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Neurophysiological markers of response to theta burst stimulation in youth depression

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Abstract

Background: Theta burst stimulation (TBS) has recently been proposed as a novel treatment for youth depression. However, the impact of TBS on the youth brain and neurophysiological predictors of response to TBS in this population have not been investigated.

Methods: Cortical reactivity was assessed at baseline and following 2 weeks of bilateral dorsolateral prefrontal cortex (DLPFC) TBS treatment in 16 youth with depression (aged 16–24 years old). In 16 age-matched health youths, cortical reactivity was assessed twice, 2 weeks apart. Transcranial magnetic stimulation (TMS) combined with electroencephalography was used to assess TMS-evoked potentials in bilateral DLPFC, motor cortices, and intraparietal lobules (IPL). Resting-state functional magnetic resonance imaging (fMRI) data was also collected at baseline.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Clinical Trial Registration Name: “Efficacy and Biological Targets of Response to rTMS Therapy in Youth Depression”.

Clinical Trial Registration Number: https://clinicaltrials.gov/ct2/show/NCT02472470.

Results: Left DLPFC pretreatment cortical reactivity, specifically the negativity at 45 ms (i.e., N45), which is related to $GABA_A$ neurotransmission, was associated with changes in depressive symptoms. Furthermore, TBS treatment was found to alter the N45 in the right IPL, a site distal to the treatment sites. The magnitude of the right IPL N45 modulation was correlated with the baseline fMRI connectivity between the right IPL and right DLPFC.

Conclusions: TMS-probed cortical inhibition at the site of TBS application may have potential as a predictor of treatment response in youth depression. Furthermore, pre-treatment functional connectivity may predict the impact of TBS on the neurophysiology of regions distal to the stimulation site. Collectively, these results offer novel neurophysiological insights into the application of TBS for youth depression, which may facilitate its wider use in the youth population.

Keywords

depression; electrophysiology; theta burst stimulation; transcranial magnetic stimulation; youth

1 | INTRODUCTION

Major depressive disorder (MDD) in youth (aged 15–24 years) has an approximate lifetime prevalence of 11.0% (Avenevoli et al., 2015). Youth MDD significantly impairs various domains of everyday functioning, including school, work, and relationships (Avenevoli et al., 2015). The initial treatment prescribed for youth MDD consists of antidepressants, psychotherapy, or a combination thereof (March et al., 2007). However, it has been estimated that 30%−50% of youth with MDD do not adequately respond to such conventional treatments (March et al., 2007). Furthermore, the use of antidepressants in youth has been associated with various side effects, including suicidal thoughts and behaviors (Hetrick et al., 2012; Stone et al., 2009). These findings suggest that alternative interventions are needed for the youth MDD population.

Repetitive transcranial magnetic stimulation (rTMS), a form of noninvasive brain stimulation, has been demonstrated to be efficacious in the treatment of adult MDD (Fitzgerald et al., 2006, Fitzgerald, Hoy, Daskalakis, et al., 2009; Fitzgerald, Hoy, McQueen, et al., 2009; Lam et al., 2008; Pascual-Leone et al., 1996). A more recent form of rTMS, known as theta burst stimulation (TBS; Huang et al., 2005), is equally effective as conventional rTMS in the treatment of adult treatment-resistant depression (Li et al., 2014), while requiring a fraction of the treatment time (Blumberger et al., 2018), thus showing promising potential as an alternative treatment for depression. Indeed, recent evidence even suggests that TBS may also be an efficacious treatment for depression in youth (Dhami et al., 2019).

Critical to the development of more efficacious treatments for MDD is a greater understanding of the neurophysiological correlates of treatment response (Williams, 2016). With regard to the relationship between TBS and neurobiology, evidence from animal and human studies suggest that TBS alters cortical inhibition by affecting various properties of interneuronal populations (Benali et al., 2011; Chung et al., 2015; Stagg et al., 2009). Furthermore, recent findings suggest that TBS can alter the GABA concentrations in sites

distal to the region of stimulation, and that the magnitude of these changes are correlated with the distal site's baseline functional connectivity to the stimulation site (Vidal-Piñeiro et al., 2015). Accordingly, as depression is associated with GABA deficits (Duman et al., 2019; Luscher et al., 2011), with such deficits hypothesized to be associated with a variety of depressive symptoms (Möhler, 2012; Northoff & Sibille, 2014), TBS may exert its therapeutic effect by modulating GABAergic interneurons. However, most of these studies have focused on the application of short-term TBS sessions with healthy adult participants. To advance TBS as a treatment for depression in youth, a greater understanding of its effects on youth neurophysiology is required. Such an understanding may aid with the development of more effective treatments and biomarkers as to which person may best respond to TBS. To our knowledge, no studies have yet investigated the neurobiological effects of TBS in the context of treatment for depression in youth.

We sought to address these questions in the context of an open label clinical trial, in which youth with MDD were recruited to participate in a bilateral dorsolateral prefrontal cortex (DLPFC) TBS intervention for 2 weeks; healthy youth controls were also recruited. The treatment protocol was based on prior evidence which showed that over a period of 2 weeks, bilateral TBS had the largest antidepressant effect compared with continuous TBS (cTBS), intermittent TBS (iTBS), and sham TBS (Li et al., 2014). Specifically, iTBS applied to the left DLPFC and cTBS to the right DLPFC was based on findings of the former region exhibiting hypoactivity (Baxter et al., 1989), and the latter exhibiting hyperactivity (Disner et al., 2011).

Participants underwent combined transcranial magnetic stimulation and electroencephalography (TMS–EEG) testing at both baseline and post-intervention. TMS–EEG was conducted at six cortical sites of interest: bilateral DLPFC, motor cortex, and intraparietal lobules (IPL). The inclusion of these six distinct cortical sites allowed us to determine if the effects of TBS on neurophysiology were site or network specific; the DLPFC is a major node of the frontoparietal network (Vincent et al., 2008; Yeterian et al., 2012), the motor cortex of the sensorimotor network (Damoiseaux et al., 2006), and the IPL of the default mode network (van den Heuvel & Hulshoff Pol, 2010).

Based on previous literature suggesting TBS affects cortical inhibition (Benali et al., 2011), we hypothesized TBS would exert its therapeutic effect by acting upon interneuronal populations to reduce excessive cortical reactivity, as measured by the magnitude of TMS-evoked potentials (TEPs), which has been observed in the DLPFC of both adults (Voineskos et al., 2018) and youth (Dhami et al., 2020) with depression. Accordingly, we speculated that higher interneuronal activation at baseline would be associated with better treatment response (Sun et al., 2016). We also postulated that any changes in TEPs at sites distal to the regions receiving TBS would be correlated with their baseline functional connectivity with the TBS sites; specifically, we hypothesized that the higher the functional connectivity between the stimulation and distal site, the greater the magnitude of change in the TEPs of the distal site. We note that the goal of the current study was to investigate the neural mechanisms of the treatment effects demonstrated in a separate manuscript (Dhami et al., 2019).

2 | MATERIALS AND METHODS

2.1 | Design

The clinical trial was designed as an open label 2-week TBS treatment trial and was registered (https://clinicaltrials.gov/ct2/show/NCT02472470).

2.2 | Sample

xIn total, 16 youth with MDD and 16 healthy youth controls were recruited. Eligibility criteria is provided in the supplementary materials. All participants provided written informed consent and the protocols were approved by Centre for Addiction and Mental Health in accordance with the Declaration of Helsinki.

2.3 | TBS intervention

The clinical intervention for youth with MDD consisted of 10 treatment sessions (i.e., once daily, 5 days a week, and for 2 weeks). Treatment sessions involved 1800 iTBS pulses applied to the left DLPFC and 1800 cTBS pulses applied to the right DLPFC. The administration order of whether iTBS or cTBS was applied first with was randomized for each participant (Li et al., 2014). For further information on the TBS intervention, please refer to Dhami et al. (2019).

2.4 | TMS–EEG testing

Each participant's MRI images were used to guide TMS coil positioning during TMS–EEG testing through the use of neuronavigation (Brainsight TMS Navigation; Rogue Resolutions). This approach provided both greater precision in targeting cortical regions of interest, as well as recording of the exact region that was assayed in the first study visit, allowing the same site to be tested for during the followup visit. The TMS–EEG testing protocol was done in accordance with current guidelines (Rossini et al., 2015), with details provided in the supplementary materials.

Participants underwent TMS–EEG testing twice. Both groups were assessed at baseline. For post TMS–EEG testing, youth with MDD were assessed within a week following the end of the 2-week TBS intervention, and healthy controls were assessed approximately 2 weeks after their baseline assessment.

2.5 | EEG recording and preprocessing

EEG was collected using a 64-channel Synamps 2 EEG system. All electrodes were referenced to an electrode positioned posterior to the Cz electrode. Before commencement of TMS–EEG testing, the impedance for all electrodes was lowered to ≤5kΩ or equal to 5 kΩ. EEG data were then recorded in DC mode with a sampling rate of 20 kHz. EEG data were preprocessed using the EEGLAB (Delorme & Makeig, 2004) and TMSEEG (Atluri et al., 2016) toolboxes as implemented in MATLAB, with further information provided in the supplementary material.

2.6 | Statistical analysis

Baseline demographic data were compared between groups using an independent-samples *t*-test or χ^2 test wherever appropriate. Changes in clinical data in the youth MDD group were assessed using dependent samples *t*-test.

For analysis of TMS–EEG measures of reactivity, the P30, N45, P60, N100, and P200 TEPs were compared between groups, independently for each stimulation paradigm. The predefined time window for each aforementioned TEP was respectively: 15–35, 30–50, 50–70, 70–120, and 150–250 ms, based on previous literature (Farzan et al., 2013; Premoli, Castellanos et al., 2014).

The statistical design was that of a 2 × 2 mixed factorial, in which group (youth MDD and healthy controls) was a two-level between group variable, and time (baseline and post-treatment) was a two-level within group variable. In accordance with previous TMS–EEG studies (Premoli et al., 2014, 2018), statistical testing was done for each TEP separately. Statistical analyses were done separately for each site of stimulation. For statistical testing in the context of a 2 × 2 mixed factorial design, as according to previous studies (Bracco et al., 2018), each statistical analysis was conducted according to the following procedure: first, an interaction effect was tested for based on the differential effect of group (youth MDD or healthy controls) depending on time (baseline and post) on the measure of interest. In other words, we assessed the difference between (youth MDD measure at baseline – youth MDD measure at post-treatment) and (controls measure at baseline – controls measure at post-treatment); if this difference was significant, an interaction was deemed present. If a significant interaction was present, we used independent or dependent *t*-tests (depending on the contrast) to assess the simple effects. If no significant interaction was present, we then assessed the main effects of group and time.

In the youth MDD sample, we conducted Pearson's correlations between neurophysiological markers and Hamilton Rating Scale for Depression (HRSD-17), Beck Depression Inventory (BDI), and Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015) scores. For sham analyses, changes in each TEP were assessed using dependent *t*-tests.

The aforementioned TMS–EEG analyses were conducted across all electrodes, with the significance threshold set at $p < .05$, and corrected for multiple comparisons using cluster-based nonparametric permutation testing (Maris & Oostenveld, 2007).

Statistical analyses of EEG data as described above were carried out using the FieldTrip toolbox (Oostenveld et al., 2011). All statistical analyses were performed using MATLAB 2018a (Mathworks Ltd.) and SPSS 25.0 (SPSS Inc.).

2.7 | Source reconstruction

Cortical sources for significant effects of interest at the sensor level were reconstructed with Brainstorm (Tadel et al., 2011). Information on the preprocessing and statistics used is available in the supplementary material.

2.8 | Resting state fMRI data acquisition and analysis

Resting-state functional magnetic resonance imaging (fMRI) data were obtained from all participants at baseline. Information on the acquisition parameters, preprocessing, and statistics used is available in the supplementary material. Analysis of the fMRI data was done with the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012).

3 | RESULTS

3.1 | Demographic and clinical characteristics

Demographic and clinical data are presented in Table 1 and Table 2, respectively. Both the youth MDD and healthy youth groups consisted of 16 participants. The number of participants' EEG data included in the final analysis varied between the six stimulation sites: left DLPFC (controls = 15, youth MDD = 13), right DLPFC (controls = 13, youth MDD = 15), left motor cortex (controls = 13, youth MDD = 14), right motor cortex (controls = 13, youth MDD = 14), left IPL (controls = 14, youth MDD = 12), and right IPL (controls = 13, youth MDD = 11).

3.2 | TEP differences between healthy youth and youth MDD and changes following TBS

TEPs following stimulation of each of the six cortical sites of interest are presented in Figure 1. Cluster-based permutation analyses revealed three main effects of group and one interaction effect between group and time. For the left DLPFC, there were two main effects of group: one for the P30 (positive cluster: $p = .009$; negative cluster: $p < .001$; Figure S1a) and one for the P200 (positive cluster: $p = .002$; negative cluster: $p = .0075$; Figure S1b). In addition, there was a group main effect for the right IPL P60 (negative cluster: $p = .0060$; Figure S1c).

For the right IPL N45 (Figure 2a), there was a significant interaction effect between group and time (positive cluster: $p = .0245$; Figure 2b). Accordingly, follow-up cluster-based permutation tests were conducted for simple effects, which revealed a significant reduction in the right IPL N45 in the youth MDD group following TBS treatment (negative cluster: $p = .0035$; Figure 2c,d); no other simple effects were found to be significant.

For both the left ($n = 7$) and right ($n = 6$) DLPFC sham conditions, no significant changes in any of the TEPs were found following TBS intervention.

3.3 | TEP associations with clinical variables in youth MDD

The baseline left DLPFC N45 was found to be significantly correlated with reduction in HRSD-17 scores following TBS treatment (positive cluster: $p = .007$ and mean cluster $r = .70$; negative cluster: $p = .024$ and mean cluster $r = -.68$; Figure 3a). No associations were found with BDI or DARS scores.

3.4 | Source reconstruction of significant TEP findings

As we were interested in significant simple effects, source reconstruction was done only for the finding of a reduction of the right IPL N45 in the youth MDD group following TBS treatment. For this effect, source analysis indicated that following TBS treatment, there was

a significant reduction of activity primarily in the left superior segment of the circular sulcus of the insula and the left intraparietal sulcus (Figure 2e).

3.5 | Association between changes in TEPs and baseline resting fMRI functional connectivity

We explored the relationship between changes in TEPs following TBS treatment and fMRI-measured baseline resting state functional connectivity. This association was initially explored for changes in the right IPL N45 in the youth MDD group, as it was the only significant pre-post neurophysiological effect that was found in our interaction models (information on how these associations were assessed are provided in the supplementary material). Changes in the right IPL N45 were found to be negatively correlated with right DLPFC and right IPL baseline connectivity (negative cluster: $p = .022$; mean cluster $r = -.72$; Figure 3b). No significant associations were found between the left DLPFC and right IPL baseline connectivity with changes in the right IPL N45.

In an exploratory analysis, we also investigated whether changes in TEPs at the remaining stimulated sites correlated with their functional connectivity with the TBS treatment sites.

For the left DLPFC, changes in its N100 were negatively correlated with its baseline functional connectivity with the right DLPFC (negative cluster: $p = .0045$; mean cluster $r = -.72$; Figure 3c). For the right DLPFC, changes in its P200 were correlated with its baseline functional connectivity with the left DLPFC (positive cluster: $p = .0015$; mean cluster $r = .64$; negative cluster: $p = .024$; mean cluster $r = -.65$; Figure 3d). For the left IPL, as well as the left and right sensorimotor regions, no associations were found with changes in their TEPs and baseline connectivity with either the left or right DLPFC.

4 | DISCUSSION

Novel treatments which generate improved efficacy are needed for youth with depression. TBS is a potential option, but the mechanisms of its antidepressant effect remain unclear. Furthermore, no study to date has assessed the neurophysiological changes following TBS in the youth MDD population. We sought to address this gap in the literature by investigating the relationship between TBS treatment and the neurophysiology of multiple cortical sites as assayed by TMS–EEG. Our key findings suggest that the baseline inhibitory properties, as measured by the N45, of the left DLPFC is associated with treatment response to bilateral DLPFC TBS. We also found TBS to modulate the N45 of the right IPL, with the magnitude of this modulation being correlated with the right IPL's baseline functional connectivity with the right DLPFC.

One of our hypotheses was that higher interneuronal activation at baseline at the stimulated sites would be associated with better treatment response. With regard to this hypothesis, we observed a correlation between the baseline N45 of the left DLPFC and reduction in depressive symptoms. The N45 is linked to $GABA_A$ neurotransmission (Premoli, Castellanos et al., 2014) as well as the inhibitory and excitatory balance between $GABA_A$ and glutamatergic neurotransmission (Darmani & Ziemann, 2019; Darmani et al., 2016; Koenig et al., 2019). This suggests that the integrity of the GABAergic system in the DLPFC

may be critical in the therapeutic potential of TBS. This is congruent with evidence that suggests the therapeutic mechanism of magnetic stimulation may be related to trans-synaptic interneuron functioning (Baeken et al., 2017; Di Lazzaro et al., 1998). It was recently reported that greater baseline TMS–EEG measures of GABA-related cortical inhibition in the DLPFC is associated with a greater reduction in suicidal ideation following magnetic seizure therapy (MST) in adults with MDD (Sun et al., 2016). It may be that a more robust interneuronal network may allow for better transsynaptic activation of neuronal circuits during either rTMS or MST, leading to a greater treatment response (Sun et al., 2016).

The collection of TEP-related differences between groups suggests youth MDD to be associated with dysregulation of cortical reactivity across the cortex (Dhami et al., 2020), which may reflect alterations in excitatory and inhibitory mechanisms. The P30 and P200, both potentially related to voltage-gated sodium channel activity (Darmani et al., 2019), were found to be altered in the left DLPFC of youth MDD. This is in partial accordance with a recent study which also found TMS–EEG measures of cortical reactivity to be altered in the left DLPFC of adults with MDD (Voineskos et al., 2018). In addition, the right IPL P60, linked to glutamatergic neurotransmission (Koenig et al., 2019), was found to differ between youth MDD and healthy controls.

Although alterations in cortical reactivity in the youth MDD group were found across the DLPFC and IPL, following the bilateral DLPFC TBS treatment, the only significant change in reactivity found in the youth MDD group was a reduction in the right IPL N45. Although the exact neural mechanisms of TBS remain unknown, both animal and human studies suggest it to have an effect on inhibitory interneuron functioning (Chung et al., 2015). TBS has been demonstrated to primarily increase the expression of enzymes related to GABA synthesis (e.g., GAD65 and GAD67), which are expressed in cortical inhibitory interneurons (Trippe et al., 2009), as well as change the cortical expression of proteins parvalbumin and calbindin D-28k. This suggest that alterations in cortical activity following TBS may be related to changes in inhibitory systems (Benali et al., 2011). When applied to the human motor cortex, cTBS acutely increases local cortical GABA concentrations (Stagg et al., 2009). iTBS of the prefrontal cortex reportedly increases the TMS–EEG elicited N100 TEP (Chung et al., 2017; Chung, Rogasch, Hoy, & Fitzgerald, 2018; Chung, Rogasch, Hoy, Sullivan, et al., 2018), which is believed to reflect $GABA_B$ neurotransmission (Premoli, Castellanos et al., 2014). In addition, animal studies suggest changes in GABA levels following rTMS may be region-dependent (Yue et al., 2009). Thus, the literature, although equivocal, collectively suggests that TBS has an effect on inhibitory interneuron functioning. This may partly explain why TBS altered the N45 of the right IPL.

Whether TBS at one cortical site can influence the neurophysiology of a distal site is critical to the interpretation of why bilateral DLPFC TBS led to a decrease in the right IPL N45. In a recent study, iTBS was applied to the left IPL while GABA and glutamate levels using magnetic resonance spectroscopy (MRS) were measured in other regions belonging to the default mode network (Vidal-Piñeiro et al., 2015). Although the authors found no local changes near the stimulation site, distal GABA levels increased in the posteromedial default mode network. GABA modulation in these distal sites was related to their baseline functional connectivity with the iTBS-targeted left IPL, suggesting that TBS may modulate

neurotransmitters in distal sites belonging to the same functional network as the stimulation site. The ratio of GABA to glutamate also reportedly decreases following TBS to the DLPFC in both regions local and distal to the site of stimulation (Iwabuchi et al., 2017); however, such studies involved the application of TBS for only a short duration in healthy controls. Here, we provide novel evidence that 10 sessions of bilateral DLPFC TBS can alter the neurophysiology of distal sites (i.e., the right IPL) associated with different functional networks in youth with depression. Furthermore, we show that neurophysiology changes at distal sites are correlated with their baseline functional connectivity with the TBS stimulation site(s). This finding provides evidence that TBS-induced activation in a targeted area may propagate to anatomically and functionally connected distal regions, potentially leading to a cascade of neurobiological changes (Bortoletto et al., 2015), and that the extent of these changes may be dependent on the functional connectivity between the stimulation site and the distal region. We do note that our sample of interest consisted of youth, making it difficult to infer whether our findings and their interpretation could be extrapolated to adult populations older than 24 years as well.

To our knowledge, only two studies to date have assessed the neurophysiological changes following rTMS treatment in youth with MDD (Croarkin et al., 2016; Yang et al., 2014); both studies applied 10-Hz rTMS to the left DLPFC and using MRS, reported treatment-induced increases in glutamate levels in the left DLPFC. In the adult MDD literature, findings are mixed as to whether significant changes in glutamate and GABA levels occur in the prefrontal cortex following treatment with 10-Hz rTMS applied to the DLPFC (Baeken et al., 2017; Dubin et al., 2016). We found no significant changes in the cortical reactivity of the DLPFC following TBS treatment. This absence may be explained, in part, by the potential nonanalogous relationship between MRS-measured free concentration levels of metabolites and their influence on neurotransmission as measured by TMS–EEG (Croarkin et al., 2013; Voineskos et al., 2018). Alternatively, 10-Hz high frequency rTMS and TBS may modulate these metabolites differently. Extending beyond rTMS, electroconvulsive therapy and antidepressants have both been reported to increase GABA levels post-treatment in adults suffering from MDD, although such findings were in the occipital cortex (Bhagwagar et al., 2004; Sanacora et al., 2002). It may be that the greatest TBS-induced changes in neurophysiology occur at distal, not local, sites (Vidal-Piñeiro et al., 2015). Irrespective of the directionality of change, modulation of GABA seems to be associated with antidepressant treatment response. To this extent, we report 2 weeks of daily DLPFC TBS to be associated with alterations in GABAergic neurotransmission in youth MDD. By assaying multiple cortical sites with TMS–EEG, we were able to find region-specific neurophysiological markers of TBS treatment in youth MDD. Our findings suggest that the therapeutic mechanism of TBS is partly related to TMS-evoked brain reactivity approximately 45 ms post-TMS, linked to GABAergic neurotransmission, in regions both local and distal to the site of stimulation. This finding ultimately suggests that the therapeutic potential of TBS may be related to the GABAergic-related interneuronal properties of regions both local and distal to the site of stimulation.

Bilateral DLPFC TBS was only found to alter the neurophysiology of the right IPL, a site distal to the stimulated regions. Furthermore, the magnitude of these changes in the right IPL were correlated with the baseline functional connectivity between this region and the

right DLPFC. These findings suggest that the therapeutic efficacy of TBS may be dependent on the functional connectivity of the stimulated region. To investigate the neurocognitive model which suggests that depression is related to the left DLPFC being hypoactive and the right DLPFC being hyperactive (Disner et al., 2011), we assessed the cortical reactivity of the left and right DLPFC before and after TBS treatment. However, we found no cortical reactivity changes in both regions. It is important to note the DLPFC asymmetry model is primarily based on abnormalities in alpha oscillations (Gotlib et al., 1998). However, how alpha abnormalities relate to the TEP measures assessed in our study remains to be established. As aforementioned, an alternate hypothesis that may explain the therapeutic effects of TBS is that TBS may exert its therapeutic impact by acting on the functional connectivity of the stimulated site. In a recent study, youth MDD was found to be associated with excessive right DLPFC connectivity (Dhami et al., 2020). As cTBS has previously been reported to reduce the functional connectivity of the stimulated region (Rahnev et al., 2013; Rastogi et al., 2017; Steel et al., 2016), it may be that the use of cTBS in our protocol reduced this excessive functional connectivity of the right DLPFC in youth with MDD. iTBS has also been found to increase the functional connectivity of the stimulated region (Halko et al., 2014), further suggesting that our bilateral DLPFC TBS treatment protocol may have exerted its therapeutic effect by altering the connectivity of the left and right DLPFC. However, assessing how TBS altered the connectivity of the stimulate sites was beyond the scope of the current study. Future research is needed with both healthy and clinical populations with large sample sizes to investigate the impact of the bilateral TBS protocol on the functional connectivity in the brains of youth.

There are some limitations in our study worth noting. First, we are unable to directly link TEPs to neurotransmission systems, although TMS–EEG pharmacological studies have made progress in establishing such relationships (Darmani & Ziemann, 2019; Darmani et al., 2019; Koenig et al., 2019; Premoli, Castellanos et al., 2014; Premoli, Rivolta et al., 2014). We also note the issue of the potential contamination of TEPs by sensory and auditory artifacts (Conde et al., 2019), although we note that the region specificity of our findings make it unlikely that they were influenced by such artifacts. Furthermore, the inclusion of sham TMS–EEG testing, which provided null results (albeit with a small sample size), suggest that the changes we found reflect alterations in TMS-probed cortical reactivity. There was also a lack of a sham control treatment arm. We also could not disentangle the distinct effects of iTBS and cTBS on the neurophysiological changes reported as the treatment consisted of application of both types of TBS; future studies may wish to investigate the unique effects of each type of TBS on cortical neurophysiology as measured by TMS–EEG. Finally, the sample size of our study was small and thus was underpowered to detect small or medium sized effects; this calls for replication of our findings with larger sample sizes in future studies.

TBS has great potential to be an alternative treatment for youth suffering from depression who do not respond to conventional treatments. However, to advance the use of TBS in the youth population, insight into the neurophysiological effects of TBS on the youth brain is required. Our results suggest that the efficacy of TBS for youth depression may in part be related to cortical inhibition at sites both local and distal to the site of therapeutic stimulation. Furthermore, we provide novel insight into the neurophysiological mechanisms

of TBS on a network level; specifically, the neurophysiological changes induced by TBS in the youth brain at distal sites may be related to the functional connectivity between the distal site and the site of TBS. Altogether, our findings elucidate the neurophysiological mechanisms of TBS for treatment of depression in youth, which may in turn aid with the advancement of using TBS in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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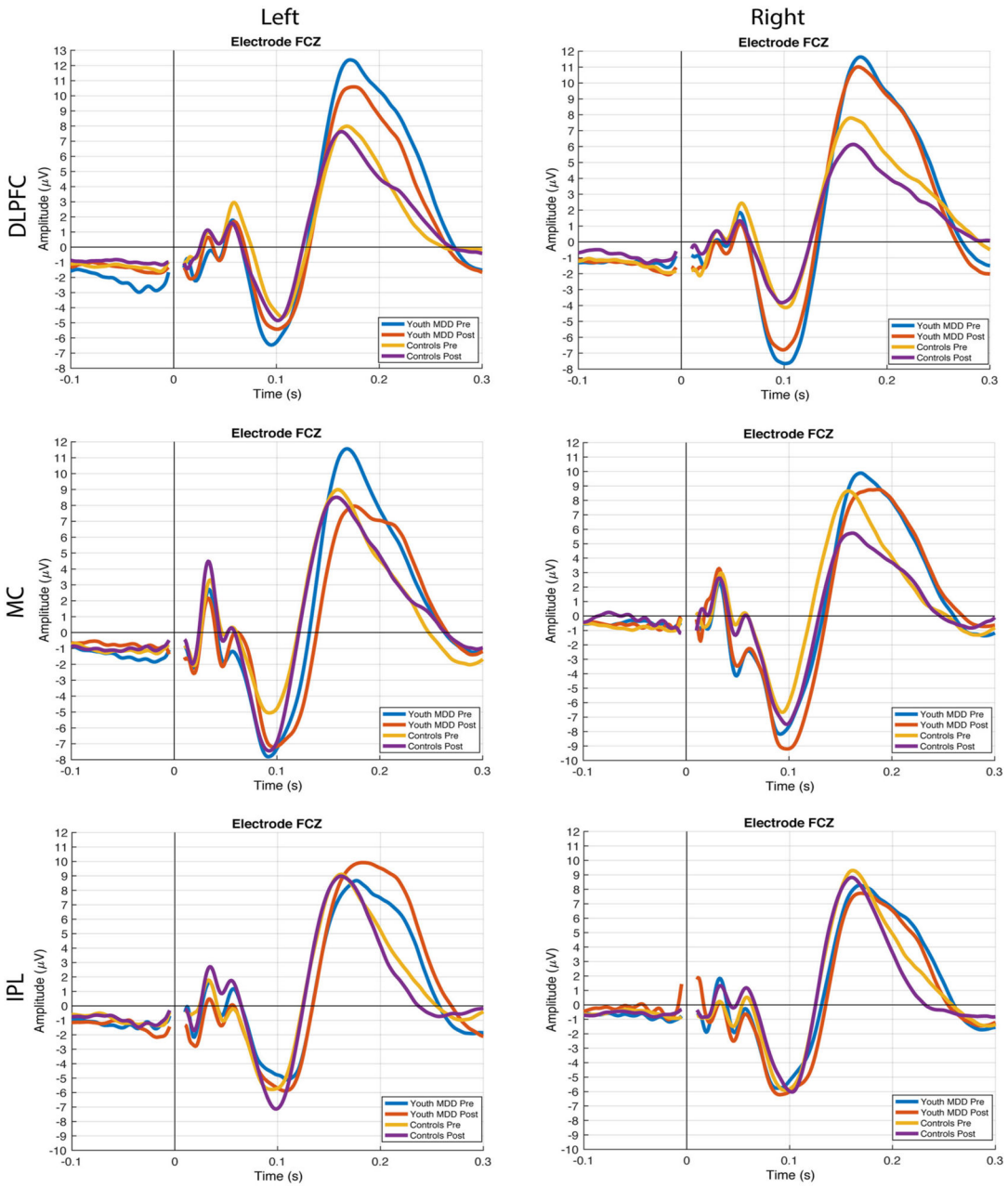

FIGURE 1.

TEPs following stimulation of each of the six cortical sites of interest. Illustrated are the TEPs from electrode FCz for each group at each time point following stimulation of the bilateral DLPFC, motor cortex (MC), and IPL. DLPFC, dorsolateral prefrontal cortex; IPL, intraparietal lobules; TEPs, transcranial magnetic stimulation-evoked potentials.

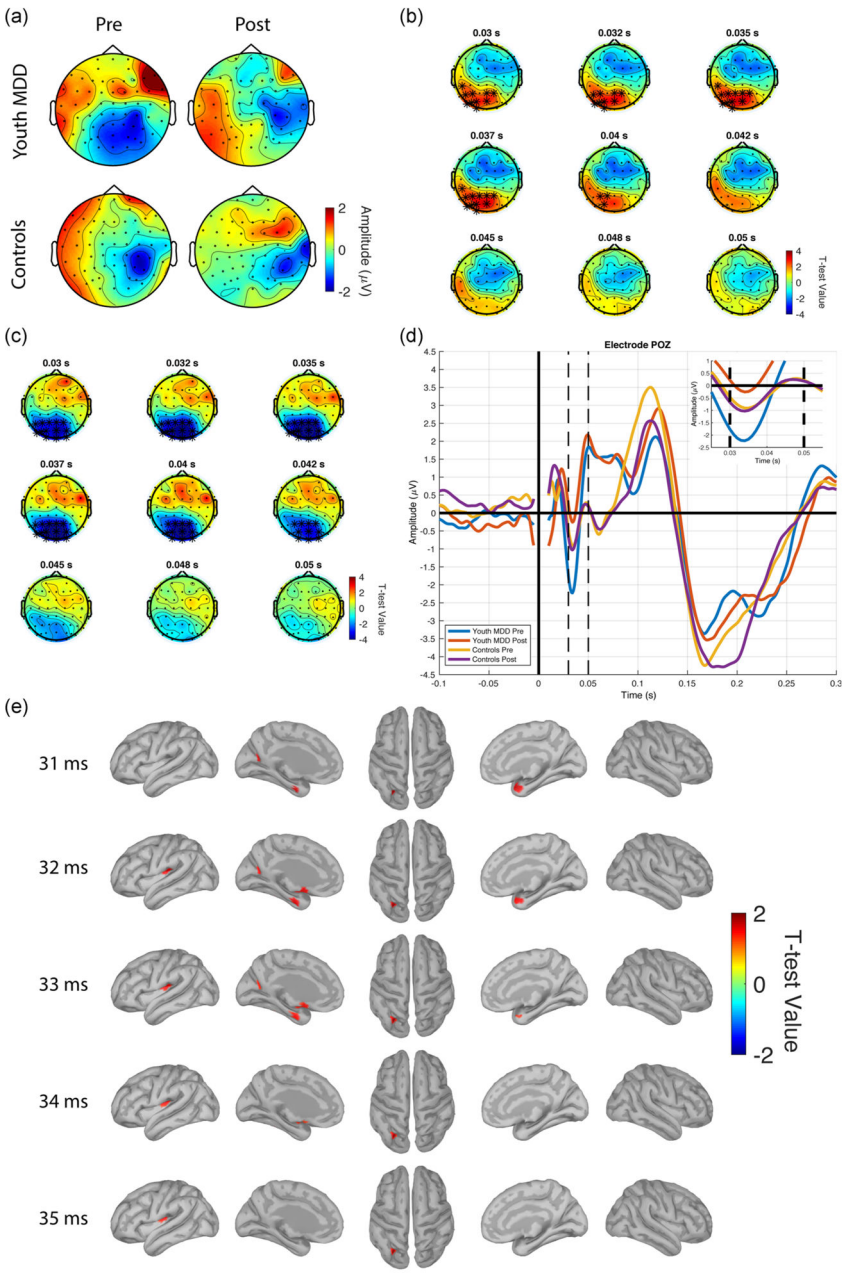

FIGURE 2.

Right IPL N45 interaction effect. (a) Mean N45 (30–50 ms) topoplots for each group by time factor. (b) Topoplots displaying electrodes (with asteriks) that belonged to a significant interaction cluster between group and time. (c) Topoplots displaying electrodes (with asteriks) that belonged to a significant cluster for the simple effect contrast of pre-treatment versus post-treatment right IPL N45 in the youth MDD group. Cold colour areas represent where and when the absolute magnitude of the N45 became smaller following TBS treatment. All other simple effects were found to be nonsignificant. (d) A TEP plot demonstrating the reduction (i.e., becoming less negative) of the right IPL N45 in the youth MDD group following TBS treatment. (e) Cortical maps illustrate areas of significant

difference (based on *t*-values derived from dependent samples *t*-test, projected on an ICBM152 cortex template) within the youth MDD group for the right IPL N45 (uncorrected threshold at $p < .05$). IPL, intraparietal lobules; MDD, major depressive disorder; TBS, theta burst stimulation; TEP, transcranial magnetic stimulation-evoked potential.

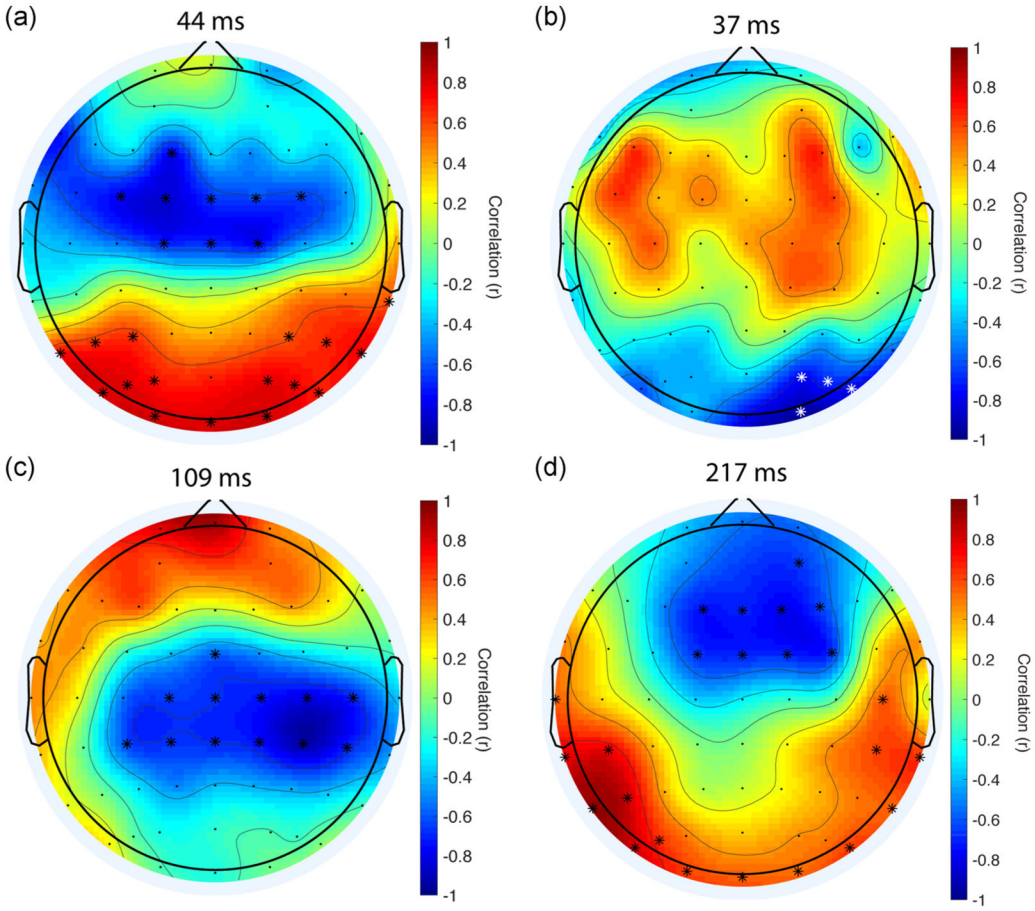

FIGURE 3.

Significant correlation results. Topoplots displaying electrodes (with asteriks) that belonged to a significant positive or negative correlation cluster at the latency provided above each topoplot. (a) Correlation between baseline left DLPFC N45 and change in depressive symptoms in youth MDD. (b) Correlation between baseline right DLPFC and right IPL functional connectivity and changes in the right IPL N45 in youth MDD. (c) Correlation between changes in left DLPFC N100 and the left DLPFC's baseline functional connectivity with the right DLPFC. (d) Correlation between changes in right DLPFC P200 and the right DLPFC's baseline functional connectivity with the left DLPFC. DLPFC, dorsolateral prefrontal cortex; IPL, intraparietal lobules; MDD, major depressive disorder

TABLE 1

Demographic data for youth with MDD and healthy youth

Characteristic	Youth MDD	Healthy youth	*p*
Sample size, *N*	16	16	NA
Age, mean (*SD*)	20.63 (2.78)	21.19 (1.91)	.509
Number of males, *N* (%)	8 (50)	7 (44)	.723
Education, mean (*SD*)	13.94 (2.29)	14.94 (1.8)	.181
Employment status, *N* (%) employed	4 (25)	7 (44)	.264

Abbreviation: MDD, major depressive disorder.

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TABLE 2

Clinical data for youth with MDD

Characteristic	Baseline	Post TBS treatment	*p*
HRSD-17, mean (*SD*)	22.00 (2.68)	13.44 (5.15)	<.001
BDI-II, mean (*SD*)	37.81 (8.07)	25.38 (13.66)	.001
DARS, mean (*SD*)	43.81 (16.65)	49.69 (20.34)	.009
ATHF, mean (*SD*)	2.63 (2.19)	NA	NA

Abbreviations: ATHF, Antidepressant Treatment History Form; BDI, Beck Depression Inventory; DARS, Dimensional Anhedonia Rating Scale; HRSD-17, Hamilton Depression Rating Scale; MDD, major depressive disorder; TBS, theta burst stimulation.