Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2026 March 01.

Published in final edited form as:

J Affect Disord. 2025 March 01; 372: 665–675. doi:10.1016/j.jad.2024.12.057.

Deep Transcranial Magnetic Stimulation for Adolescents with Treatment-Resistant Depression: Behavioral and Neural Correlates of Clinical Improvement

Aparna U. Nair[a,*], **Bonnie Klimes-Dougan**[b], **Thanharat Silamongkol**[c], **Zeynep Başgöze**[a], **Donovan J. Roediger**[a], **Bryon A. Mueller**[a], **Cristina S. Albott**[a], **Paul E. Croarkin**[d], **Kelvin O. Lim**[a], **Alik S. Widge**[a], **Ziad Nahas**[a], **Lynn E. Eberly**[e], **Kathryn R. Cullen**[a,**], **Michelle E. Thai**[b,f,**]

[a]Department of Psychiatry & Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA

[b]Department of Psychology, University of Minnesota, Minneapolis, MN, USA

[c]Graduate School of Applied and Professional Psychology, Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

[d]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

[e]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[f]Center for Depression, Anxiety, and Stress Research, McLean Hospital, Belmont, MA, USA and Department of Psychiatry, Harvard Medical School, Boston, MA, USA

[*] Corresponding author: nair0035@umn.edu, University of Minnesota, Twin Cities, Masonic Institute for the Developing Brain, 2025 East River Parkway Minneapolis, MN 55414.

[**]Co-senior authors

Authorship Contribution Statement

Aparna U. Nair: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. Bonnie Klimes-Dougan: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. Thanharat Silamongkol: Writing – review & editing, Writing – original draft, Project administration, Data curation. Zeynep Başgöze: Writing – review & editing, Methodology, Conceptualization. Donovan J. Roediger: Writing – review & editing, Methodology. Bryon A. Mueller: Writing – review & editing, Methodology, Conceptualization. C. Sophia Albott: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. Paul E. Croarkin: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. Kelvin O. Lim: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. Alik S. Widge: Writing – review & editing, Supervision, Project administration, Methodology, Investigation. Ziad Nahas: Writing – review & editing, Project administration, Methodology, Investigation. Lynn E. Eberly: Writing – review & editing, Supervision, Formal analysis. Kathryn R. Cullen (co-senior author): Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. Michelle Thai (co-senior author): Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis, Data curation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declarations of interest:

Dr. Croarkin has received research grant support from the Agency for Healthcare Research and Quality, the National Institutes of Health, the National Science Foundation, the Brain and Behavior Research Foundation, the Mayo Clinic Foundation, Pfizer, Inc., Neuronetics, Inc., and NeoSync, Inc. He has received equipment support from Neuronetics, Inc. and MagVenture, Inc. He has received supplies and genotyping services from Assurex Health, Inc. for an investigator-initiated study. He was the principal investigator for a multicenter study funded by Neuronetics, Inc., and a site principal investigator for a study funded by NeoSync, Inc. He has served on advisory boards or as a consultant for Engrail Therapeutics, Myriad Neuroscience, and Sunovion. He has served as a paid consultant for Meta Platforms, Inc. and Procter & Gamble Company. He receives compensation for work as the Editor-in-Chief of the *Journal of Child and Adolescent Psychopharmacology*. He is employed by Mayo Clinic.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Abstract

Background: Affective bias towards negativity is associated with depression and may represent a promising treatment target. Stimulating the dorsolateral prefrontal cortex (dlPFC) with deep Transcranial Magnetic Stimulation (dTMS) could lead to shifts in affective bias. The current study examined behavioral and neural correlates of affective bias in the context of dTMS in adolescents with treatment-resistant depression (TRD).

Methods: Adolescents completed a Word-Face Stroop (WFS) task during an fMRI scan before and after 30 sessions of dTMS targeting the left dlPFC. In the task, participants were shown words superimposed on faces in either a "congruent" (both word and face were positive or both negative) or an "incongruent" fashion; in both cases, participants identified whether the words were positive or negative. We examined pre-post intervention neural and behavioral WFS changes and their correlations with clinical improvement.

Results: Usable pre- and post-intervention WFS data were available for 10 adolescents with TRD (Age, years: M = 16.3, *SD* = 1.09) for behavioral data; 9 for neuroimaging data. After treatment, although changes in behavioral performance did not suggest improved affective bias, amygdala activation decreased during the negative word/happy face condition, which correlated with clinical improvement. Overall, clinical improvement correlated with decreased neural activation during congruent conditions.

Limitations: Major limitations include the small sample size, lack of a sham control group, and unknown psychometric properties.

Conclusions: Preliminary findings suggesting improving neural efficiency and normalizing affective bias in those with the most clinical improvement highlight the potential importance of targeting affective bias in treating adolescents with TRD.

Keywords

Depression; Treatment-resistance; Transcranial Magnetic Stimulation; Affective Bias; Adolescence

Introduction

Depressive disorders are a leading cause of years lived with disability in adolescents 14 years and older around the globe (GBD 2019 Mental Disorders Collaborators, 2022). Depression is highly impairing, impacting not only the emotional health of adolescents but also their cognitive and physical well-being. Only 70% of adolescents improve adequately following evidence-based antidepressant treatments (Kennard et al., 2009; March et al., 2004), highlighting the need for novel interventions. Furthermore, research on neural and cognitive mechanisms of novel treatments can inform our understanding of *how* such treatments work and provide a framework for their optimization.

Repetitive transcranial magnetic stimulation (rTMS) is an effective intervention for treatment-resistant depression (TRD), a form of depression in which individuals do not respond adequately to at least one standard treatment, in adults (Gaynes et al., 2014) and adolescents (Bloch et al., 2008; Croarkin et al., 2021; Maalouf et al., 2011; Mayer et al.,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2012; Wall et al., 2016). The Food and Drug Administration (FDA) approved TMS for adults with major depressive disorder (MDD) in 2008 and recently approved the NeuroStar TMS therapy as an adjunctive treatment for MDD in patients aged 15–21 (U. S. Food and Drug Administration, 2024). More recently, deep TMS (dTMS) using the H1 coil, an FDA-cleared treatment for TRD in adults (Filipčić et al., 2019; Kaster et al., 2018; Levkovitz et al., 2015, 2009), was developed to increase efficacy in treating depression by targeting deeper subcortical and dorsolateral prefrontal cortex (dlPFC) connections. This may facilitate the improvement of not only top-down cognitive control but also emotion regulation, reward processing, and rumination (De Raedt et al., 2015; Parazzini et al., 2017; Roth et al., 2007; Zibman et al., 2021). Furthermore, preliminary evidence suggests the H1 coil may have greater effects on symptom reduction than the standard figure-of-eight coil (Gellersen and Kedzior, 2019). Although there is insufficient research testing dTMS in adolescents, preliminary evidence supports its safety and efficacy (Levkovitz et al., 2015; Muir et al., 2020; Thai et al., 2024). Further research is needed to confirm the efficacy of dTMS and understand its treatment mechanisms in adolescents. Moreover, identifying behavioral and neural correlates of clinical improvement in this population could guide the personalization of treatment parameters to maximize efficacy.

Affective biases are a critical mechanism implicated in depression that may be relevant for understanding the mechanisms of dTMS. Individuals with MDD tend to excessively engage with and struggle to disengage from negative stimuli (Gotlib and Joormann, 2010). This bias is closely linked to rumination (Joormann, 2010), which, in turn, exacerbates depression, resulting in a vicious cycle of worsening distress (Joormann, 2010; Nolen-Hoeksema et al., 2008). Moreover, the bias toward negativity is accompanied by a bias away from positivity (LeMoult and Gotlib, 2019). As a result, depressed individuals tend to be more easily distracted by negative than positive information. This bias can be measured by Emotional Stroop and Dot-Probe tasks in which participants must attend to one aspect of an emotional stimulus (the target) while ignoring another (the distractor; Epp et al., 2012; Peckham et al., 2010). For instance, in an Emotional Stroop task called the Word-Face Stroop (WFS) task (Başgöze et al., 2015; Thai et al., 2020), participants are shown competing emotional items: an emotionally charged word (the target) superimposed on a happy or sad human face (the distractor). The WFS task has been found to effectively probe affective bias as depressed participants performed more accurately to negative target words and positive distractors, whereas healthy controls showed the opposite pattern and a bias towards positivity (Başgöze et al., 2015).

Four neural networks have been implicated in depression and affective biases: the frontolimbic, dorsal corticostriatal, ventral corticostriatal, and default mode (DMN) networks (Elliott et al., 2011). First, hypoactivation of prefrontal regions and hyperactivation of limbic regions such as the amygdala and subcallosal cortex in the frontolimbic network underlie the bias toward negativity (Chechko et al., 2013; Fales et al., 2008; Fu et al., 2008, 2007; Hamilton and Gotlib, 2008; Lee et al., 2008; Suslow et al., 2010; Victor et al., 2010; Williams, 2017). Specifically, in individuals with MDD, these limbic regions have been found to be hyperactive in response to negative stimuli (Phan et al., 2002; Suslow et al., 2010). Secondly, underactivity of the dorsal corticostriatal network contributes to difficulties with cognitive control and flexibility (Dichter et al., 2009; Fales et al., 2008; Kaiser et al.,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2015; Levin et al., 2007; Rogers et al., 2004; Wang et al., 2008). Third, hypoactivation of the ventral anterior cingulate cortex and striatum in the ventral corticostriatal network is linked to blunted responsivity to reward and positivity (Elliott et al., 2002; Forbes et al., 2006; Pizzagalli et al., 2009). Additionally, hyperactivation and nonsuppression of the DMN is associated with rumination and poor task engagement (Guha et al., 2021; Marchetti et al., 2012).

The potential for dTMS to target subcortical prefrontal, limbic, and striatal brain regions (Zibman et al., 2021) makes it a promising tool for treating depression by reducing affective bias. To our knowledge, no study has examined the effects of TMS on affective bias in adolescents or adults. The current preliminary study aimed to investigate the neurocognitive effects of an open-label dTMS trial (Thai et al., 2024) that found preliminary evidence for tolerability and effectiveness in treating adolescents with TRD. We examined pre- to post-treatment behavioral and neural changes in affective bias and their associations with clinical improvement. At the behavioral level, we expected dTMS to reduce affective bias assessed by the WFS task (Başgöze et al., 2015; Thai et al., 2020), evidenced by reduced engagement with and distraction by negative stimuli and increased engagement with and distraction by positive stimuli. Neurally, we expected dTMS to increase activation in the left dlPFC (targeted region), the dorsal corticostriatal network (a neural signature of improved behavioral flexibility), and the ventral corticostriatal network, specifically, the nucleus accumbens (due to increased engagement with positivity). In contrast, we expected decreased activation in the limbic regions of the frontolimbic network (due to reduced engagement with negativity) and decreased DMN activation (due to reduced task-irrelevant processing and rumination). We expected the largest changes in behavior and activation during the incongruent condition with a negative distractor, as it is typically the most challenging for depressed individuals (Başgöze et al., 2015). We further predicted that the behavioral reduction in affective bias and neural changes would correlate with improvement in depression.

Materials and Methods

Study Design and Participants

The study (ClinicalTrials.Gov NCT02611206; Investigational Device Exemption # G150132) was approved by the University of Minnesota Institutional Review Board. Trial details are available in a previous manuscript (Thai et al., 2024). Briefly, this was an open-label, single cohort study. The treatment protocol consisted of 30 dTMS sessions (BrainsWay H1 coil, 10 Hz, 20s inter-train interval, 3.6s train duration, 55 trains; 1980 pulses/session, stimulation intensity: 80% to 120% of motor threshold) administered over six weeks targeting the left dlPFC. We recruited adolescents aged 12–18 years old with MDD and treatment resistance as defined by failure to respond adequately to at least one antidepressant treatment (Dwyer et al., 2020; Fava, 2003). An initial telephone screening was followed by informed consent and assent from participants and their parents/guardians. Eligible participants completed clinical and behavioral assessments and a functional magnetic resonance imaging (fMRI) scan before and after treatment.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Clinical Assessment

Depression severity was measured using the clinician-administered Children's Depression Rating Scale-Revised (CDRS-R; total scores range from 17 to 113; Poznanski and Mokros, 1996) and the participant-reported Beck Depression Inventory (BDI-II; total scores range from 0 to 63; Osman et al., 2004). CDRS-R scores were based on a consensus rating between teen and parent reports. Clinical improvement was measured as percent change using the formula: [(baseline score - post-treatment score)/(baseline score - minimum possible total score)]*100 (Tao et al., 2009). Higher percent changes indicate greater clinical improvement post-treatment.

Behavioral Assessment

The WFS task, tested in Turkish and English, and utilized in multiple samples (Başgöze, 2015; Başgöze et al., 2015; Luciana et al., 2018; Thai et al., 2020), was administered during each fMRI scan. In this task, participants were shown words printed over happy or sad human faces and were asked to identify whether the word had a positive (e.g., sunset) or negative (e.g., infection) emotional connotation (i.e., the word's valence; see Figure S1; Başgöze et al., 2015). Stimuli were presented for 2000 milliseconds (ms), with fixation crosses appearing for 2, 4, or 6 seconds between trials. The stimuli could be congruent (word and facial expression matched in valence) or incongruent (word and facial expression did not match in valence), resulting in four embedded stimuli conditions: Congruent Positive (positive word/happy face), Congruent Negative (negative word/sad face), Incongruent Positive (positive word/sad face), and Incongruent Negative (negative word/happy face). The task consisted of 128 trials divided into four runs of 32 trials each to prevent fatigue and boredom. Reaction time (RT) and accuracy (percentage of accurate responses) were assessed as dependent variables. For calculating RT, only accurate trials were included, and trials with RT less than 350 ms and missing responses (missing response range across the four runs for the final dataset: 0 to 23/128) were discarded. Subjects who did not complete all four runs or had accuracy (mean accuracy across all embedded conditions and runs) below 60% at either time point were excluded (see Figure 1). Changes in RT and accuracy were calculated by subtracting pre- from post-treatment scores, with higher change scores indicating greater accuracy and slower reaction times post-treatment.

Neuroimaging Assessment

Participants completed fMRI scans at the Center for Magnetic Resonance Research at the University of Minnesota in a Siemens 3 Tesla Prisma scanner (Erlangen, Germany) and a 32-channel receive-only head coil. Four fMRI scans were acquired using the Human Connectome Project (HCP) multiband pulse sequences (Multiband Factor [MB] = 3, Repetition Time [TR] = 2,000 ms, Echo Time [TE] = 37 ms, 2 mm isotropic voxel size, 100 volumes [~3.5 min per run]).

MRI Data quality was assessed using a method similar to Power et al. (2012). Volumes with framewise displacement greater than 0.5 mm and/or a DVARS (an index of the rate of change of brain signal intensity at each volume; D = temporal derivative of time series; VARS = root mean squared variance over voxels) greater than 8, together with the volume before and the two volumes after, were flagged. Sessions with greater than 30% of volumes

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

flagged were excluded from further analysis. The MRI data were processed using the HCP minimal preprocessing pipelines (Glasser et al., 2013; see supplemental Section S1 for more detail), including the first and second-level task analysis scripts. For each run, the task model was regressed onto the fMRI data using a first-level analysis with the four embedded task conditions relative to baseline as explanatory variables. These results were then combined across runs within each time point using a second-level fixed effects analysis. Mean-centered RTs were added as a covariate to control for individual differences in RT. Z-scores were extracted from the selected regions of interest (ROIs) defined using the Glasser Atlas (Glasser et al., 2016).

Four key networks and nine key within-network regions were selected as ROIs for analyses: the (1) hippocampus, (2) amygdala, and (3) subcallosal cortex within the (4) frontolimbic network; the (5) dorsal anterior cingulate cortex and medial prefrontal cortex region (dACC/mPFC) and the (6) left and (7) right dlPFC within the (8) dorsal corticostriatal network; the (9) ventral anterior cingulate cortex and medial prefrontal cortex region (vACC/mPFC) and the (10) accumbens within the (11) ventral corticostriatal network; and the (12) posterior cingulate cortex (PCC) within the (13) DMN (see Table S1 for details). Network activation values were calculated by averaging the z-scores for within-network ROIs. Changes in activation were calculated by subtracting pre- from post-treatment z-scores, with higher change scores indicating increased activation post-treatment.

Statistical Analysis

Data analyses were conducted in R version 4.0.3. Behavioral performance on the WFS task was assessed with a three-way (2×2×2) repeated measures analysis of variance (ANOVA) test with congruency (congruent/incongruent), word valence (positive/negative), and time (pre/post) as within-subject independent variables for the dependent variables of RT and accuracy. Neural activity during the task was examined using two-way (2×4) repeated measures ANOVAs to test the effects of time (pre/post) and embedded condition (Congruent Positive/Congruent Negative/Incongruent Positive/Incongruent Negative) on activation. Post-hoc ANOVA and Hochberg-corrected pairwise t-tests were conducted to probe significant interactions. For ANOVA tests, partial eta squared was calculated, and Greenhouse-Geisser correction was used when the sphericity assumption was violated. Square-root transformation was applied to accuracy data since it was not normally distributed. Pearson's correlation tests were conducted to examine the associations between changes in behavioral performance, neural activation, and clinical improvement by embedded condition. For correlation tests, due to the limited power from our small sample size, we focused on effect sizes and unadjusted p-values in addition to Hochberg-corrected p-values. The strength of effect sizes was determined as follows: 0.3 to 0.5 = medium to large; > 0.5 = large to very large effect size (Cohen, 2013).

Results

Participants

As shown in the CONSORT diagram (Figure 1), 13 participants underwent the pre-treatment, and 12 underwent the post-treatment MRI scan. After excluding participants with

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

unusable or incomplete data at one or both time points, 10 participants were included in the behavioral and 9 in the neural analyses. Baseline demographic characteristics are presented in Table 1, and clinical outcomes are described in supplemental Section S2.

Behavioral

Reaction Time—There was a main effect of congruence on RT; participants responded slower on incongruent than congruent trials, $F(1, 9) = 24.048$, $p < .001$, $\eta p^2 = .728$. Additionally, there was a three-way interaction, $F(1, 9) = 7.46$, $p = .023$, $\eta p^2 = .453$ (see Figure 2A). Post-hoc two-way ANOVAs revealed an interaction between congruence and valence pre-treatment ($F[1, 9] = 9.98$, $p = .012$) but not post-treatment ($p = .163$). Although post-hoc Hochberg-corrected pairwise t-tests revealed a congruency effect for positive ($p_{adj} = .045$) and negative ($p_{adj} = .024$) conditions pre-treatment, this effect was numerically but non-significantly larger for negative (mean difference in RT = 52.24 [SD = 46.51] ms) than positive conditions (mean difference in RT = 23.74 [SD = 25.1] ms; see Figure 2A). In contrast, post-treatment, there was a numerical but non-significant congruency effect that was larger for positive (mean difference in RT = 49.19 [SD = 59.24] ms; $p_{adj} = .056$) than negative words (mean difference in RT = 18.8 [SD = 43.96] ms; $p_{adj} = .209$; see Figure 2A). Additionally, participants became numerically but non-significantly faster at Incongruent Negative trials from pre to post-treatment (unadjusted $p = .053$; $p_{adj} = .212$). There were no main effects of valence, time, or other interactions (all p's > .38).

Accuracy—There was a two-way interaction between congruence and valence (see Figure 2B), $F(1, 9) = 10.342$, $p = .011$, $\eta p^2 = .535$. Post-hoc Hochberg-corrected pairwise t-tests examining valence effects (collapsing across time) revealed lower accuracy during Incongruent Positive than Incongruent Negative ($p_{adj} = .004$) but similar accuracy during Congruent Positive and Congruent Negative ($p_{adj} = 0.696$; see Figure 2B). Additionally, we only found the congruency effect for positive ($p_{adj} = .018$) but not negative words ($p_{adj} = .082$). There were no main effects of congruence ($p = .704$), valence, time, or any other interactions (all p's > .22).

Brain Activation

There was a significant main effect of embedded condition on activation in the right dlPFC ($F[1.74, 13.94] = 5.443$, $p = .021$, $\eta p^2 = .405$) and subcallosal cortex ($F[3, 24] = 4.613$, $p = .011$, $\eta p^2 = .366$; see Figure 3A). Post-hoc Hochberg-corrected pairwise t-tests revealed that mean activations were lower during Incongruent Negative than Congruent Positive for right dlPFC ($p_{adj} = .035$) and subcallosal cortex ($p_{adj} = .012$). Additionally, mean right dlPFC activation was lower during Incongruent Negative than Incongruent Positive ($p_{adj} = .018$; see Figure 3A). There was no main effect of time (all p's > .26), but there was a significant interaction between embedded condition and time for amygdala activation ($F[3, 24] = 4.837$, $p = .009$, $\eta p^2 = .377$; see Figure 3B). Post-hoc Hochberg-corrected pairwise t-tests demonstrated a significant reduction in amygdala activation for Incongruent Negative ($p_{adj} = .044$; see Figure 3B) but not for other embedded conditions over time (all $p_{adj} > .69$).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Behavioral and Neural Correlates of Clinical Improvement

Figure 4 shows correlations between clinical improvement and changes in behavioral and neural variables. No findings survived Hochberg correction. For the remainder of this section, we focus on effect sizes and unadjusted p-values.

Behavioral Correlates of Clinical Improvement—Although non-significant, there were medium to very large correlations between clinical improvement and increased accuracy during Congruent Negative, Incongruent Negative, and Incongruent Positive trials (see Figures 4, S2). Correlations were numerically stronger for the Incongruent Positive condition and self-reported clinical improvement (BDI-II).

Neural Correlates of Clinical Improvement—Overall, most neural correlations were negative (i.e., between clinical improvement and *decreased* activation). For congruent conditions, there were medium to very large correlations between clinical improvement and reduced activation of ROIs within all four networks examined (see Figures 4, S3). Significant results based on unadjusted p-values were only found for ROIs within the corticostriatal networks. Specifically, clinical improvement significantly correlated with decreased Congruent Positive activation of the dorsal corticostriatal network (CDRS-R only), and the left (CDRS-R and BDI-II) and right (CDRS-R only) dlPFC (p's < .028). Additionally, improvement in CDRS-R significantly correlated with decreased Congruent Negative activation of the right dlPFC (p = .047). There was only one significant correlation within the ventral corticostriatal network: BDI-II and decreased Congruent Positive activation of vACC/mPFC (p = .03)

There was a similar pattern of medium to very large negative correlations for the Incongruent Negative condition within three of the four networks examined (frontolimbic, the dorsal and ventral corticostriatal networks) and for the Incongruent Positive condition for the left dlPFC (see Figures 4, S3). The direction of correlations was the opposite for some ROIs during the incongruent conditions: there were medium to large correlations between clinical improvement and *increases* in Incongruent Negative activation of the PCC and Incongruent Positive activation of the amygdala, accumbens, and PCC. None of the correlations for incongruent conditions were significant.

Additional Analyses—To better interpret the neural changes, we performed Pearson's correlations between neural and behavioral changes (see Figure S4) and compiled these findings with the prior results (see Figure 5 for patterns). Overall, decreases in activation during congruent conditions generally corresponded with clinical and, although not significantly, with behavioral improvements. Although non-significant, the incongruent conditions showed mixed associations where, for some regions (primarily prefrontal), decreased activation was associated with improved outcomes, whereas for others (PCC, hippocampus), decreased activation was associated with *worsened* behavioral and/or clinical outcomes.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

In this preliminary study, we investigated the neurocognitive mechanisms of a 6-week course of dTMS in a small sample of 10 adolescents with TRD. Key strengths of the study include the longitudinal design, the experimental therapeutics approach using neuromodulation to probe the neural circuitry underpinning the specific domain of interest (affective bias), and the focus on the understudied population of adolescents with TRD. Although behavioral performance on the WFS task did not change significantly, amygdala activation during the task decreased following dTMS, which may represent a reduction in excessive engagement with negative patterns of thinking and feeling. This finding may be particularly meaningful when considering the high depression severity and treatment resistance of the sample. Clinical improvement was associated with improved accuracy on the WFS task and, for congruent conditions, with decreased activation across brain regions involved in cognitive control, the experience of negative affect, reward processing, and rumination and introspection, which may represent more efficient neural processing. Together, these results suggest that dTMS may alleviate depression by normalizing affective bias, specifically by decreasing engagement with negativity. However, due to the preliminary nature of this study, replication in larger samples with a sham comparison group is needed to substantiate these interpretations.

Behavioral

Consistent with our hypothesis and the expected WFS task performance (Başgöze et al., 2015; Thai et al., 2020), participants showed a congruency effect and responded significantly slower to incongruent trials. Contrary to our prediction and previous findings from emotional Stroop tasks (Chechko et al., 2013; Zhu et al., 2010), there was no overall effect of congruence on accuracy. However, participants were less accurate on Incongruent Positive trials with sad face distractors than on Incongruent Negative trials with happy face distractors (see Figure 2B), demonstrating the expected affective bias in this sample.

With respect to time, the congruency effect for RT appeared to be numerically but non-significantly stronger for negative words pre-treatment and positive words post-treatment. Visual inspection of Figure 2A suggests that this switch might be due to the participants becoming faster at Incongruent Negative trials post-treatment, although this change was non-significant. This contradicts our hypothesis and suggests that participants may have become more attentive to negative words and/or less distracted by happy faces. This indicates a possible increase in affective bias, which may be due to the overrepresentation of treatment non-responders in this sample (70%). It may also be due to the sample being treatment-resistant and the persistent nature of attentional biases, as research suggests that these biases endure past remission from depressive episodes (Bower, 1981; LeMoult and Gotlib, 2019).

Consistent with our hypotheses, those who showed greater improvement in task accuracy showed larger clinical improvements (see Figures 4, S2). This association was strongest, though non-significant, for those who showed reduced affective bias through improved Incongruent Positive accuracy. Since this condition is typically the hardest for depressed individuals, it is expected that improvement in depression severity would be particularly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

associated with improved performance during this condition, possibly as a result of reduced distractibility of sad faces or increased engagement with positive words (i.e., reduced affective bias). Correlations were also stronger for BDI-II, possibly because self-report measures may be more sensitive to cognitive changes (Cuijpers et al., 2010).

Brain Activation

Right dlPFC activation was significantly lower during Incongruent Negative compared to positive word conditions across time (see Figure 3A), which may be explained by this region's role in top-down attentional control (Vanderhasselt et al., 2007). Specifically, since the Incongruent Negative condition is easy for depressed individuals due to high engagement with negative words and the low distractibility of happy faces, participants likely did not need to recruit the right dlPFC as much as they did for the conditions with positive words that are less engaging to depressed individuals. Unexpectedly, activation in the subcallosal cortex was also significantly lower during Incongruent Negative compared to Congruent Positive trials (see Figure 3A), even though this region has been found to be hyperactive in those with MDD in response to negative stimuli (Laxton et al., 2013; Phan et al., 2002). It is possible that higher subcallosal cortex activation during the Congruent Positive condition reflects discomfort with happiness, consistent with research demonstrating positive mood induction can increase sadness in depressed individuals (Joormann et al., 2007).

Consistent with our hypothesis, amygdala activation during the Incongruent Negative condition decreased over time (see Figure 3B), indicating a possible normalization of the amygdala hyperactivity to negativity that is commonly observed in depressed individuals (Suslow et al., 2010; Victor et al., 2010). Importantly, this decreased activation was associated with clinical improvement ($r = -0.63$; see Figure 4). These findings may indicate reduced affective bias and improved emotion regulation post-treatment, such that participants, particularly those who improved the most clinically, fixated less strongly on and disengaged more easily from negative stimuli. Several possibilities may explain the discrepancy between this neural change and the lack of significant behavioral changes. First, the WFS task may not be as sensitive in detecting changes in affective bias as our neural measure of fMRI activation. Second, dTMS, in the way it was delivered here, may not be capable of modulating affective bias as measured by the WFS task. Changing treatment parameters (e.g., duration of dTMS) or combining dTMS with other treatments to magnify its effects may result in larger changes in affective bias that may change brain and behavior. A third possibility is that since hypoactive frontal regions, hyperactive limbic regions (including, but not limited to, the amygdala), *and* frontolimbic connectivity (Chechko et al., 2013) contribute to the negative attentional bias, the observed reduction in amygdala activation alone may have been insufficient in producing observable behavioral improvements. Moreover, decreased amygdala activation may reflect an improvement in certain aspects of affective bias (excessive engagement with negative target) but not other aspects (difficulty inhibiting negative distractor). Since the WFS task measures both these aspects of bias simultaneously, behavioral changes could be masked. Finally, it is possible that neural changes may precede behavioral changes and that longer-term follow-up post-treatment may reveal affective bias changes.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Contrary to our expectation, there were no activation changes for other ROIs, including the left dlPFC, despite it being the target site for dTMS in this study. The absence of change in dlPFC activation may be due to the low focality (i.e., more diffuse electric field) of the H-coil (Guadagnin et al., 2015) or limitations of the "5-cm rule" used to locate the dlPFC (Perera et al., 2016; Zibman et al., 2021), both of which may have resulted in stimulation of neighboring regions of the dlPFC. Future studies may benefit from using MRI-guided approaches. Moreover, it has been theorized that antidepressant effects of dTMS to the dlPFC are due to the strengthening of subcortical dlPFC connections rather than induced changes in local activity (Zibman et al., 2021). Hence, post-treatment, the dlPFC may have become more efficient at downregulating limbic regions (potentially explaining the decreased amygdala activation) without a need to recruit greater neural resources. Examining other metrics of brain functioning, like dynamic functional connectivity, may clarify the exact neural mechanisms of dTMS.

Neurally, decreased activations during the congruent conditions were generally associated with better clinical and behavioral outcomes (see Figures 4, 5, S3, S4). This is consistent with previous findings in a ketamine trial for adolescents with TRD using the WFS task (Thai et al., 2020), except that in the previous study, these correlations with clinical improvements were found for all embedded conditions. The difference between the two studies may be related to differences in treatment mechanisms since ketamine exerts generalized neural effects, whereas dTMS may more directly affect the left dlPFC. The correlations between decreased activation and clinical improvement are consistent with our hypotheses for ROIs within the frontolimbic network and the DMN, possibly indicating normalization of limbic and DMN hyperactivity in those who improved the most clinically. The strongest and significant associations with clinical improvement were within the corticostriatal networks. However, the direction of these correlations was opposite to our hypotheses for these networks. Decreased activation in these networks might instead reflect increased efficiency in using neural resources in those who experienced larger clinical improvements.

In contrast, although non-significant, the incongruent conditions showed a mixed pattern of associations. Prefrontal regions (dlPFC, vACC/mPFC), hippocampus, and the subcallosal cortex showed similar findings as the congruent conditions. However, clinical improvement was associated with *increased* Incongruent Positive activation of the amygdala and accumbens, as well as PCC activation during both incongruent conditions. Increased Incongruent Positive amygdala activation might suggest that participants with larger clinical improvements were better at activating this saliency-detecting brain region to properly attend to the positive stimuli and distinguish between the target and distractor to perform better. Increased Incongruent Positive accumbens activation might suggest that participants who experienced larger clinical improvements found the positive word and/or the challenging nature of this condition more rewarding post-treatment. Finally, since DMN deactivation, specifically the PCC, is lower during easier tasks (Singh and Fawcett, 2008), it is possible that participants who experienced larger clinical improvements found incongruent conditions easier.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Limitations and Future Directions

There are several limitations to consider when interpreting the results of this study. First, we had a small sample size, which limited the power and introduced the risk of spurious results. Second, the primary outcome measures were behavior and fMRI activations during the WFS task, neither of which have been psychometrically validated for test-retest reliability or individual difference measurement, likely limiting their ability to reliably detect effects of interventions (Enkavi and Poldrack, 2021; Karvelis et al., 2023). Third, the sample had low racial and ethnic diversity, limiting the generalizability of our findings. Additionally, since this study was open-label without a randomized sham-controlled design, we are unable to conclusively attribute any observed pre- to post-treatment changes to dTMS. Moreover, due to the lack of a healthy control group, we cannot determine whether dTMS normalized affective bias or brain functioning. Due to the small sample size, we were also unable to test whether differences in stimulation intensities impacted our findings. Thus, the findings of this study must be considered preliminary, and these limitations need to be considered when interpreting the results. Additional research addressing these limitations is needed to demonstrate causality and provide additional support for these preliminary results and observed trends. Future studies with additional follow-up assessments may also provide insight into the long-term impacts of dTMS. Behavioral findings from this study take into consideration limitations of the WFS task, such as practice effects and challenges with interpreting task performance (e.g., worse behavioral performance in the task may reflect difficulty engaging with the target word and/or disengaging from the distractor). Likewise, since response latencies are affected by biases in initial attention and response selection (Mogg et al., 2000); slower Incongruent Positive responses, for instance, may reflect difficulty attending to the positive word or identifying the word’s valence. Additionally, since task repetition can lead to changes in brain activation (Lohmann et al., 2004), we cannot isolate treatment effects without a sham control group. Finally, in using an ROI-based approach for analysis, we may have been unable to detect changes in brain areas not examined. Future whole-brain analyses may be useful in expanding the results of this study.

Conclusions

Our preliminary findings suggest that dTMS for adolescent TRD may operate through increasing neural efficiency and normalizing affective bias, specifically by decreasing engagement with negativity. More research is needed, with larger samples and incorporating a randomized control design, to further investigate the role of normalizing affective bias in treating adolescent TRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors sincerely thank all the adolescents and families who donated their time and energy to participate in this study and the staff and volunteers who helped conduct it.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Role of Funding Source

This work was supported by the Minnesota's Discovery, Research, and InnoVation Economy (MnDRIVE) Brain Innovations Grant awarded to KC. Trainee support was provided to MT by the University of Minnesota's MnDRIVE Fellowship. Additional support was provided by the Minnesota Supercomputing institute and Clinical and Translational Science Institute (CTSI); the Clinical Research Support Center is supported by the National Institutes of Health's National Center for Advancing Translational Sciences, grant UL1TR002494.

Abbreviations

BDI-II	Beck Depression Inventory
CDRS-R	Children's Depression Rating Scale-Revised
dTMS	deep Transcranial Magnetic Stimulation
DMN	default mode network
dACC/mPFC	dorsal anterior cingulate cortex and medial prefrontal cortex region
dlPFC	dorsolateral prefrontal cortex
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
HCP	Human Connectome Project
MDD	major depressive disorder
PCC	posterior cingulate cortex
RT	Reaction time
ROI	region of interest
rTMS	Repetitive transcranial magnetic stimulation
TRD	treatment-resistant depression
vACC/mPFC	ventral anterior cingulate cortex and medial prefrontal cortex region
WFS	Word-Face Stroop

References

Başgöze Z, 2015. The localization of emotional stroop activations in healthy and major depressive disorder populations using fMRI.

Başgöze Z, Gönül AS, Baskak B, Gökçay D, 2015. Valence-based Word-Face Stroop task reveals differential emotional interference in patients with major depression. Psychiatry Res 229, 960–967. 10.1016/j.psychres.2015.05.099 [PubMed: 26272019]

Bloch Y, Grisaru N, Harel EV, Beitler G, Faivel N, Ratzoni G, Stein D, Levkovitz Y, 2008. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. J. ECT 24, 156–159. 10.1097/YCT.0b013e318156aa49 [PubMed: 18580562]

Bower GH, 1981. Mood and memory. Am. Psychol 36, 129. 10.1037/0003-066X.36.2.129 [PubMed: 7224324]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Chechko N, Augustin M, Zvyagintsev M, Schneider F, Habel U, Kellermann T, 2013. Brain circuitries involved in emotional interference task in major depression disorder. J. Affect. Disord 149, 136–145. 10.1016/j.jad.2013.01.013 [PubMed: 23394712]

Cohen J, 2013. Statistical power analysis for the behavioral sciences. Academic press.

Croarkin PE, Elmaadawi AZ, Aaronson ST, Schrodt GR, Holbert RC, Verdoliva S, Heart KL, Demitrack MA, Strawn JR, 2021. Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial. NEUROPSYCHOPHARMACOLOGY 46, 462–469. 10.1038/s41386-020-00829-y [PubMed: 32919400]

Cuijpers P, Li J, Hofmann SG, Andersson G, 2010. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. Clin. Psychol. Rev 30, 768–778. 10.1016/j.cpr.2010.06.001 [PubMed: 20619943]

De Raedt R, Vanderhasselt M-A, Baeken C, 2015. Neurostimulation as an intervention for treatment resistant depression: From research on mechanisms towards targeted neurocognitive strategies. Clin. Psychol. Rev 41, 61–69. 10.1016/j.cpr.2014.10.006 [PubMed: 25468571]

Dichter GS, Felder JN, Smoski MJ, 2009. Affective context interferes with cognitive control in unipolar depression: An fMRI investigation. J. Affect. Disord 114, 131–142. 10.1016/j.jad.2008.06.027 [PubMed: 18706701]

Dwyer JB, Stringaris A, Brent DA, Bloch MH, 2020. Annual Research Review: Defining and treating pediatric treatment-resistant depression. J. Child Psychol. Psychiatry 61, 312–332. 10.1111/jcpp.13202 [PubMed: 32020643]

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ, 2002. The Neural Basis of Mood-Congruent Processing Biases in Depression. Arch. Gen. Psychiatry 59, 597–604. 10.1001/archpsyc.59.7.597 [PubMed: 12090812]

Elliott R, Zahn R, Deakin JFW, Anderson IM, 2011. Affective Cognition and its Disruption in Mood Disorders. Neuropsychopharmacology 36, 153–182. 10.1038/npp.2010.77 [PubMed: 20571485]

Enkavi AZ, Poldrack RA, 2021. Implications of the lacking relationship between cognitive task and self-report measures for psychiatry. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 6, 670–672. 10.1016/j.bpsc.2020.06.010 [PubMed: 32712212]

Epp AM, Dobson KS, Dozois DJ, Frewen PA, 2012. A systematic meta-analysis of the Stroop task in depression. Clin. Psychol. Rev 32, 316–328. 10.1016/j.cpr.2012.02.005 [PubMed: 22459792]

Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, Mathews J, Sheline YI, 2008. Altered Emotional Interference Processing in Affective and Cognitive-Control Brain Circuitry in Major Depression. Biol. Psychiatry 63, 377–384. 10.1016/j.biopsych.2007.06.012 [PubMed: 17719567]

Fava M, 2003. Diagnosis and definition of treatment-resistant depression. Biol. Psychiatry 53, 649–659. 10.1016/S0006-3223(03)00231-2 [PubMed: 12706951]

Filipčić I, Šimunović Filipčić I, Milovac Ž, Sučić S, Gajšak T, Ivezić E, Bašić S, Bajić Ž, Heilig M, 2019. Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-Coil in treatment of major depressive disorder; A randomized clinical trial. J. Psychiatr. Res 114, 113–119. 10.1016/j.jpsychires.2019.04.020 [PubMed: 31059991]

Forbes EE, Dahl RE, 2012. Research Review: Altered reward function in adolescent depression: what, when and how? J. Child Psychol. Psychiatry 53, 3–15. 10.1111/j.1469-7610.2011.02477.x [PubMed: 22117893]

Forbes EE, Dahl RE, 2005. Neural systems of positive affect: relevance to understanding child and adolescent depression? Dev. Psychopathol 17, 827–850. 10.1017/S095457940505039X [PubMed: 16262994]

Forbes EE, May JC, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, Birmaher B, Axelson DA, Dahl RE, 2006. Reward-Related Decision-Making in Pediatric Major Depressive Disorder: An fMRI Study. J. Child Psychol. Psychiatry 47, 1031–1040. 10.1111/j.1469-7610.2006.01673.x [PubMed: 17073982]

Fu CHY, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SCR, Brammer MJ, 2008. Pattern Classification of Sad Facial Processing: Toward the Development of Neurobiological

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Markers in Depression. Biol. Psychiatry, The Neurobiology and Therapeutics of Antidepressant-Resistant Depression 63, 656–662. 10.1016/j.biopsych.2007.08.020

Fu CHY, Williams SCR, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM, Bullmore ET, 2007. Neural Responses to Happy Facial Expressions in Major Depression Following Antidepressant Treatment. Am. J. Psychiatry 164, 599–607. 10.1176/ajp.2007.164.4.599 [PubMed: 17403973]

Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, Jonas DE, Swinson Evans T, Viswanathan M, Lohr KN, 2014. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J. Clin. Psychiatry 75, 477–489; quiz 489. 10.4088/JCP.13r08815 [PubMed: 24922485]

GBD 2019 Mental Disorders Collaborators, 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9, 137–150. 10.1016/S2215-0366(21)00395-3 [PubMed: 35026139]

Gellersen HM, Kedzior KK, 2019. Antidepressant outcomes of high-frequency repetitive transcranial magnetic stimulation (rTMS) with F8-coil and deep transcranial magnetic stimulation (DTMS) with H1-coil in major depression: a systematic review and meta-analysis. BMC Psychiatry 19, 139. 10.1186/s12888-019-2106-7 [PubMed: 31064328]

Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178. 10.1038/nature18933 [PubMed: 27437579]

Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, 2013. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80, 105–124. 10.1016/j.neuroimage.2013.04.127 [PubMed: 23668970]

Gotlib IH, Joormann J, 2010. Cognition and Depression: Current Status and Future Directions. Annu. Rev. Clin. Psychol 6, 285–312. 10.1146/annurev.clinpsy.121208.131305 [PubMed: 20192795]

Guadagnin V, Parazzini M, Fiocchi S, Liorni I, Ravazzani P, 2015. Deep transcranial magnetic stimulation: modeling of different coil configurations. IEEE Trans. Biomed. Eng 63, 1543–1550. 10.1109/TBME.2015.2498646 [PubMed: 26560868]

Guha A, Yee CM, Heller W, Miller GA, 2021. Alterations in the default mode-salience network circuit provide a potential mechanism supporting negativity bias in depression. Psychophysiology 58, e13918. 10.1111/psyp.13918 [PubMed: 34403515]

Hamilton JP, Gotlib IH, 2008. Neural Substrates of Increased Memory Sensitivity for Negative Stimuli in Major Depression. Biol. Psychiatry 63, 1155–1162. 10.1016/j.biopsych.2007.12.015 [PubMed: 18281017]

Joormann J, 2010. Cognitive Inhibition and Emotion Regulation in Depression. Curr. Dir. Psychol. Sci 19, 161–166. 10.1177/0963721410370293

Joormann J, Siemer M, Gotlib IH, 2007. Mood regulation in depression: Differential effects of distraction and recall of happy memories on sad mood. J. Abnorm. Psychol 116, 484. 10.1037/0021-843X.116.3.484 [PubMed: 17696704]

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA, 2015. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry 72, 603–611. 10.1001/jamapsychiatry.2015.0071 [PubMed: 25785575]

Karvelis P, Paulus MP, Diaconescu AO, 2023. Individual differences in computational psychiatry: A review of current challenges. Neurosci. Biobehav. Rev 148, 105137. 10.1016/j.neubiorev.2023.105137 [PubMed: 36940888]

Kaster TS, Daskalakis ZJ, Noda Y, Knyahnytska Y, Downar J, Rajji TK, Levkovitz Y, Zangen A, Butters MA, Mulsant BH, Blumberger DM, 2018. Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: a prospective randomized controlled trial. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 43, 2231–2238. 10.1038/s41386-018-0121-x

Kennard BD, Silva SG, Tonev S, Rohde P, Hughes JL, Vitiello B, Kratochvil CJ, Curry JF, Emslie GJ, Reinecke M, March J, 2009. Remission and recovery in the Treatment for Adolescents with

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Depression Study (TADS): acute and long-term outcomes. J. Am. Acad. Child Adolesc. Psychiatry 48, 186–195. 10.1097/CHI.0b013e31819176f9 [PubMed: 19127172]

Laxton AW, Neimat JS, Davis KD, Womelsdorf T, Hutchison WD, Dostrovsky JO, Hamani C, Mayberg HS, Lozano AM, 2013. Neuronal coding of implicit emotion categories in the subcallosal cortex in patients with depression. Biol. Psychiatry 74, 714–719. 10.1016/j.biopsych.2013.03.029 [PubMed: 23773792]

Lee B-T, Seok J-H, Lee B-C, Cho SW, Yoon B-J, Lee K-U, Chae J-H, Choi I-G, Ham B-J, 2008. Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 778–785. 10.1016/j.pnpbp.2007.12.009 [PubMed: 18207298]

LeMoult J, Gotlib IH, 2019. Depression: A cognitive perspective. Clin. Psychol. Rev 69, 51–66. 10.1016/j.cpr.2018.06.008 [PubMed: 29961601]

Levin RL, Heller W, Mohanty A, Herrington JD, Miller GA, 2007. Cognitive deficits in depression and functional specificity of regional brain activity. Cogn. Ther. Res 31, 211–233. 10.1007/s10608-007-9128-z

Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, Sheer A, Gersner R, Zangen A, 2009. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. Brain Stimulat. 2, 188–200. 10.1016/j.brs.2009.08.002

Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, Tendler A, Daskalakis ZJ, Winston JL, Dannon P, Hafez HM, Reti IM, Morales OG, Schlaepfer TE, Hollander E, Berman JA, Husain MM, Sofer U, Stein A, Adler S, Deutsch L, Deutsch F, Roth Y, George MS, Zangen A, 2015. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 14, 64–73. 10.1002/wps.20199

Lohmann H, Deppe M, Jansen A, Schwindt W, Knech S, 2004. Task Repetition Can Affect Functional Magnetic Resonance Imaging-Based Measures of Language Lateralization and Lead to Pseudoincreases in Bilaterality. J. Cereb. Blood Flow Metab 24, 179–187. 10.1097/01.WCB.0000100066.36077.91 [PubMed: 14747744]

Luciana M, Bjork JM, Nagel BJ, Barch DM, Gonzalez R, Nixon SJ, Banich MT, 2018. Adolescent neurocognitive development and impacts of substance use: Overview of the adolescent brain cognitive development (ABCD) baseline neurocognition battery. Dev. Cogn. Neurosci 32, 67–79. 10.1016/j.dcn.2018.02.006 [PubMed: 29525452]

Maalouf FT, Atwi M, Brent DA, 2011. Treatment-Resistant Depression in Adolescents: Review and Updates on Clinical Management. Depress. ANXIETY 28, 946–954. 10.1002/da.20884 [PubMed: 21898710]

March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J, Treatment for Adolescents With Depression Study (TADS) Team, 2004. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 292, 807–820. 10.1001/jama.292.7.807 [PubMed: 15315995]

Marchetti I, Koster EHW, Sonuga-Barke EJ, De Raedt R, 2012. The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. Neuropsychol. Rev 22, 229–251. 10.1007/s11065-012-9199-9 [PubMed: 22569771]

Mayer G, Aviram S, Walter G, Levkovitz Y, Bloch Y, 2012. Long-term follow-up of adolescents with resistant depression treated with repetitive transcranial magnetic stimulation. J. ECT 28, 84–86. 10.1097/YCT.0b013e318238f01a [PubMed: 22531199]

Mogg K, Millar N, Bradley BP, 2000. Biases in eye movements to threatening facial expressions in generalized anxiety disorder and depressive disorder. J. Abnorm. Psychol 109, 695. 10.1037/0021-843X.109.4.695 [PubMed: 11195993]

Muir O, Ruiz D, Abbott-Sinclair R, MacMillan C, 2020. TMS Treatment With The H1 Coil in Youth Age 10–21 Effective In Ameliorating MDD Symptoms. Brain Stimul. Basic Transl. Clin. Res. Neuromodulation 13, 1854. 10.1016/j.brs.2020.06.056

Nolen-Hoeksema S, Wisco BE, Lyubomirsky S, 2008. Rethinking rumination. Perspect. Psychol. Sci 3, 400–424. 10.1111/j.1745-6924.2008.00088.x [PubMed: 26158958]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Osman A, Kopper BA, Barrios F, Gutierrez PM, Bagge CL, 2004. Reliability and validity of the Beck depression inventory–II with adolescent psychiatric inpatients. Psychol. Assess. 16, 120. 10.1037/1040-3590.16.2.120 [PubMed: 15222808]

Parazzini M, Fiocchi S, Chiaramello E, Roth Y, Zangen A, Ravazzani P, 2017. Electric field estimation of deep transcranial magnetic stimulation clinically used for the treatment of neuropsychiatric disorders in anatomical head models. Med. Eng. Phys 43, 30–38. 10.1016/j.medengphy.2017.02.003 [PubMed: 28236602]

Peckham AD, McHugh RK, Otto MW, 2010. A meta-analysis of the magnitude of biased attention in depression. Depress. Anxiety 27, 1135–1142. 10.1002/da.20755 [PubMed: 21049527]

Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS, 2016. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimulat. 9, 336–346. 10.1016/j.brs.2016.03.010

Phan KL, Wager T, Taylor SF, Liberzon I, 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16, 331–348. 10.1006/nimg.2002.1087 [PubMed: 12030820]

Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M, 2009. Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Individuals With Major Depressive Disorder. Am. J. Psychiatry 166, 702–710. 10.1176/appi.ajp.2008.08081201 [PubMed: 19411368]

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE, 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154. 10.1016/j.neuroimage.2011.10.018 [PubMed: 22019881]

Poznanski EO, Mokros HB, 1996. Children's depression rating scale, revised (CDRS-R).

Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, Fukuda M, Kato N, 2004. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. Neurosci. Res 50, 1–11. 10.1016/j.neures.2004.05.003 [PubMed: 15288493]

Roth Y, Amir A, Levkovitz Y, Zangen A, 2007. Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils. J. Clin. Neurophysiol. 24, 31. 10.1097/WNP.0b013e31802fa393 [PubMed: 17277575]

Singh KD, Fawcett IP, 2008. Transient and linearly graded deactivation of the human default-mode network by a visual detection task. Neuroimage 41, 100–112. 10.1016/j.neuroimage.2008.01.051 [PubMed: 18375149]

Suslow T, Konrad C, Kugel H, Rumstadt D, Zwitserlood P, Schöning S, Ohrmann P, Bauer J, Pyka M, Kersting A, Arolt V, Heindel W, Dannlowski U, 2010. Automatic Mood-Congruent Amygdala Responses to Masked Facial Expressions in Major Depression. Biol. Psychiatry, Stimulating Research on the Treatment of Depression: Electroconvulsive Therapy, Transcranial Magnetic Stimulation, and Deep Brain Stimulation 67, 155–160. 10.1016/j.biopsych.2009.07.023

Tao R, Emslie G, Mayes T, Nakonezny P, Kennard B, Hughes C, 2009. Early prediction of acute antidepressant treatment response and remission in pediatric major depressive disorder. J. Am. Acad. Child Adolesc. Psychiatry 48, 71–78. 10.1097/CHI.0b013e318190043e [PubMed: 19057412]

Thai M, Başgöze Z, Klimes-Dougan B, Mueller BA, Fiecas M, Lim KO, Albott CS, Cullen KR, 2020. Neural and behavioral correlates of clinical improvement to ketamine in adolescents with treatment resistant depression. Front. Psychiatry 11, 820. 10.3389/fpsyt.2020.00820 [PubMed: 33013493]

Thai M, Nair AU, Klimes-Dougan B, Albott S, Silamongkol T, Corkrum M, Hill D, Roemer JW, Lewis CP, Croarkin PE, 2024. Deep transcranial magnetic stimulation for adolescents with treatment-resistant depression: A preliminary dose-finding study exploring safety and clinical effectiveness. J. Affect. Disord 10.1016/j.jad.2024.03.061

U. S. Food and Drug Administration, 2024. 510(k) Premarket Notification [WWW Document]. URL https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K231926 (accessed 7.31.24).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Vanderhasselt M-A, De Raedt R, Baeken C, Leyman L, Clerinx P, D'haenen H, 2007. The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. Brain Res 1137, 111–116. 10.1016/j.brainres.2006.12.050 [PubMed: 17229406]

Victor TA, Furey ML, Fromm SJ, Öhman A, Drevets WC, 2010. Relationship Between Amygdala Responses to Masked Faces and Mood State and Treatment in Major Depressive Disorder. Arch. Gen. Psychiatry 67, 1128–1138. 10.1001/archgenpsychiatry.2010.144 [PubMed: 21041614]

Wall CA, Croarkin PE, Maroney-Smith MJ, Haugen LM, Baruth JM, Frye MA, Sampson SM, Port JD, 2016. Magnetic Resonance Imaging-Guided, Open-Label, High-Frequency Repetitive Transcranial Magnetic Stimulation for Adolescents with Major Depressive Disorder. J. Child Adolesc. Psychopharmacol. 26, 582–589. 10.1089/cap.2015.0217 [PubMed: 26849202]

Wang L, LaBar KS, Smoski M, Rosenthal MZ, Dolcos F, Lynch TR, Krishnan RR, McCarthy G, 2008. Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. Psychiatry Res. Neuroimaging 163, 143–155. 10.1016/j.pscychresns.2007.10.004

Williams LM, 2017. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress. Anxiety 34, 9–24. 10.1002/da.22556 [PubMed: 27653321]

Zhu X, Zhang H, Wu T, Luo W, Luo Y, 2010. Emotional conflict occurs at an early stage: Evidence from the emotional face–word Stroop task. Neurosci. Lett 478, 1–4. 10.1016/j.neulet.2010.04.036 [PubMed: 20417689]

Zibman S, Pell GS, Barnea-Ygael N, Roth Y, Zangen A, 2021. Application of transcranial magnetic stimulation for major depression: Coil design and neuroanatomical variability considerations. Eur. Neuropsychopharmacol. 45, 73–88. 10.1016/j.euroneuro.2019.06.009 [PubMed: 31285123]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- dTMS may alleviate adolescent treatment-resistant depression (TRD).
- dTMS may normalize amygdala hyperactivity in adolescents with TRD.
- dTMS may treat TRD by improving neural efficiency and normalizing affective bias.
- Additional research is needed to demonstrate causality and confirm findings.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

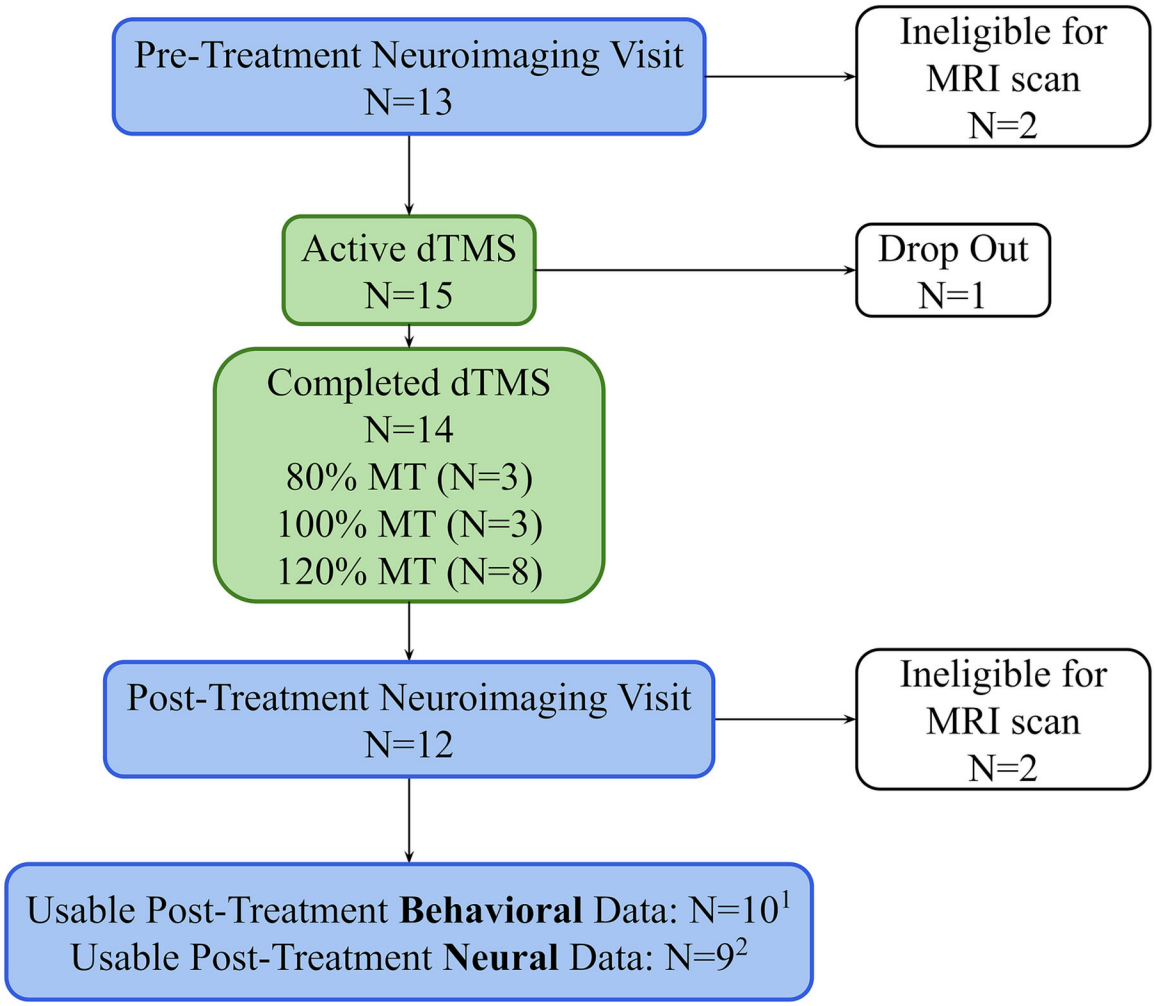


Figure 1.
CONSORT Diagram.
Note. MRI = Magnetic Resonance Imaging; dTMS = deep Transcranial Magnetic Stimulation; MT = Motor Threshold
[1] One participant had incomplete behavioral data (missing data for one run at one time point), and one participant had <60% accuracy at one time point. Both participants were excluded from all analyses.
[2] One participant's neural data was excluded due to excessive movement during the post-treatment scan.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

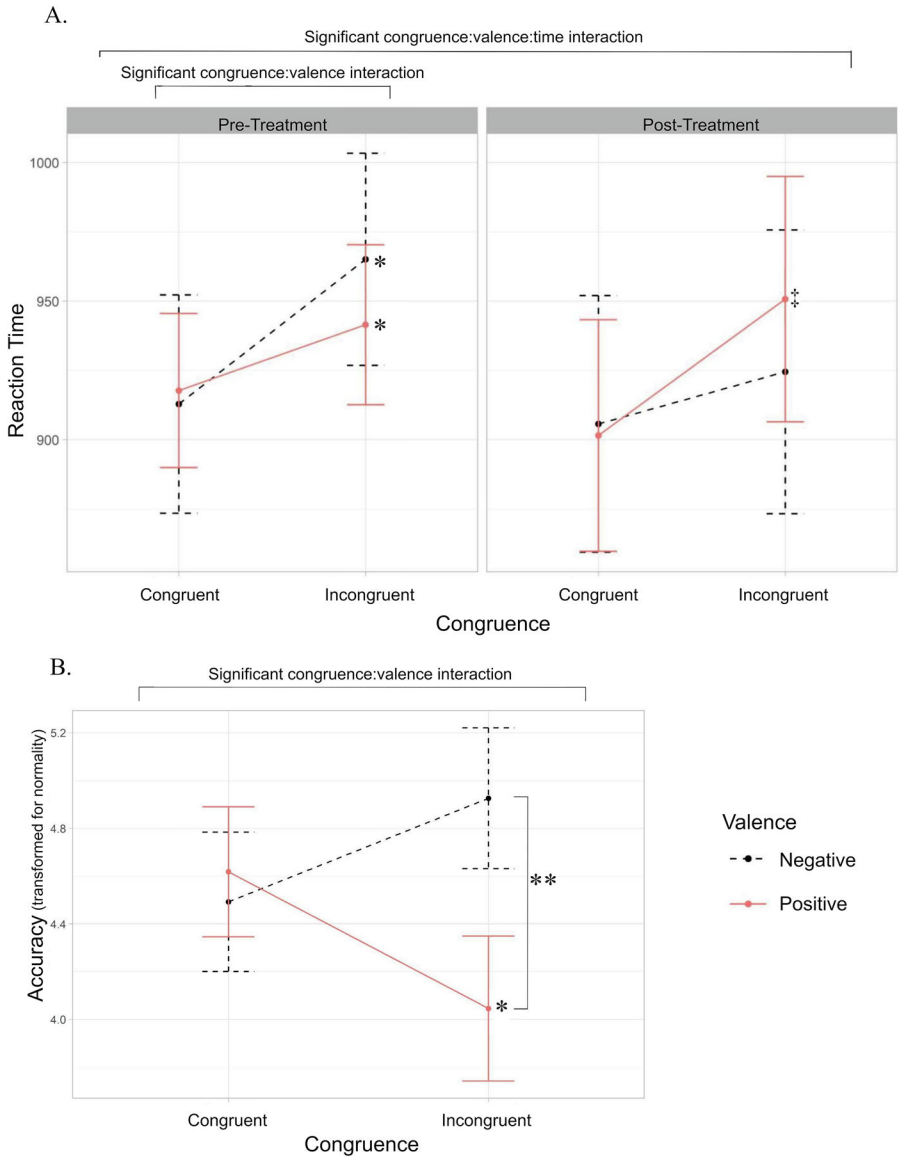


Figure 2.

Reaction Time and Accuracy by Congruence and Valence Across Time.

Note. Figure 2A shows reaction time (in milliseconds) by congruence and valence pre- and post-treatment. Figure 2B shows accuracy by congruence and valence averaged across time. Error bars are ± SE of the mean.

*$p_{adj} < .05$

**$p_{adj} < .01$

‡Numerical but non-significant (unadjusted $p = .028$; $p_{adj} = .056$) difference in reaction time between congruent and incongruent trials for positive word conditions at post-treatment.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

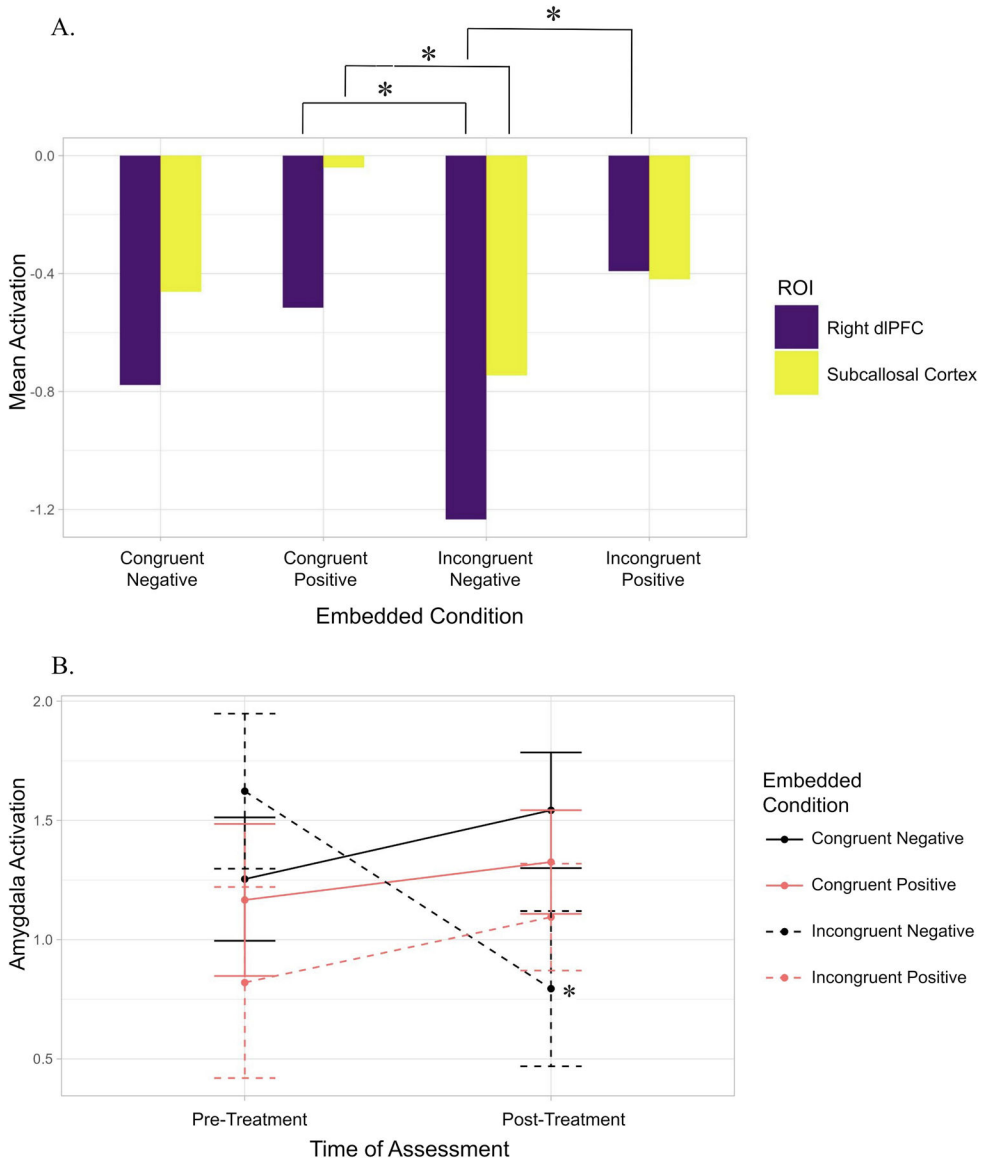


Figure 3.

Mean Activation by Embedded Condition Across Time.

Note. dlPFC = dorsolateral prefrontal cortex. Figure 3A shows mean activation by embedded condition and ROI averaged across time. Figure 3B shows mean amygdala activation by embedded condition pre- and post-treatment. Mean activation values on the Y-axes are z-scores. Error bars are ± SE of the mean.

*$p_{adj} < .05$

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

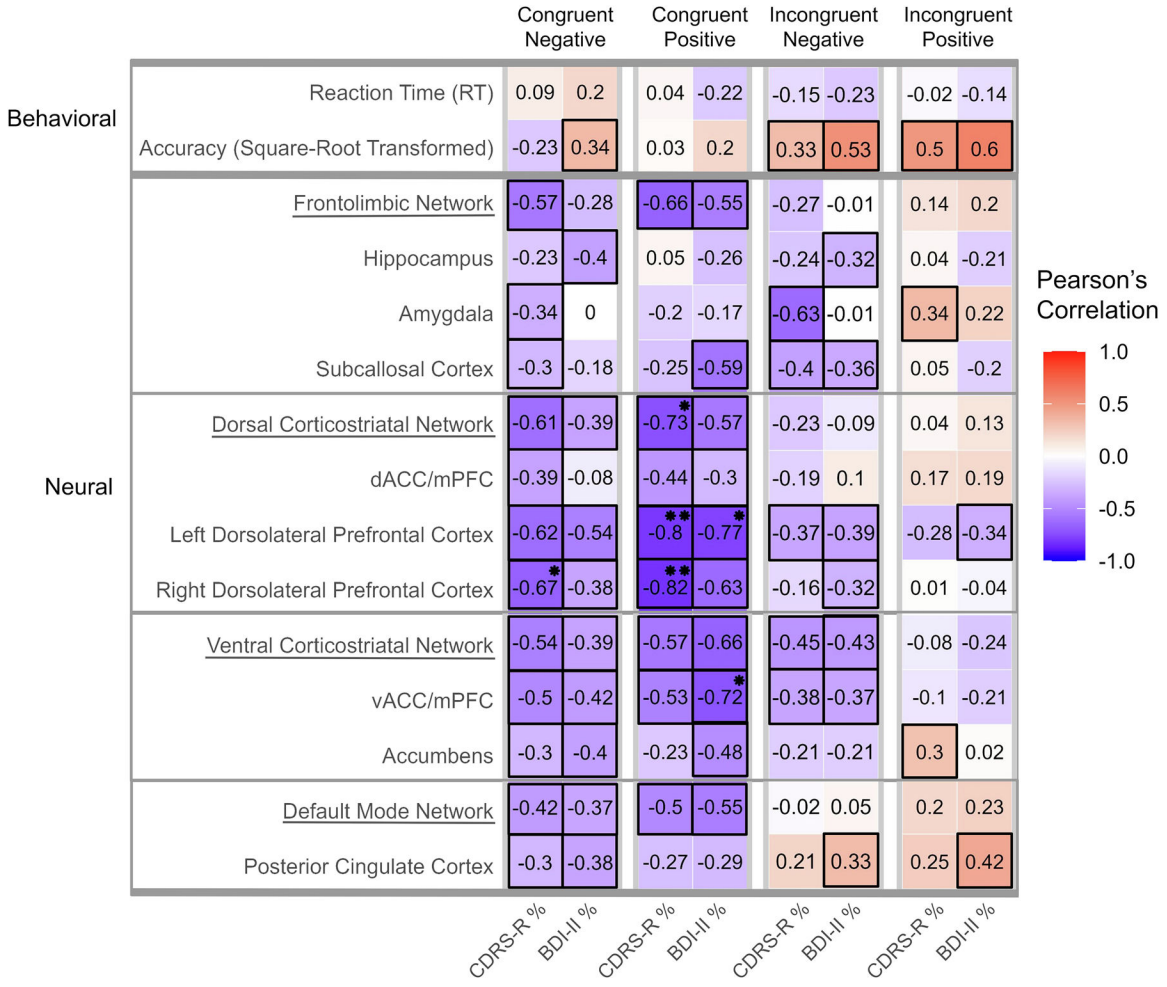


Figure 4.

Correlations Between Clinical Improvement and Neural and Behavioral Changes.

Note. vACC/mPFC = ventral anterior cingulate cortex and medial prefrontal cortex region; CDRS-R = Children's Depression Rating Scale-Revised; BDI-II = Beck Depression Inventory. Correlations are between change scores: Higher change scores indicate greater clinical improvement, greater accuracy, slower reaction times, and increased neural activation from pre- to post-treatment. Correlations ≥ 0.3 are highlighted.

*p<.05 (uncorrected p-value)

**p<.01 (uncorrected p-value)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

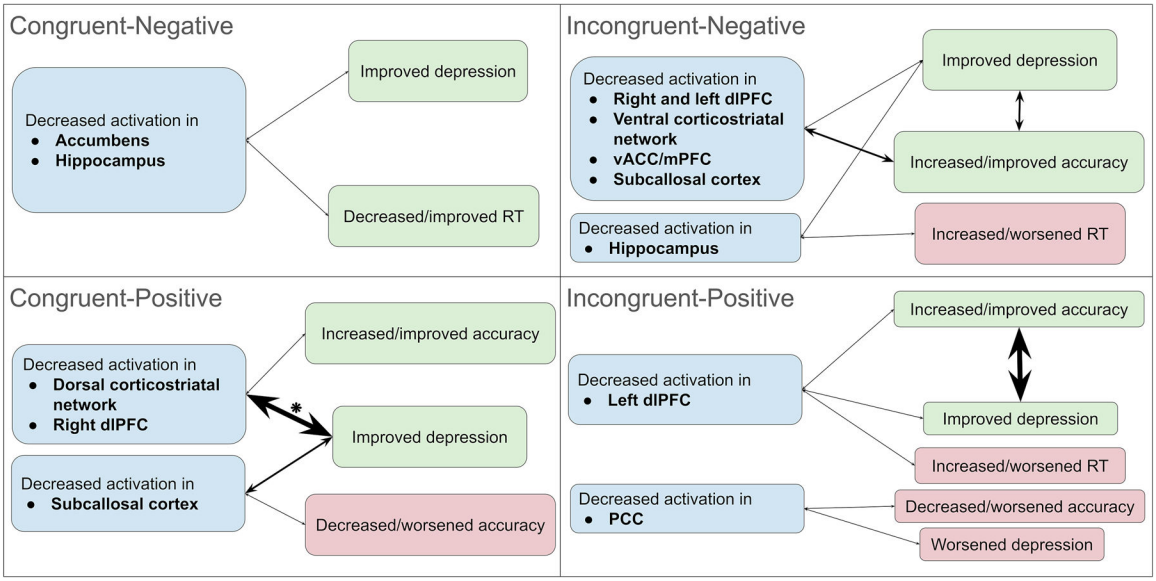


Figure 5.

Neural Activation Changes and Clinical and Behavioral Outcomes.

Note. RT = Reaction Time; dlPFC = Dorsolateral Prefrontal Cortex; vACC/mPFC = ventral anterior cingulate cortex and medial prefrontal cortex region; PCC = Posterior Cingulate Cortex. ROIs were chosen if they had ≥ 0.3 correlations with both a clinical *and* a behavioral variable. The thickness of the arrows is based on the strength of correlation coefficients: Thinnest if ≤ 0.5, medium if some were ≤ 0.5 and others were > 0.5, and thickest if > 0.5. *p<.05 (uncorrected p-value)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Baseline Clinical and Demographic Characteristics

Variable	Total (*N* = 10) *n* (%)
Age in years, mean (SD)	16.3 (1.09)
Sex assigned at Birth	
Female	6 (60%)
Male	4 (40%)
Race	
White	8 (80%)
More Than One Race	2 (20%)[1]
Ethnicity	
Not Hispanic or Latin(o/a)/Latinx	10 (100%)
Depression Severity	
CDRS-R score, mean (SD)	62.2 (13.65)
BDI-II score, mean (SD)	30.4 (11.27)
Treatment-resistance	
Number of failed treatments[2]	
One failed treatment	1 (10%)
Two failed treatments	4 (40%)
Three failed treatments	2 (20%)
Four failed treatment	2 (20%)
Five failed treatments	1 (10%)
Classes of failed treatments (medications)[2]	[n (%) of failed treatments[3]]
Selective serotonin reuptake inhibitor (SSRI)	7 (70%) [13 (46.43%)]
Serotonin and norepinephrine reuptake inhibitors (SNRI)	3 (30%) [6 (21.43%)]
Other antidepressant	4 (40%) [4 (14.29%)]
Antipsychotic	4 (40%) [4 (14.29%)]
Mood stabilizer	1 (10%) [1 (3.57%)]
Any medications during study	7 (70%)
Any antidepressant medication	7 (70%)
Selective serotonin reuptake inhibitor (SSRI)	5 (50%)
Serotonin and norepinephrine reuptake inhibitors (SNRI)	1 (10%)
Other antidepressant	3 (30%)
Any psychotropic medication (other than antidepressant)	5 (50%)
Antipsychotic	3 (30%)
Mood stabilizer	3 (30%)
Anxiolytic	2 (20%)
Stimulant	1 (10%)

Note. SD = Standard deviation; CDRS-R = Children's Depression Rating Scale-Revised; BDI-II = Beck Depression Inventory. Data are n (%) of participants unless indicated otherwise.

[1] One participant identified as Black or African American and White, and the other identified as Asian or Asian American and White.

[2] Based on the Antidepressant Treatment Record.

[3] [n (%) of failed treatments] refers to failed treatments across participants (medications; total failed treatments = 28) that fall under the listed medication class.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript