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Neurostimulation and Threat Response

In a proof-of-concept study, a single session of transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) reduced amygdala threat response in subjects with high trait anxiety. The study provides the first evidence in humans of causal associations between the prefrontal cortex, attention control networks, and the amygdala in regulating the response to threats.

Background: The amygdala is a critical part of the neural circuitry underlying fear processing. Patients with anxiety or depression have been shown to have hyperactive amygdala responses to emotional information. The present experiment was designed to test whether deficient prefrontal control results in overactivity of the amygdala, which directs attention to threatening stimuli in patients with high trait anxiety.

Methods: The study enrolled only women to avoid gender-related differences in brain activation and because the prevalence of anxiety disorders is higher in women than men. Participants were 18 women, aged 18–42 years, who were recruited from the community and met screening criteria for high levels of trait anxiety. They attended 2 study sessions, 1 month apart, during which active and sham tDCS were administered in random order. tDCS was administered bilaterally to the DLPFC using a single dose from a multisession protocol used in clinical trials of major depression. After the stimulation was completed, participants performed an attention control task while undergoing functional MRI (fMRI). The task, which was briefly superimposed on a background distracter (i.e., faces that had either fearful or neutral expressions), was completed under low and high attentional loads. The experiment tested the hypothesis that, under conditions of low attentional load with fearful distracters, active tDCS would increase cortical activation, decrease amygdala activation, and improve task accuracy.

Results: Data were analyzed from the 16 women (mean age, 23 years) who completed the experiment. Following sham stimulation, the right amygdala was activated during trials with fearful distracters only when the attentional load was low, confirming the sensitivity of the test in detecting amygdala threat signaling. Following active tDCS, the difference in the amygdala signal between tests with fearful and neutral distracters was reduced when the attentional load

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was low, indicating a lessened response to the fearful distracter. These effects were observed in both the right and left amygdala. Whole-brain analysis revealed that stimulation significantly increased activation in frontal, temporal, and parietal clusters associated with attention and action selection in response to the fearful distracter, again only during the low attentional load condition. Although the test was not designed to measure behavioral differences, task accuracy was increased by about 12% during active versus sham tDCS.

Discussion: The prefrontal cortex may fail to inhibit the amygdala threat response in patients with trait anxiety. These results support a proposed mechanism of action for antidepressants—reduced amygdala hyperactivity—that was previously suggested by animal experiments. In addition, this research may have identified an fMRI biomarker that has potential for testing new stimulation protocols and accelerating treatment development for anxiety and depression.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Ironside M, Browning M, Ansari T, Harvey C, et al: Effect of prefrontal cortex stimulation on regulation of amygdala response to threat in individuals with trait anxiety: a randomized clinical trial. *JAMA Psychiatry* 2019;76 (January):71–78. doi 10.1001/jamapsychiatry.2018.2172. From the University of Oxford, U.K.; and other institutions. **Funded by the Medical Research Council; and other sources. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Possible Brain Stimulation Target for Depression

The lateral orbitofrontal cortex (OFC) may be a promising target for electrical brain stimulation in depression, according to an experiment conducted in patients undergoing intracranial electrode placement for epilepsy.

Background: The OFC has a role in emotion regulation and has been previously approached using repetitive transcranial magnetic stimulation (rTMS) in preliminary studies. It may have advantages over other deep brain stimulation targets including better surgical accessibility than other targets.

Methods: Study participants were 25 adults with drug-resistant epilepsy undergoing intracranial electrode implantation for seizure localization. Participants were also required to have baseline trait depression ranging from minimal to severe. Electrode implantation was by clinical indication, and subjects typically had electrodes implanted in multiple regions involved in emotion regulation including the OFC. Mood was assessed beginning several days before the experiment using the Immediate Mood Scaler (IMS) questionnaire and on the day of surgery using the Beck Depression Inventory. OFC stimulation was conducted after the collection of clinical seizure data. Mood was assessed during 2 intensities of OFC stimulation and sham stimulation using patients' subjective reports and the IMS. The effect of OFC stimulation on other brain regions involved in mood regulation was also assessed.

Results: During stimulation for seizure localization, patients generally reported no changes in mood. However, during lateral OFC stimulation, most individuals reported marked mood improvement. The composite mood score (CMS), derived by integrating the IMS and word valences from a mood self-report, was significantly higher during real rather than sham OFC stimulation. Increases in the CMS were statistically significant only in the subjects with moderate or severe baseline depression and were more marked in those receiving higher amplitude stimulation. Mood improvement was associated with decreased low-frequency OFC activity during stimulation. OFC stimulation also suppressed low-frequency power broadly in the other limbic and paralimbic structures implicated in mood regulation.

Discussion: The OFC may act as a hub within brain networks that mediate affective cognition. It has been identified as a key point involved in the emotional reaction to anticipating aversive

events. The mood effects of OFC stimulation were limited to persons with low mood and did not induce supraphysiologic mood states. Persons with depression had slowed speech rates, which were increased to normal but not beyond. Thus, the result of OFC stimulation appears to normalize rather than elevate mood.

Rao V, Sellers K, Wallace D, Shanechi M, et al: Direct electrical stimulation of lateral orbitofrontal cortex acutely improves mood in individuals with symptoms of depression. *Current Biology* 2018; doi 10.1016/j.cub.2018.10.026. From the University of California, San Francisco; and the University of Southern California, Los Angeles. **Funded by the Defense Advanced Research Projects Agency (DARPA); and other sources. The authors declared no competing interests.**

Prevalence of Orthorexia Nervosa

Orthorexia nervosa (ON)—a pathological obsession with the quality of food consumed—is not yet recognized as a psychiatric disorder. However, a cross-sectional study showed nearly 20% of Spanish university students may be at risk.[1]

Background: It appears that a majority of clinicians who treat eating disorders recognize that ON is frequently present in their patients and is a problem deserving greater recognition. Like anorexia nervosa, ON is characterized by a lack of pleasure related to eating and a need to control intake of food to improve self-esteem and give the individual a sense of control over their life. Severity is variable, at worst involving malnutrition, affective instability, and social isolation. Questionnaire-based studies have resulted in extremely varied estimates of its prevalence.

Methods: Students enrolled at a university in Spain were invited to participate in the survey-based study. Orthorexia risk was evaluated using the ORTO-11-ES questionnaire, which measures obsessive food-related behaviors in 3 domains: cognitive-rational, clinical, and emotional. Participants also completed the Eating Disorder Inventory-2 (EDI-2), which measures 11 domains of eating disorder symptoms, attitudes, and behaviors.

Results: A total of 454 students completed the questionnaires. The mean respondent age was 22 years (range, 18–51 years); two-thirds were women; and 20% were smokers. Scores below a predetermined cutoff on the ORTO-11-ES indicated 76 participants (17%) were at risk of orthorexia nervosa. The prevalence of increased risk was higher in women than men (19% vs 12%) and somewhat higher in smokers than nonsmokers, but was not related to age or body mass index. Persons at risk for ON had a higher prevalence of most of the eating-disorder traits measured with the EDI-2. In decreasing size of correlation, they had significantly higher rates of drive for thinness, body dissatisfaction, interoceptive awareness, bulimia, perfectionism, ineffectiveness, impulse regulation, asceticism, social insecurity, interpersonal distrust, and maturity fears.

Discussion: Diagnostic criteria have been proposed, but ON is not a recognized diagnosis in DSM-5 or in the International Classification of Diseases-10 (ICD-10). Currently there is debate over whether ON is a distinct disorder or a subsyndrome of anorexia nervosa. ON can reflect an obsession with healthy eating that can progress to anorexia or bulimia, or it can represent a stage in recovery from an eating disorder.

Editor's Note: According to the National Eating Disorders Association, there are no treatments developed specifically for orthorexia. However, many eating-disorder experts treat orthorexia as a variant of anorexia and/or obsessive-compulsive disorder, usually with psychotherapy to increase the variety of foods eaten and exposure to anxiety-provoking foods, as well as weight restoration when needed.[2]

[1]Parra-Fernández ML, Rodriguez-Cano T, Onieva-Zafra M, Perez-Haro M, et al: Prevalence of orthorexia nervosa in university students and its relationship with psychopathological aspects of eating behaviour disorders. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1943-0. From the University of Castilla-La-Mancha, Ciudad Real, Spain; and other institutions. **This research was conducted without funding. The authors declared no competing interests.** See related story in *Psychiatry Alerts NOS* 2015; 7 (March):15.

[2]Orthorexia; National Eating Disorders Association website. Available at www.nationaleatingdisorders.org. Accessed January 20, 2019.

rTMS for Suicidal Ideation in Resistant Depression

Bilateral repetitive transcranial magnetic stimulation was superior to sham treatment in inducing resolution of suicidal ideation in patients with treatment-resistant depression in a combined analysis of 2 clinical trials. Improvement in suicidality was only weakly correlated with improvement in depression, which suggests the efficacy of rTMS may be specific to suicide.

Methods: The present study analyzed pooled data from 2 previously published studies conducted by the same researchers. In both studies, patients with treatment-resistant depression, nonresponsive to ≥2 medications from different classes, were randomly assigned to receive bilateral rTMS, left unilateral rTMS, or sham stimulation. Treatment consisted of 15 sessions over 3 weeks, which was repeated if patients did not achieve remission of depression. Suicidality was scored from 0 (absent) to 4 points (suicide attempts) on the suicide item of the Hamilton Rating Scale for Depression (HAM-D). Acute suicidality (score, >3) was an exclusion criterion of the studies, and the outcome analysis was limited to patients who had baseline suicidality scores greater than zero. The primary outcome of the analysis was a decrease from any nonzero baseline score to a score of zero.

Results: After removing 33 patients who had no baseline suicidality, the analysis included 156 study participants, who had a mean suicidality score of nearly 2. After treatment, suicidal ideation resolved in 40% of patients who received bilateral rTMS, 27% of those who received left unilateral rTMS, and 19% of those who received sham treatment. Bilateral rTMS differed significantly from sham rTMS (odds ratio* for remission, 3.03; p=0.02), while unilateral stimulation did not. Changes in suicidal ideation and depression total scores were moderately correlated (correlation coefficient [r],* 0.38; p<0.001), but there was no difference between suicide remitters and nonremitters in the change in HAM-D score. (See table.)

Outcomes with Bilateral rTMS, Unilateral rTMS, and Sham Treatment

	Bilateral rTMS (n=52)	Unilateral rTMS (n=56)	Sham (n=48)
Patients with Resolved Suicidal Ideation	21	15	9
Odds Ratio for Resolution	3.03	1.59	—
Mean Baseline HAM-D Score	22.7	24.3	24.3
Mean Endpoint HAM-D Score	15.8	19.4	19.6
Mean % Reduction in HAM-D Score	30%	20%	19%
Mean % Reduction in HAM-D Suicide Item Score	50%	36%	32%

Discussion: Other studies of the effects of rTMS on suicidal ideation have had varied methods and mixed results. The present findings support neuroanatomic data suggesting that suicidal ideation could be a specific target symptom for rTMS delivered to the bilateral dorsolateral prefrontal cortex. Future studies should measure suicide using a more nuanced instrument and in patients with more severe suicidality.

Weissman C, Blumberger D, Brown P, Isserles M, et al: Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.17m11692. From the University of Toronto, Canada; and other institutions. T**his research was conducted without specific funding. Six of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Improving Adherence in Bipolar Disorder

In a randomized controlled trial, customized adherence enhancement (CAE) improved medication adherence and functional status and reduced resource use in patients with bipolar disorder.

Methods: The clinical trial compared CAE with non-individualized bipolar-specific education in 183 patients with bipolar disorder, type I or II. Patients were required to have been ill for ≥2 years and nonadherent with their prescribed medication on ≥20% of days in the past month. CAE was flexibly delivered in ≤4 treatment modules based on each patient's reasons for nonadherence, which were identified at baseline. The modules covered psychoeducation about the role of medication in managing the disorder, motivational enhancement therapy to address interference from substance abuse, communication with clinicians, and routines to incorporate medication taking into the patient's lifestyle. The comparison treatment, bipolar-specific patient education, was based on the patient workbook used in the control group of the NIMH STEP-BD study. Both treatments were delivered by social workers and consisted of 4 core sessions, 1 phone call, and a final booster session. The primary study outcome was treatment adherence, measured using the Tablets Routine Questionnaire (TRQ).

Results: Adherence was poor at baseline; patients missed medication on 55% of days in the prior week and 48% of days in the prior month. Most patients reported multiple barriers to medication adherence: 94% had problems with medication routines, 92% had deficient knowledge of bipolar disorder, 85% had poor clinician communications, and 77% had adherence impaired by substance abuse. Nearly two-thirds of patients had all 4 barrier types.

About half of participants attended all 5 of their assigned sessions. As expected, medication adherence improved between the screening evaluation and the baseline visit (see table), as a result of observation. Adherence continued to improve with both treatments, but to a significantly greater degree in patients who received CAE. However, there were no differences between groups in disease outcomes, measured with the Brief Psychiatric Rating Scale, Montgomery-Asberg Depression Rating Scale, Young Mania Rating Scale, or Clinical Global Impression scales, possibly because baseline symptom levels were too low to easily show a difference between treatments. Function, measured with the Global Assessment of Functioning, was improved by 6 months, more so in patients receiving CAE. Both groups reported using more outpatient mental health services after 6 months than at baseline, possibly because of better recall during the study. Increases in resource use were smaller in the CAE group than the education group.

Change from screening visit through 26 weeks in treatment adherence

TRQ score prior week†	Screening	Baseline	10 Weeks	26 Weeks	Significance
CAE	55.4%	43%	25.7%	20.7%	p=0.001
Education	55%	45.4%	35%	30.3%	p=0.048

†Score indicates proportion of days with missed medication doses

Discussion: These results suggest that a brief, individualized adherence promotion approach may have better effects than generalized interventions, the authors say. Although CAE can be implemented by social workers, it would likely be most effective when it involves all members of the treatment team.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Sajatovic M, Tatsuoka C, Cassidy K, Klein P, et al: A 6-month, prospective, randomized controlled trial of customized adherence enhancement versus bipolar-specific educational control in poorly adherent individuals with bipolar disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m12036. From Case Western Reserve University School of Medicine, Cleveland, OH; and other institutions. **Funded by NIMH; and the Clinical Translational Science Awards Program. Six of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

CBT in Schizophrenia

According to a pooled analysis of studies of cognitive behavioral therapy in patients with schizophrenia, about half of patients will experience at least modest symptom improvement. CBT is especially likely to produce response in patients who are not treatment resistant and who receive treatment from expert therapists.

Background: Studies have shown that participation in CBT results in improved scores on standardized symptom rating scales in patients with schizophrenia, but there has been little analysis of response rates. However, efficacy measured with rating scales is difficult to interpret, and most studies report treatment effects relative to an alternative intervention. Calculating response rates can help to clarify the absolute treatment effects.

Methods: A systematic literature review identified studies in adults with a diagnosis of schizophrenia or a related disorder, in which CBT was compared with any other nonpharmacological treatment or a control condition. CBT was usually administered in addition to standard care, which included pharmacotherapy. The primary outcome of the analysis was an overall decrease of ≥20% on any symptom scale—usually the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale—indicating at least minimal improvement. A ≥50% reduction indicated substantial improvement.

Results: The authors identified 33 randomized controlled trials with a total of 1142 participants in the CBT arms. A total of 44.5% of these patients had a ≥20% reduction in schizophrenia symptoms, and 13% improved by ≥50%. When considering positive symptoms only, 53% of patients had a ≥20% improvement and 25% improved by ≥50%. Response rates were significantly lower in patients with resistant disease (33% vs 53%) and higher in studies in which therapists were evaluating their own protocols (51% vs 33%). By a smaller margin, treatment was more effective in studies where clinicians were experts rather than trainees. Higher baseline illness severity had a borderline association with better response, but treatment duration, number of sessions, patient age, and gender were not associated with the likelihood of response. Because few studies reported specifics regarding concomitant pharmacotherapy, the effects of antipsychotics could not be determined.

Bighelli I, Huhn M, Schneider-Thoma J, Krause M, et al: Response rates in patients with schizophrenia and positive symptoms receiving cognitive behavioural therapy: a systematic review and single-group meta-analysis. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1964-8. From the Technische Universität München, Munich, Germany; and other institutions. **Funded by the European Union. Three of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Correlation Coefficient (r): A measure of the closeness of the relationship between two variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.