



# PULSE

A Monthly Update on Advances in Neuromodulation



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## Improvements in Depression in Patients with Schizophrenia Spectrum Disorders receiving rTMS

Michael K Leuchter, MD reviewing Voineskos et al. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020 November

*This study was a randomized controlled trial of bilateral rTMS for cognitive and depressive symptoms in Schizophrenia Spectrum Disorders (SSDs). While active rTMS did not significantly improve cognition, it was associated with a significant increase in cortical thickness of the stimulated region. This increase was correlated with a decrease in depressive symptoms.*

Negative symptoms in Schizophrenia Spectrum Disorders (SSDs) are notoriously difficult to treat. In a previous small pilot study, researchers demonstrated improvement in a cognitive task in those with SSDs after treatment with repetitive

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Transcranial Magnetic Stimulation (rTMS). This larger, more thorough follow-up study examines the same topic of the efficacy of rTMS as a treatment for cognitive impairment in those with SSDs.

Researchers performed a double-blind, randomized controlled trial of 83 patients diagnosed with schizophrenia or schizoaffective disorder. All patients received 750 pulses of 20 Hz stimulation at 90% of resting motor threshold sequentially to the left and right DLPFC. The sham condition was a single-wing tilt position. Patients completed 20 sessions, five days per week, for four weeks. Forty-two patients were randomized to active treatment, and clinical measures were performed before, immediately after, and 1 month after the completion of treatment. These measures included four cognitive batteries, the Calgary Depression Scale for

Schizophrenia (CDSS), the Positive and Negative Syndrome Scale (PANSS), and the Scale for the Assessment of Negative Symptoms (SANS). Imaging measures were examined before and 1 month after treatment, and consisted of the thickness of cortical regions of interest (ROIs), most notably of the bilateral DLPFC.

The primary outcome (change in accuracy on a complex n-back working memory task) was not significantly different between groups ( $p=0.62$  in the intention to treat (ITT) sample). While most cortical ROIs showed no between-group differences in thickness, the active group had a substantial increase in RDLPFC thickness compared to the sham group ( $p=0.01$ ). There was also a decrease in depressive symptom burden among study completers in the active group relative to sham as measured by CDSS scores

( $p=0.04$  for completers; not significant in the ITT sample). This reduction in depression was found to be correlated with the increase in cortical thickness ( $r=-0.47$ ,  $p=0.008$ ) in an exploratory post-hoc analysis. Given the large number of males ( $n=52$ ) in the study, the effects on RDLPFC thickness and CDSS scores were also examined in males alone and found to be stronger.

**Impact: This multi-center, double-blind, randomized controlled trial found no significant benefit using rTMS to treat cognitive symptoms in SSDs. However, increases in right DLPFC cortical thickness were correlated with a reduction of depression in the active treatment group, indicating there may be a benefit to using rTMS to treat depression associated with SSDs.**

Voineskos AN, Blumberger DM, Schifani C, et al. Effects of Repetitive Transcranial Magnetic Stimulation on Working Memory Performance and Brain Structure in People With Schizophrenia Spectrum Disorders: A Double-Blind, Randomized, Sham-Controlled Trial. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2021;6(4):449-458.

## Stimulation of Dorsomedial Prefrontal Cortex May Alleviate Symptoms of Borderline Personality Disorder

Michael K Leuchter, MD reviewing Calderón-Moctezuma et al. *Brazilian J Psychiatry* 2020 August

***This randomized controlled trial investigated the use of rTMS to the DMPFC as a treatment for the symptoms of BPD. Over the course of 15 treatment sessions (3 weeks), investigators found modest between-group differences favoring active treatment with regard to impulsivity and anxiety.***

Borderline Personality Disorder (BPD) is characterized by symptoms including emotional dysregulation/lability, impulsivity, and interpersonal instability. Diminished activity in prefrontal structures linked to emotional regulation, such as the dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC), have inspired prior work using repetitive transcranial magnetic stimulation (rTMS) to target the DLPFC. This study examines the effect of rTMS to the DMPFC as a treatment for BPD symptoms.

This study was a single-site single-blind randomized controlled trial of 14 patients diagnosed with BPD. All patients received 15 treatment sessions. Active treatment ( $n=7$ ) consisted of 5-Hz rTMS (30 trains of 50 pulses with 10-second interval) to DMPFC (Fpz EEG electrode site) with intensity at 100% of motor threshold. Sham treatment ( $n=7$ ) consisted of identical coil placement but with the coil in placebo mode with a TENS unit simulating rTMS stimulation. Prior to treatment, all patients completed a battery of

psychological testing, consisting of the short version Borderline Symptoms List (BSL), Clinical Global Impression for BPD (CGI-BPD), Borderline Evaluation of Severity over Time (BEST), Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Barratt's Impulsivity Scale (BIS), and three neuropsychological tests. All testing was performed at baseline and after completion of treatment, with scales also being performed on a weekly basis.

A statistically significant between-group difference in CGI-BPD impulsivity scores and HARS scores ( $p < 0.05$ ) were observed favoring the active treatment group. The active group alone also demonstrated within-group improvements in the scores of: CGI-BPD total, CGI-BPD abandonment, CGI-BPD paranoia, BEST total, HDRS, HARS, and risk-taking ( $p < 0.05$ ). The sham group demonstrated

improvement in decision-making in neuropsychological testing ( $p < 0.05$ ) and no other significant changes in outcome measures.

**Impact: This small, single-blind, randomized controlled trial examined the use of excitatory rTMS over DMPFC as a treatment for BPD symptoms. Modest improvements were observed within the**

**active group in measures of impulsivity, anxiety, and depression, as well as between-group differences in anxiety (favoring the active group). This study is limited by its sample size, shorter duration of treatment, and a single-blind design, but these preliminary findings warrant consideration and further study.**

Calderón-Moctezuma AR, Reyes-López J V., Rodríguez-Valdés R, et al. Improvement in borderline personality disorder symptomatology after repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex: preliminary results. *Brazilian J Psychiatry*. 2021;43(1):65-69

## Transcranial Direct Current Stimulation Improves Cognitive Control in Adults with ADHD

David Carlson, MD reviewing Dubreuil-Vall L et al. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2021 April

**In this randomized controlled trial, adult participants with ADHD showed improvements in interference cognitive control but not action cancellation after receiving tDCS to the left DLPFC. These improvements were correlated with neurophysiologic biomarkers.**

Attention-deficit hyperactivity disorder (ADHD) affects approximately 2.8% of adults worldwide and is associated with significant morbidity and mortality. Pharmacologic and behavioral therapies exist, but patients with ADHD often exhibit persistent impairments in executive function, including interference cognitive control (the ability to resist or resolve distracting, irrelevant information) and action cancellation (the ability to suppress a dominant, automatic response that has been initiated). Can transcranial direct current stimulation (tDCS) improve cognitive performance in these domains for adults with ADHD?

Forty adults with ADHD participated in a sham-controlled, double-blind, crossover study to assess the cognitive and physiological effects of tDCS. In this study, performance in two cognitive tasks – the Eriksen Flanker Task (EFT) and the Stop-Signal Task (SST) – was used to assess for executive function, which was later correlated with neurophysiologic biomarkers. Participants completed the cognitive tasks at baseline while

experimenters examined their performance and electrophysiological measures of four event-related potentials (ERPs) – N200, P200, P300 and Pe – which have been correlated with attentional functions. Participants then underwent sham procedure, tDCS of the left dorsolateral prefrontal cortex (DLPFC), and tDCS of the right DLPFC in a randomized, blinded manner before repeating the same cognitive tasks. Active stimulation involved 2mA of anodal stimulation over right or left DLPFC, with the cathode over the contralateral supraorbital region. The sham condition involved application of current during 15-second ramp-up and ramp-down phases; as constant stimulation is usually not noticeable, patients remained blinded during the 30-minute treatment period.

Participants receiving tDCS of the left DLPFC showed improved reaction time (12ms  $\rightarrow$  6ms) compared to sham in EFT trials with incongruent (conflicting) information. This effect was seen to a lesser degree, but still present, with right DLPFC stimulation. Improved reaction time was

correlated with increased P300 amplitude, which supports the role of P300 as a marker of conflict resolution and interference control. In SST trials, participants receiving tDCS of left DLPFC showed some improvement in cognitive control, but not in action cancellation. Of note, improvements in neurophysiological measures P300 and N200 were greater for participants with ADHD than healthy controls.

**Impact: This sham-controlled, double-blind study suggests a role for tDCS in treating ADHD in addition to established pharmacologic and behavioral approaches. The authors demonstrate direct effects on performance in attention-related tasks involving cognitive control, but not action cancellation. This study also provides further correlation of neurophysiologic findings associated with improved performance in these cognitive domains. This study provides further support for the existence of multiple impulsivity constructs with distinct but related neuroanatomical substrates, with potential implications for individualized treatment.**

Dubreuil-Vall L, Gomez-Bernal F, Villegas AC, et al. Transcranial Direct Current Stimulation to the Left Dorsolateral Prefrontal Cortex Improves Cognitive Control in Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Behavioral and Neurophysiological Study. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2021;6(4):439-448.



# A Review of Neuromodulation for Suicidal Ideation

Collin M Price, MD reviewing Chen et al. *Brain Behav* 2021 May

***This systematic review examined studies using non-invasive neuromodulation to treat suicidal ideation and behavior. Among the 26 studies identified, ECT was the only modality to have clear evidence of efficacy in suicidality, while rTMS, MST, and tDCS require further investigation.***

Although psychiatrists are well-versed in the management of suicidal ideation, few treatments exist that can rapidly reduce or eliminate the subjective suffering of suicidal patients. Electroconvulsive therapy (ECT) has been used for decades in severe cases of nearly every psychiatric condition, including suicide, while newer neuromodulation modalities such as repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), and transcranial direct current stimulation (tDCS) are being tested across the psychopathologic spectrum. This review aimed to summarize the literature assessing the efficacy of these neuromodulation modalities on suicidality.

The reviewers initially gathered 1,019 articles via keyword searches in multiple databases containing English language clinical trials. They assessed the titles and abstracts for eligibility criteria, which included suicidality as a main or secondary outcome, inclusion of at least one of the specified neuromodulation techniques as the main intervention, and quality of evidence. The Sackett Scale, a hierarchy of evidence in scientific studies, was used to evaluate quality, and only studies in levels 1-3 (out of 5) were included. Fifty-eight articles received a full-text evaluation, with 26 articles ultimately meeting inclusion criteria.

The 26 studies included analyses of ECT (n=14), rTMS (n=9), MST (n=2), and tDCS (n=1). Newer treatment modalities had the highest quality evidence (Sackett Scale level 1), with the only blinded randomized controlled trials (RCTs) examining rTMS (n=5) and tDCS (n=1). Non-blinded randomized trials and prospective studies, level 2 on the Sackett Scale, were found for ECT (n=5), rTMS (n=4), and MST (n=2), while the rest of the retrospective ECT studies (n=9) were rated level 3. The sample included 3,589 patients who were primarily diagnosed with affective disorders, as well as personality, anxiety, and psychotic disorders. There was large variability in treatment parameters among the ECT and rTMS studies, including stimulation settings as well as number and frequency of visits, whereas the two MST studies were nearly identical in their characteristics. All rTMS studies and the tDCS study targeted the dorsolateral prefrontal cortex. Suicidal ideation was the main variable extracted from 17 of the studies, while the remainder included data on suicide attempts and completions.

ECT was found to significantly improve suicidality in 10 of the 14 studies, with 5 studies showing improvements in suicidal ideation and another 5 showing reductions in

suicide attempts and completions. Three ECT studies saw no impact on suicidality, while 1 study described an increase in suicide rates with ECT. There was also considerable heterogeneity in the results for rTMS; 4 studies supported its use for suicidal ideation, while 4 others saw no benefit of active rTMS compared to sham and 1 study showed worsened outcomes with active rTMS. Multiple stimulation parameters were successful in treating suicidality, including unilateral left 10 Hz, bilateral (left: 1 Hz, right: 10 Hz), and 20 Hz deep TMS. Both MST studies and the single tDCS study showed significant improvements in suicidal ideation.

**Impact: This systematic review sought to assess the current evidence for use of neuromodulation techniques in the treatment of suicidality. ECT had the largest evidence base, which generally supported its use, while rTMS had a somewhat equivocal literature. The small body of evidence for MST and tDCS in suicidality has thus far been positive. Although the overall quality of the evidence in this review was low and significant heterogeneity precluded a meta-analysis, the findings nonetheless support further investigation into neuromodulation as a treatment for suicidal ideation and behavior.**

Chen Y, Magnin C, Brunelin J, Leaute E, Fang Y, Poulet E. Can seizure therapies and noninvasive brain stimulations prevent suicidality? A systematic review. *Brain Behav*. 2021;11(5):e02144.

