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Transcranial DCS for Negative Symptoms

In a sham-controlled trial, adjunctive transcranial direct current stimulation (tDCS) reduced negative symptoms in a group of patients with schizophrenia.[1]

Background: tDCS is a noninvasive, low-cost brain stimulation technique that uses weak, direct currents delivered via electrodes positioned on the scalp. Previous research has suggested it may ameliorate negative symptoms,[2] and a recent pilot study confirmed the feasibility and safety of remotely-monitored, in-home self-administered stimulation in patients with depression.[3]

Methods: The trial recruited outpatients with a diagnosis of schizophrenia and prominent negative symptoms, evidenced by a score of ≥20 on the negative symptoms subscale of the Positive and Negative Syndrome Scale (PANSS). Patients were required to be clinically stable for ≥4 weeks and receiving consistent doses of antipsychotic medication. Antidepressant drugs were discontinued before study entry. Participants were randomly assigned to receive 5 consecutive days of twice daily active or sham tDCS delivered with anode placement over the left prefrontal cortex and cathode placement over the left temporoparietal junction. Because effects were expected to develop over a prolonged time, outcomes were evaluated at intervals up to 6 and 12 weeks. The primary endpoint was change from baseline in the PANSS negative symptom score.

Results: Of 100 patients who began randomized treatment, 95 completed the study. The mean baseline PANSS negative symptom score was 25 in both groups. At week 6, active tDCS was superior to sham treatment, with a mean decrease in negative symptom score of 4.5 points vs 1.8 points in the sham group (effect size,* 0.57; $p<0.001$). Improvements were generally maintained at 12 weeks. Response was defined as a ≥20% improvement in PANSS negative symptom score. At week 6, the response rates were 40% in tDCS group and 4% in the control group ($p<0.001$; number needed to treat,* 3.18). At week 12, response rates were 38% and 4%, respectively. There were no treatment-related differences in other secondary outcomes, such as PANSS total or positive symptoms, depression, auditory hallucinations, or various measures of function. No adverse effects other than a burning sensation were related to tDCS.

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Discussion: Although differences between the active and sham groups were significant for negative symptom improvement, absolute changes were relatively small, and larger effects have been reported for some medications. Additional research to optimize the technique in patients with psychotic disorders appears to be warranted. tDCS could be evaluated as an add-on treatment in outpatient settings and could be used at home, with remote supervision, for prolonged administration.

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

[1]Valiengo L, Goerigk S, Gordon P, Padberg F, et al: Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.3199. From the Universdade de São Paulo, Brazil; and other institutions. **Funded by the Stanley Medical Research Institute. Six of 14 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Brunelin J, et al: Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *American Journal of Psychiatry* 2012;169(7):719–724.

[3]Alonzo A, et al: Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of Affective Disorders* 2019;252:475–483. See *Psychiatry Alerts NOS* 2019;11 (April):19–20.

Infectious Diseases and Bipolar Disorder

A case–control study found that in adults with bipolar disorder, levels of anticytomegalovirus (CMV) antibodies were increased and antibodies to *Toxoplasma gondii* were decreased, compared with healthy controls. These observations suggest immune modulators and anti-inflammatory interventions may be a promising avenue for bipolar disorder treatment.

Methods: Antibodies to CMV, *T. gondii*, and measles, as well as levels of the inflammatory marker C-reactive protein, were assayed in samples from the Mayo Clinic Bipolar Biobank and the Mayo Clinic Biobank, representing non-Hispanic white individuals from the American Midwest (minorities were excluded because of a low level of participation in the biobanks). The study population consisted of 1207 adults with bipolar disorder stratified by bipolar disorder subtype, age at onset (with early onset defined as ≤19 years), and history of psychotic mania. Seropositive rates were compared between case patients and 745 controls matched for age, sex, and educational level if available.

Results: Compared with controls, patients with bipolar disorder had higher rates of CMV seropositivity (odds ratio,* 1.24; p=0.03) and lower rates of *T. gondii* seropositivity (odds ratio, 0.69; p=0.01). Rates of a combined CMV-positive/*T. gondii*-negative status were also significantly higher in patients with bipolar disorder (odds ratio, 1.33; p=0.004). The rate of combined CMV-positive/*T. gondii*-negative status was positively associated with the subphenotypes of bipolar type I disorder, nonearly onset, and a history of manic psychosis. Patients who received medications with antitoxoplasma activity had lower titers of antibody to this organism, but controlling for use of these medications did not affect the study results. Levels of C-reactive protein and measles antibody titers did not differ between cases and controls.

Discussion: Previous research suggests bipolar disorder is a multisystem inflammatory disease of the brain and body. The results of this study contrast with previous investigations that found increased *T. gondii* seroprevalence in patients with bipolar disorder. The difference maybe the result of geography and variance in selection criteria for research subjects. Both CMV and *T. gondii* are associated with neurocognitive impairment, but neither causality nor the time sequence of exposure to the infectious agent, the immune response, and onset of bipolar disorder could be determined in the present study.

Frye M, Coombes B, McElroy S, Jones-Brando L, et al: Association of cytomegalovirus and *Toxoplasma gondii* antibody titers with bipolar disorder. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.2499. From the Mayo Clinic, Rochester, MN; and other institutions. **Funded by the Marriott Foundation. Seven of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Computer-Assisted CBT for Depression

According to the results of a meta-analysis, computerized cognitive-behavioral therapy (CCBT) with a moderate amount of interpersonal help or support has large positive effects on depressive symptoms. Self-guided CCBT was less effective. Treatment had the strongest effects in patients with the most severe depression.

Background: Previous meta-analyses have confirmed the efficacy of CCBT. The present analysis was conducted to include a greater number of recent studies and to examine the effects of potential moderators, such as human support and baseline depression severity.

Methods: A comprehensive literature search identified all available randomized trials of CCBT in depression. For inclusion, studies were required to have a control group that did not receive standard face-to-face CBT, to include patients aged ≥16 years, and to measure outcomes with validated scales. CCBT interventions involved use of a computer or mobile app that covered core methods of CBT to deliver all or part of the treatment.

Results: The analysis included 40 studies, which were of generally good quality. The overall post-treatment effect size* for CCBT versus control conditions was 0.50 ($p<0.001$), indicating moderate efficacy. Effects were larger for studies that provided support by a clinician, technician, or other helping person, compared with studies offering no or minimal support (effect sizes, 0.67 and 0.24, respectively; $p<0.001$ for both). This effect size difference would correspond to about a 15% difference in response rates on the Hamilton Rating Scale for Depression. Effects were larger for studies that provided face-to-face support than those offering e-mail or telephone support (effect sizes, 0.83 vs 0.56 and 0.78, respectively; $p<0.001$ for all). Studies in patients with baseline depression severity scores that were above the mean for the entire group had larger effect sizes than studies of patients with less severe depression (0.87 vs ≤0.48).

Discussion: These results suggest the efficacy of CCBT is strongly influenced by the support of a clinician or other helper. Of the studies reporting a significant amount of support—about an hour or more—most used telephone, e-mail, or similar methods, with no face-to-face contact. Thus it appears various support methods and combinations can be used effectively. The authors note that many of the studies in this analysis used criteria, such as cutoffs on the educational level or access to a computer, that would exclude disadvantaged populations

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Wright J, Owen J, Richards D, Eells T, et al: Computer-assisted cognitive-behavior therapy for depression: a systematic review and meta-analysis. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18r12188. From the University of Louisville School of Medicine, KY; and other institutions. T**his study was conducted without funding. Seven of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Chronotherapy for Depression

Results of a meta-analysis support the efficacy of chronotherapy (i.e., sleep deprivation, sleep phase shifting and/or the use of bright light) in the treatment of depression. Positive effects of treatment were rapid and evident in patients with unipolar and bipolar depression.

Background: The aims of chronotherapy are to resynchronize patients' circadian rhythms and to stabilize sleep timing. This is likely accomplished through several mechanisms, such as regulation of monoamines and melatonin so that they are released at the proper time of day. Chronotherapy may also effect cortical neuroplasticity and glial cell cycles, peripheral hormonal rhythms, and reactivity to external HPA axis stimuli. It may also directly impact brain regions that contribute to affect control.

Methods: Randomized controlled trials and case series of chronotherapy for the treatment of depression were identified in the literature. For inclusion in the meta-analysis studies were required to examine partial or total sleep deprivation followed by sleep phase advance or delay with or without light therapy in adults experiencing a unipolar or bipolar depressive episode. Depressive symptoms were assessed with validated observer-rated or self-rated measures. Data from controlled trials and case series were analyzed separately.

Results: A total of 16 studies met inclusion criteria: 4 controlled trials and 12 open-label case series. All but 1 study were conducted in an inpatient setting. Pooled samples comprised 150 patients with unipolar depression and 58 with bipolar depression for controlled trials and 174 patients with unipolar depression and 330 with bipolar depression for the case series. All patients enrolled in controlled trials and about 80% of those in the case series were receiving medication. The primary outcome was change in depression, measured on days 1–2, days 5–7, and at 7–9 week follow-up.

Substantial positive effects of chronotherapy compared with baseline were evident at day 1–2. Effects sizes* (corrected for small sample bias) for chronotherapy were 2.23 and 1.75 in controlled trials and case series, respectively. At day 5–7, pooled effect sizes were 0.62 for controlled trials and 1.79 for case series. In the controlled trials, beneficial effects were attenuated but continued to favor chronotherapy at weeks 7–9 (effect size, 0.35). Also in the controlled trials, the weighted response rate (i.e., ≥50% reduction in depressive symptoms) was 33.0% for chronotherapy, compared with 1.5% for control interventions (odds ratio* for response, 7.58). Case series had a weighted mean response rate of 62%. Subgroup analyses in patients with unipolar or bipolar depression found similar effects in both groups. Chronotherapy was well tolerated, with no serious adverse effects reported, and <1% of patients with bipolar disorder switched to mania.

Discussion: Pooled estimates indicate that chronotherapy can produce rapid antidepressant effects in patients with unipolar or bipolar depression. However, efficacy appears to wane and no firm conclusions could be drawn about the long-term sustainability of response. Although the results are positive, chronotherapy procedures and control interventions varied across the included studies, and standardized research is required to replicate the findings.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Humpston C, Benedetti F, Serfaty M, Markham S, et al: Chronotherapy for the rapid treatment of depression: a meta-analysis. *Journal of Affective Disorders* 2019; doi 10.1016/j.jad.2019.09.078. From King's College, London; and other institutions. **Funded by the National Institute for Health Research Biomedical Research Centre; and other sources. The authors did not include disclosure of potentially relevant financial relationships.**

***See Reference Guide.**

Parkinson's Disease Risk in Bipolar Disorder

Patients with bipolar disorder have a substantially increased risk of developing Parkinson's disease, according to a systematic review and meta-analysis of observational studies.

Methods: A comprehensive literature review identified 4 cohort studies and 3 cross-sectional studies that compared rates of idiopathic Parkinson's disease in patients with and without bipolar disorder. Study samples of patients with bipolar disorder ranged in size from about 1200 to >56,000 patients. Most of the study reports did not state the criteria used to diagnose Parkinson's disease.

Results: Each of the individual studies showed an association between bipolar disorder and Parkinson's disease. According to the meta-analysis, a diagnosis of bipolar disorder was associated with risk of developing Parkinson's disease (odds ratio,* 3.35). Risk was elevated to the

greatest extent in studies with a <9-year follow-up period (odds ratio, 5.2), but was also elevated in studies with longer follow-up (odds ratio, 1.75).

Discussion: The authors suggest the association may be explained by the dopamine dysregulation process. Dopamine receptor sensitivity is downregulated in manic states but is later compensated during manic states. Over time this cyclic activity may lead to an overall reduction in dopaminergic activity, the prototypical Parkinson's disease state. However, bipolar disorder is not associated with overt evidence of neurodegeneration, and other neurotransmitter processes may be involved. It is also possible that parkinsonian symptoms are drug-induced, particularly in patients treated with lithium, or that long-term lithium use may increase risk of idiopathic Parkinson's disease. In patients with bipolar disorder demonstrating parkinsonian symptoms, functional neuroimaging may help distinguish between drug-induced parkinsonism and idiopathic Parkinson's disease. Regardless of the etiology, patients with bipolar disorder may require monitoring for signs and early deficits of Parkinsons' disease and could benefit from risk mitigation by medication selection and nonpharmacologic treatment.

Study Rating*—16 (89%): This study met most criteria for a meta-analysis; however, the source of funding was not disclosed.

Faustino P, Duarte G, Chendo I, Caldas A, et al: Risk of developing Parkinson disease in bipolar disorder: a systematic review and meta-analysis. *JAMA Neurology* 2019; doi 10.1001/jamaneurol.2019.3446. From the Universidade de Lisboa, Portugal; and other institutions. **Source of funding not stated. One of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Brain Markers for Dissociative Identity Disorder

Although recognized in the DSM, the diagnosis of dissociative identity disorder (DID) is controversial and can be challenging. The existence of imitative DID further complicates the issue. A structural brain imaging study found it possible to distinguish between patients with the disorder and healthy controls based on brain morphology.

Methods: Subjects with a DSM diagnosis of DID, independently confirmed by a structured clinical interview, were recruited from outpatient psychiatry clinics and private practices in the Netherlands and Switzerland. Each participant was matched for age, gender, ancestry, and education with a medication-free healthy control with no psychiatric disease. MRI scans were obtained and compared across the groups.

Results: A total of 32 patients with DID enrolled in the study; all were women. All had a comorbid diagnosis of posttraumatic stress disorder (PTSD), 3 of whom had achieved remission, and about half had an additional psychiatric comorbidity. Comparison of MRI scans found widespread patterns of abnormal brain morphology in individuals with DID as compared with healthy controls. These differences in brain structure accurately discriminated between individuals with DID and healthy controls with significant sensitivity and specificity* (72% and 74%, respectively; $p<0.01$).

Compared with healthy controls, patients with DID were found to have relative decreases in grey matter volume across several brain regions: the bilateral middle, superior and dorsolateral frontal gyrus; left medial and right orbitofrontal gyrus; bilateral anterior cingulate gyrus; bilateral middle temporal gyrus; bilateral fusiform gyrus; right inferior temporal gyrus; left inferior parietal lobule and supramarginal gyrus and bilateral superior occipital gyrus. Regional volumes of the left superior frontal gyrus, left medial parietal lobule, and bilateral cerebellum were relatively increased in DID patients.

Additionally, patients with DID were found to have reduced white matter volume in several regions: the bilateral inferior fronto-occipital tract, the left corticospinal tract, and the right superior and left inferior longitudinal fasciculus. Compared with healthy controls, patients with DID also had increased white matter volume in the left inferior and superior longitudinal fasciculus, the left inferior fronto-occipital fasciculus and the right corticospinal tract.

Discussion: Although they require replication, these results provide evidence supporting a biological distinction between patients with DID and healthy controls. Future research will need larger, more diverse patient samples, and should attempt to determine the effects of medication and comorbid PTSD on brain morphology. Furthermore, as DID is often misdiagnosed as borderline personality disorder or schizophrenia, future studies should attempt to distinguish patients with DID from patients with confirmed cases of these disorders.

Reinders A, Marquand A, Schlumpf Y, Chalavi S, et al: Aiding the diagnosis of dissociative identity disorder: pattern recognition study of brain biomarkers. *British Journal of Psychiatry* 2019;215:536–544. doi 10.1192/bjp.2018.255. From King's College London, U.K.; and other institutions. **Funded by the National Institute for Health Research Biomedical Research Centre; and other sources. The authors declared no relevant financial relationships with commercial sources.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

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.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified and specificity measures the proportion of negatives that are correctly identified. A perfect predictor would have 100% sensitivity and specificity.

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.

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