ± 1.27 and frequency of 2.56 ± 0.88. On average 3 ± 2 adverse events were reported per patient during the treatment trial. The vast majority of these adverse events were headaches (reported at least once by 13 patients); other adverse events included chest tightness, scalp pain, feeling of anxiety, nausea, gastrointestinal symptoms, nasopharyngitis, restlessness, and general discomfort. The mean severity grade of all reported events was 1.0 ± 0.2 (i.e., mild).

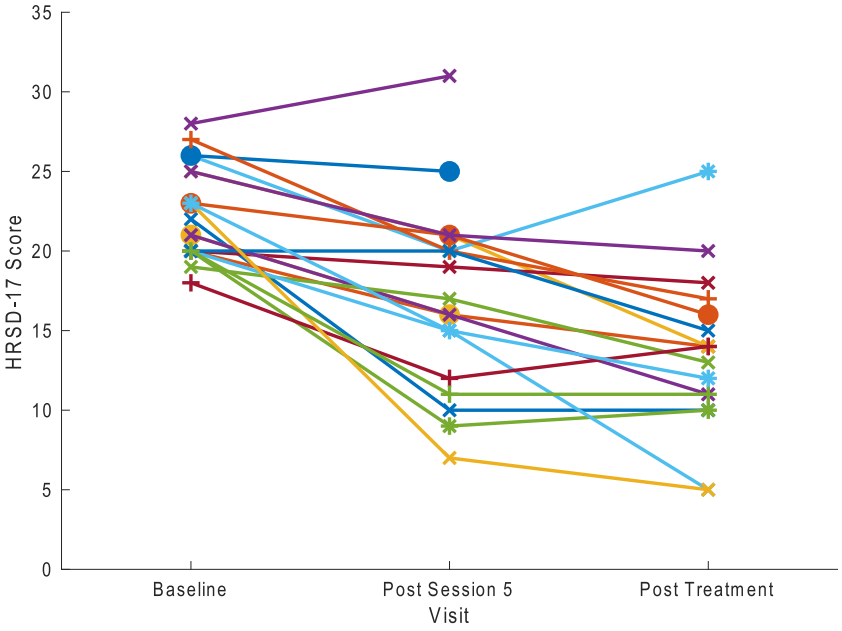

Fig. 2. Clinical assessments in youth receiving theta burst stimulation. Changes in depressive symptoms assessed by Hamilton Rating Scale for Depression (HRSD-17) before (baseline) theta burst stimulation (TBS), after 5 daily TBS sessions (post five treatment sessions), and within a week post all 10 treatment sessions in 20 youth MDD (each colored line). 20 youth MDD were enrolled, 18 completed all the treatments, and 17 completed the study in its entirety. Mean decrease in HRSD-17 was 38.58% (± 20.2%), including 8 participants showing > 40% HRSD-17 improvement, and 4 with ≥ 50% improvement.

4. Discussion

To our knowledge, the current study is the first to assess the clinical effects of TBS as a potential treatment for youth TRD. Our findings suggest that TBS is a feasible, safe, and clinically effective treatment option for youth TRD. In addition to being well-tolerated in this study, TBS necessitates a fraction of conventional rTMS treatment time, with non-inferior clinical effectiveness reported in adult trials (Blumberger et al., 2018). This characteristic has the potential to lower associated treatment costs. Furthermore, safety is of paramount importance when using rTMS in youth due to a risk of seizure, hearing damage, pain, or impaired cognition (Croarkin et al., 2010). However, surveys of brain stimulation literature in youth suggest that rTMS is safe and tolerable for this population, especially when safety guidelines are followed, with reported adverse side effects often being minor and transient (Krishnan et al., 2015; Mayer et al., 2012b). Following a rigorous monitoring procedure and strict adherence to safety guidelines, all patients received and tolerated at least six TBS treatment sessions in our study, with reports of only mild adverse events. Finally, there was a significant improvement in depressive symptoms between baseline and both post treatment sessions five and ten, despite the brief daily sessions and short treatment duration. The overall improvement in depressive symptoms following TBS complements previous findings (Bloch et al., 2008; Loo et al., 2006; Wall et al., 2011), further supporting TBS as a viable treatment for youth TRD. We also highlight our finding of greater baseline anhedonia (i.e., lower DARS score) being associated with lesser improvements in depressive symptoms following rTMS treatment, which has been found in adults treated with rTMS (Downar et al., 2014) and youth with SSRIs (McMakin et al., 2012). These findings suggest that anhedonia may predict whether a person with MDD will respond to treatments, including brain stimulation in youth.

In comparing our study to the current literature, there are some critical differences that should be highlighted. Most importantly, to our knowledge, this study is the first to assess the clinical effects of TBS as a potential treatment for youth TRD. Previous studies on rTMS for youth TRD have utilized conventional rTMS paradigms, as in LF- and/or HF-rTMS (Bloch et al., 2008; Loo et al., 2006; Wall et al., 2011); many of these studies only used high frequency stimulation (e.g. 10 Hz) over the left-DLPFC, a common procedure in the application of rTMS for treatment of adult MDD. In comparison, we utilized iTBS and cTBS to target the left and right DLPFC respectively, both of which are implicated in the pathophysiology and treatment of MDD (Chen et al., 2013). Although the mechanism remains unclear, high and low rTMS may selectively modulate cortical excitability and inhibitory circuits in targeted and connected areas (Daskalakis et al., 2006).

Our study also had a relatively short duration period compared to other rTMS studies in youth MDD. Nonetheless, we found significant improvements in depressive symptoms. This finding coheres with the adult literature, which has reported similar tolerability and efficacy in TBS as HF-rTMS, while requiring a fraction of the treatment time (Bakker et al., 2015; Blumberger et al., 2018). Furthermore, there are studies with adults which have shown that the same duration period as used in our study (i.e. ten sessions of rTMS over the course of two weeks) is efficacious for the treatment of depressive symptoms (Chistyakov et al., 2010; Li et al., 2014). The short treatment time required for TBS was evident in our study, as we found a significant decrease in HRSD-17 scores by an average of 24.2%, after only 5 treatment sessions, with four participants exhibiting a reduction of symptoms greater than 40%.

Table 2
Scores for clinical outcomes.

	Baseline	Post session 5	Post treatment	Significance (Cohen's d)
HRSD-17	22.4 ± 2.9	17.1 ± 5.73	13.5 ± 5.00	$p < 0.00001$ (1.862)
BDI-II	38.6 ± 8.6	30.8 ± 13.0	25.5 ± 13.2	$p = 0.004$ (1.127)
Q-LES-Q	178.7 ± 62.25	199.85 ± 69.75	231.9 ± 57.7	$p = 0.0004$ (1.138)
CDRS-R	68.0 ± 2.6	39.66 ± 21.13	42.7 ± 16.3	$p = 0.04$ (1.847)

HRSD-17: Hamilton Depression Rating Scale (HDRS)- 17 Item; BDI – II: Beck Depression Inventory-II; Q-LES-Q: The Quality of Life Enjoyment and Satisfaction Questionnaire. CDRS- R: Children's Depression Rating Scale, revised-version. Significance column values are based on the *t*-test between baseline and post treatment for each clinical outcome.

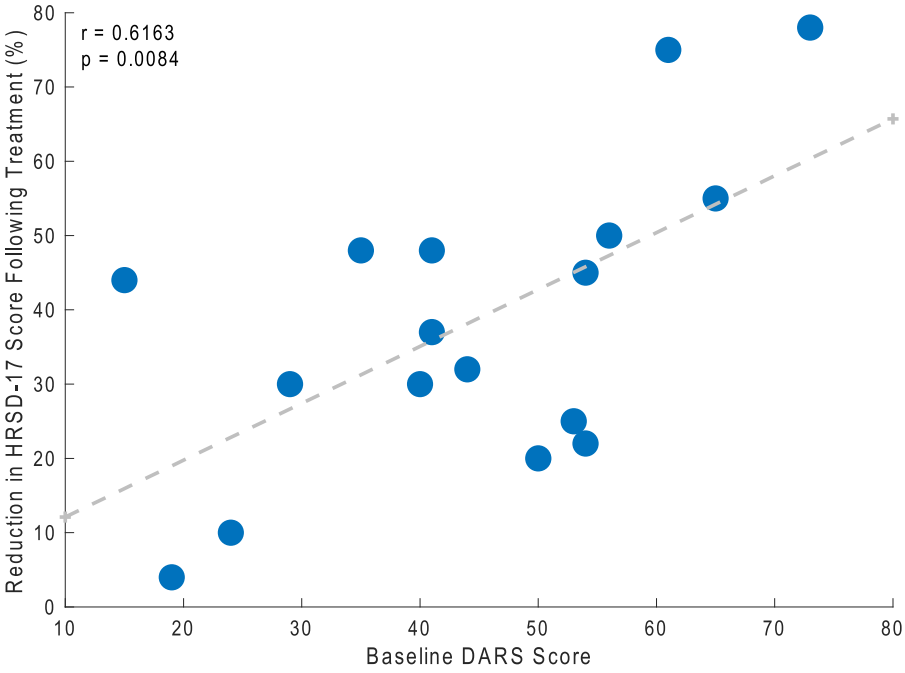

Fig. 3. Association between baseline dimensional anhedonia rating scale (DARS) and change in 17-Item Hamilton Rating Scale for Depression (HRSD-17). Scatter plot depicts a positive correlation between reduction in HRSD-17 scores following treatment and baseline DARS score, suggesting that greater severity of anhedonia at baseline (i.e., lower DARS score) may be a negative predictor as to whether a youth with MDD will respond to rTMS treatment.

We also highlight the age range of our sample group. Studies on the application of rTMS for the treatment of depression are commonly done in those ≥18 years old. However, although the stated age range of adult trials may be ≥18 years, many of these studies have a mean age range being between approximately 40 to 60 years old (Berlim et al., 2014; Brunoni et al., 2017; Mutz et al., 2018), suggesting that youth (e.g., 18–24) are underrepresented. Furthermore, studies on the use of rTMS for adolescent MDD have often reported as having an upper age limit of 18 years old (Bloch et al., 2008; Loo et al., 2006; Wall et al., 2011). Thus, by having an age range between 16–24 years old, we were able to assess the use of rTMS for depression in youth. This age group has traditionally been overlooked in the literature, yet it has a substantial rate of suicide (approximately 4.16 per 100,000 persons) which is closely linked to depression and other mental health disorders (Cash and Bridge, 2009).

As previously described, many of the participants in our study had comorbid diagnoses. We did not exclude such participants as their comorbidities were reflective of the youth MDD population. Indeed, youth MDD is associated with a myriad of other comorbid diagnoses, with estimates including two thirds of youth with depression having at least one comorbid psychiatric disorder (Ford et al., 2003). More specifically, youth with MDD have been reported as having an increased risk for Generalized Anxiety Disorder, Attention Deficit Hyperactivity Disorder, and Substance Use Disorders (Avenevoli et al., 2015). Although speculative, since changes in severity of comorbid diseases were not systematically assessed in this study, our TBS protocol may have exerted some therapeutic effect on symptoms related to these comorbid disorders. For example, rTMS to the prefrontal cortex has been used successfully in the treatment of symptoms related to Generalized Anxiety Disorder (Bystritsky et al., 2008; Dilkov et al., 2017; Du et al., 2018; Machado et al., 2012; Paes et al., 2011), which was the most common comorbid disorder in our sample. Thus, TBS may have the potential to improve symptoms related to comorbidities – a hypothesis to be more carefully examined in a future trial in a larger cohort of patients.

There are several limitations in the current study worth noting. Firstly, there was no sham rTMS group to act as a control, although previous studies in the adult MDD literature do suggest that rTMS is significantly more effective than sham rTMS in regard to response and remission rates (Berlim et al., 2014). Furthermore, we did not include a conventional LF- and/or HF-rTMS group to compare safety, feasibility, and clinical changes of TBS in our youth sample. However, such comparisons were recently conducted in the context of adult MDD; TBS was found to be just as safe, feasible, and efficacious as conventional rTMS in the treatment of depressive symptoms, while requiring far less time (Blumberger et al., 2018). We also note that our sample size of 20 participants, although relatively large when compared to previous studies on rTMS and youth MDD, was also relatively small to studies done in adults. This small sample size also prevented us from drawing any conclusions as to whether TBS had also improved symptoms of comorbid diseases found in our sample. Furthermore, as part of the exclusion criteria, participants were required to have had no changes in their treatment for at least four weeks prior to their participation in the study. Although this may allow one to infer that the clinical changes were attributable to the TBS therapy and not their prior treatment, we cannot definitively rule out the influence of their prior treatments on the clinical results. Additionally, while patients were clinically assessed for duration of their current and past MDD episodes by the study psychiatrists, this information was not systematically recorded for each participant. Finally, we note that our treatment duration was only 10 sessions over the course of two weeks, much fewer than the session numbers reported in previous rTMS studies (Donaldson et al., 2014). Despite the short treatment duration period, we still found a significant improvement in depressive symptoms between baseline and post treatment sessions #5 and #10, and improvement between post treatment sessions #5 and #10 in completers. Future studies could investigate the extent of the benefits gained by extending the number of TBS treatment sessions, and to delineate the optimal number of treatment sessions for youth MDD.

5. Conclusion

This study suggests that TBS has promise for the treatment of TRD in youth. Larger, sham-controlled trials are warranted.

CRediT authorship contribution statement

Prabhjot Dhami: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Yuliya Knyahnytska:** Data curation, Writing - review & editing. **Sravya Atluri:** Data curation, Writing - review & editing. **Jonathan Lee:** Data curation, Writing - review &

editing. **Darren B. Courtney:** Data curation, Writing - review & editing. **Paul E. Croarkin:** Conceptualization, Writing - review & editing. **Daniel M. Blumberger:** Conceptualization, Writing - review & editing. **Zafiris J. Daskalakis:** Conceptualization, Writing - review & editing. **Faranak Farzan:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Supervision, Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Supplementary materials

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