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Volume XI / March 2019 / Number 3

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Brain Stimulation in Anxiety

Evidence is accumulating that noninvasive brain stimulation may be useful in treating anxiety disorders, according to a systematic review. Effective treatment protocols target the dorsolateral prefrontal cortex (DLPFC) and are believed to work by upregulating positive reactions to positive emotional stimuli or outcomes and downregulating negative reactions that underlie anxiety symptoms.

Background: Noninvasive brain stimulation techniques may address a suggested pathological mechanism in anxiety disorders, the maladaptive structural and functional neuroplasticity of prefrontal and limbic regions. Anxiety is thought to be associated with hypoactivation of the left DLPFC, which inhibits the amygdala, resulting in heightened threat detection and processing. There is also evidence for increased activation of the right DLPFC, which may contribute to the emergence and chronicity of cognitive/emotional deficits.

Methods: A comprehensive literature search identified 26 peer-reviewed, English-language studies of noninvasive brain stimulation techniques—either transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS)—to treat diagnosed anxiety disorders in adult populations. Treated anxiety disorders included specific phobias, social anxiety disorder, agoraphobia, panic disorder, and generalized anxiety disorder (GAD). Studies of PTSD and obsessive compulsive disorder were not included as these are no longer classified as anxiety disorders in the DSM-5.

Results: Few studies of brain stimulation have been conducted in patients with specific phobias, social anxiety disorder, or agoraphobia. Of those identified, 3 studies provide preliminary support for rTMS or tDCS over the prefrontal cortex in specific phobias; but the heterogeneity of symptoms, protocols, cortical targets, and other features preclude any conclusions. An additional 2 reports, from a single group with a total of 3 patients, reported positive effects of rTMS in social anxiety disorder. In a small sham-controlled trial of tDCS in patients with social anxiety disorder, a single session of treatment resulted in changes in a surrogate measure of anxiety. There has been only a single study of brain stimulation in agoraphobia, with negative results.

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5641) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2019 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

The evidence concerning rTMS in panic disorder consists mainly of single-case studies and small open-label studies, with a few sham-controlled trials. rTMS over the right DLPFC, in 20 sessions over 4 weeks, was effective in a randomized, sham-controlled study in 25 patients with panic disorder and comorbid depression. In another study in 15 patients with SSRI-resistant panic disorder, rTMS of the right DLPFC was not more effective than sham treatment, possibly a result of small sample size. There is only a single case report of tDCS efficacy in panic disorder. The available studies showed significant improvement with inhibitory stimulation of the right DLPFC and excitatory stimulation of the left DLPFC. However, it is unclear whether the effects of brain stimulation on panic disorder are the result of improvement in comorbid depression.

For GAD, evidence from 3 sham-controlled trials of rTMS and 1 of tDCS suggests that inhibitory brain stimulation over the right DLPFC may be effective. An additional sham-controlled study found that inhibitory rTMS over the right parietal lobe relieved GAD and insomnia symptoms. Further work is needed to determine whether excitatory treatment of the left DLPFC is helpful in GAD.

Discussion: Overall, the studies support the idea that noninvasive brain stimulation is a promising approach for anxiety disorders. The DLPFC was the target in nearly all of the studies, consistent with what is known about its involvement in networks associated with attention, mood, and reward processing. The review suggests that there is a precise relationship between the brain hemisphere to be stimulated (left or right) and the type of stimulation (excitatory or inhibitory). Both up- and down-regulatory mechanisms might be prompted with excitatory stimulation of the left DLPFC.

Vicario C, Salehinejad M, Felmingham K, Martino G, et al: A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience and Biobehavioral Reviews* 2019;96:219–231. doi 10.1016/j.neubiorev.2018.12.012. From the Università di Messina, Italy; and other institutions. Funded by the Alexander von Humboldt Foundation, Germany; and other sources. The authors declared no competing interests.

Diet and Depression

In a small, cross-sectional study, depression was associated with high consumption of sweets and refined sugars and low consumption of legumes, fruits, and vegetables. Although causality could not be evaluated, there are plausible biological mechanisms that may explain the association.

Methods: The study, conducted in Spain, included 132 patients admitted to a psychology and neurology clinic with a diagnosis of anxiety, a depressive disorder, marital conflicts, or behavioral problems. Persons taking antioxidant or omega-3 fatty acid supplements and those with an eating disorder or substance addiction were excluded. All patients were administered the Beck Depression Inventory, and those with a score of ≥ 10 were classified as having depression. All patients also filled out a dietary questionnaire, specifically reporting their consumption of legumes, nuts, whole-grain foods, fruits and vegetables, chocolate, sweet foods, and refined sugars.

Results: Of the 132 participants, 76 met study criteria for depression and 56 did not. Those with depression were more than twice as likely as those without to consume no legumes (46% vs 23%; $p < 0.05$; age- and gender-adjusted odds ratio, * 2.60). Those with depression were also more likely to consume < 3 servings of fruits and vegetables per week (80% vs 58%; $p < 0.01$; adjusted odds ratio, 2.69) and to consume ≥ 3 servings per week of sweets and refined sugars (37% vs 16%; $p < 0.05$; adjusted odds ratio, 1.91). Effect sizes for these associations were in the small to medium range. There were no significant differences in consumption of nuts, whole grains, or chocolate.

Discussion: Several previous cross-sectional studies have suggested that a healthy diet may reduce the risk of depression, but the subject has received little investigation. Due to its retrospective design, this study does not clarify whether diet influences depression or vice-versa or whether a third mechanism influences both. Other shortcomings of the study are the use of a nonvalidated food questionnaire and the inclusion of persons with other emotional problems as a comparison group. However, possible mechanisms that could explain an association include the availability of tryptophan, inositol, magnesium, and other nutrients in legumes; the possibility that vegetable consumption prevents oxidative stress; and the contribution of sweet foods and refined sugars to oxidative stress.

Grases G, Colom M, Sanchis P, Grases F: Possible relation between consumption of different food groups and depression. *BMC Psychology* 2019; doi 10.1186/s40359-019-0292-1. From the Centro de Enseñaza Superior Alberta Jimenez, Palma de Mallorca, Spain; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Brain Activation and Body Image in Anorexia Nervosa

Results of a small study in patients with anorexia nervosa suggest that distorted body image may be associated with underactivation of the right hemisphere. Forced activation of the right hemisphere, via left-sided muscle contractions or eye movement desensitization and reprocessing (EMDR), could reduce body-image distortions in these patients and potentially increase the effectiveness of cognitive behavioral therapy.

Methods: Study subjects were 42 women, 20 with confirmed anorexia nervosa and 22 healthy controls with no eating-disorder history. Following presentation of self-described positive and negative primes on a computer screen, participants were shown a picture of their own body in either the right or left visual field, representing left or right hemispheric activation, respectively. Subjects were asked to indicate the body size of the picture as thinner than their body, the exact size of their body, or fatter than their body. Each participant underwent 90 experimental trials with the body image presented in each visual field using both positive and negative primes. The experiments were repeated following right-handed muscle contractions to activate the left hemisphere, and left-handed contractions to activate the right hemisphere. The primary outcome was accuracy of judgements regarding participants' actual body size.

Results: Following negative self-primes, the patients with anorexia nervosa made a large number of errors, indicating the picture shown was fatter than their actual body, when the picture was presented to the left hemisphere (right visual field) but not when they were presented to the right hemisphere (left visual field). This pattern was not found in the control group. Body size judgements were improved following right hemisphere activation using left-sided muscle contraction, such that following negative primes, patients with anorexia showed similar accuracy to healthy controls under no hemispheric activation. Activation of the left hemisphere did not improve body distortions in patients with anorexia.

Discussion: The aim of cognitive behavioral therapy for anorexia nervosa is to change disturbing and unrealistic beliefs about the body, food, and weight, but the treatment is effective in only about half of patients. The present results suggest that distorted body image in patients with anorexia can be improved via activation of the right hemisphere. This activation can be achieved through left-hand muscle contractions and presumably through EMDR. The resulting reduction in body-image distortions could improve cognitive behavioral therapy outcomes in patients with anorexia.

Kazen M, Baumann N, Twenhofel J, Kuhl J: When do anorexic patients perceive their body as too fat? Aggravating and ameliorating factors. *PLOS One* 2018 14(2); doi 10.1371/journal.pone.0212612. From the University of Trier, Germany. **Funded by the university. The authors declared no competing interests.**

Schizophrenia and GI Bleeding

Results of a large population-based study indicate that risk of upper gastrointestinal bleeding, as well as bleeding and nonbleeding ulcers, is increased in patients with schizophrenia. This increase is accompanied by an increase in mortality.

Background: Schizophrenia is associated with a 12–20-year decrease in life expectancy, with a substantial proportion of the excess mortality attributable to somatic illness. Despite a theoretical elevation in risk due to the high prevalence of comorbid substance abuse, few studies have addressed the association between schizophrenia and upper GI bleeding or ulcers.

Methods: A retrospective cohort of patients with new-onset schizophrenia in 1980–2011 were identified from linked population-based registries in Denmark. Patients were followed until 2012, until death or emigration, or until a study outcome of upper GI bleeding or a bleeding or nonbleeding ulcer. Incidence of these outcomes was compared among patients with schizophrenia and a matched cohort of patients without schizophrenia. Mortality in the year following a study outcome was also compared in matched samples of patients with schizophrenia who did and did not experience GI bleeding or ulcer.

Results: The study cohort comprised nearly 40,000 patients with schizophrenia (43% women), 16% of whom had comorbid alcohol use disorder and 14% with comorbid disorders relating to other substance use. During an average of about 460,000 person-years of follow-up, 1264 cases of upper GI bleeding, 459 cases of bleeding ulcer, and 808 cases of nonbleeding ulcer were identified. Compared with population norms, standardized incidence ratios* in the patients with schizophrenia were 2.92 for upper GI bleeding, 2.36 for bleeding ulcers, and 2.00 for nonbleeding ulcers. Patient age and gender had little-to-no effect on outcomes. Risk factors for upper GI bleeding and ulcers included age at schizophrenia diagnosis, nonbleeding somatic comorbidity, alcohol use disorders, and other substance use comorbidity. (See table.) Risk was also increased with concomitant use of medications known to cause bleeding and ulcers (e.g. antithrombotics, aspirin, nonaspirin NSAIDs; hazard ratios,* 1.27–3.38), and those indicative of bleeding risk (e.g., PPIs, H2 antagonists; hazard ratios, 1.93–6.94) or psychiatric comorbidity (e.g., SSRIs, antipsychotics, anticonvulsants; hazard ratios, 0.81–4.96).

Adjusted Hazard Ratios for Upper GI Bleeding and Ulcers in Patients with Schizophrenia			
Risk Factor	Upper GI Bleeding	Bleeding Ulcer	Nonbleeding Ulcer
Age >35 vs <20 years at schizophrenia diagnosis	2.32	8.5	2.76
Nonbleeding somatic comorbidity	2.53	2.48	2.62
Alcohol use disorders	1.63	1.14	1.24
Other substance use comorbidity	1.25	1.07	1.39

Overall mortality rates per 100 person-years were 8.79 following upper GI bleeding, 10.17 following bleeding ulcers, and 6.85 following nonbleeding ulcers. Compared with patients with schizophrenia who did not experience a study endpoint, adjusted mortality rate ratios* were 1.85 for upper GI bleeding, 1.75 for bleeding ulcers, and 1.43 for nonbleeding ulcers. Comorbid alcohol and other substance use disorders, as well as somatic comorbidities, increased mortality risk.

Discussion: These study findings are consistent with previously documented increases in medical comorbidity and shortened life expectancy in patients with schizophrenia. Although a

direct biologic effect of schizophrenia on upper GI bleeding and ulcers is unlikely, it cannot be ruled out. However, more likely is an association between schizophrenia and patients' reluctance to receive medical care and poor compliance with medical treatment. The authors note that because Denmark has universal healthcare, making access to medical and psychiatric treatment more accessible, the risk estimates in this study may be lower than in areas where access to services may be more limited.

Cotton C, Farkas D, Foskett N, Sorensen H, et al: Risk of upper gastrointestinal bleeding and gastroduodenal ulcers in persons with schizophrenia: a Danish cohort study. *Clinical and Translational Gastroenterology* 2019; doi 10.14309/ctg.0000000000000005. From the University of North Carolina, Chapel Hill; and other institutions. **Funded by RocheProd Ltd; and other sources. All study authors disclosed potentially relevant financial relationships.**

*See Reference Guide.

Antisocial Behavior After Childhood Maltreatment

Results of a cross-sectional study suggest that nearly half of all antisocial behaviors in adults may be associated with harsh physical punishment or maltreatment during childhood. Prevention efforts could potentially reduce the prevalence of adult antisocial behaviors.

Methods: Study data were collected from National Survey on Alcohol and Related Conditions Wave 3 participants, aged ≥ 18 years, who underwent in-person interviews between April 2012 and June 2013 (n=36,309; 48% men). Antisocial personality disorder behaviors after the age of 15 years were assessed using the Alcohol Use Disorder and Associated Disabilities Interview. The 6 antisocial behavior categories included: failure to conform to social norms with respect to lawful behaviors; deceitfulness, as indicated by repeated lying etc. for personal profit or pleasure; impulsivity or failure to plan ahead; irritability and aggressiveness, as indicated by repeated fights or assaults; reckless disregard for safety of self or others; and consistent irresponsibility, as indicated by repeated failure to sustain consistent work or honor financial obligations. In addition, participants were surveyed using a 5-point Likert scale (ranging from never to very often) about their experiences before age 18 years with harsh physical punishment; physical abuse; sexual abuse; emotional abuse; emotional neglect; physical neglect; and exposure to intimate partner violence. Specifically, harsh physical punishment included pushing, grabbing, shoving, slapping, and hitting. All other outcomes were grouped as child maltreatment.

Results: In this nationally representative sample, 18% of respondents endorsed having been exposed to harsh physical punishment and 47% endorsed childhood maltreatment. Adult antisocial behaviors were significantly associated with harsh physical punishment only (β coefficient,* 0.62), child maltreatment only (β coefficient, 0.65), and combined harsh physical punishment and child maltreatment (β coefficient, 1.46). After adjustment for age, race, marital status, and educational attainment, the population-attributable fractions* for harsh physical punishment and child maltreatment and antisocial behaviors were 45.5% in men and 47.3% in women. The association with antisocial behavior was larger among adults who had experienced both harsh physical punishment and child maltreatment, indicating that the more violence a child experiences, the greater the association with antisocial behaviors in adulthood.

Discussion: These results establish a temporal order, with antisocial behavior following harsh punishment and/or maltreatment during childhood. However, because of the cross-sectional design of the study, the causality of the association cannot be assumed.

Afifi T, Fortier J, Sareen J, Taillieu T: Associations of harsh physical punishment and child maltreatment in childhood with antisocial behaviors in adulthood. *JAMA Open* 2019;2(1):e187374; doi 10.1001/jamanetworkopen.2018.7374. From the University of Manitoba, Canada. **Funded by the Canadian Institutes for Health Research. The authors declared no competing interests.**

*See Reference Guide.

Medical Devices to Prevent Opioid Misuse

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks group in combination with the FDA convened an expert panel to address the potential for medical devices to stem the increasing prevalence of opioid use disorder. The panel identified 3 specific target areas for development of devices to prevent the disorder. Although each of the target areas is associated with substantial barriers to both development and widespread use, they are important components of the FDA efforts to address the opioid crisis. As a result, the agency launched the "Innovations in Medical Devices to Prevent Opioid Use Disorder" challenge to spur development of new devices that could overcome some of these barriers.

1. Opioid sparing/replacing devices that specifically address pain treatment. Medical devices that target pain could reduce or eliminate the use of opioids for some patients. These may include neuromodulation techniques such as deep brain stimulation, transcranial magnetic stimulation, transcutaneous vagal nerve stimulation, and novel types of spinal cord stimulation.

2. Devices that would be useful in identifying and treating patients who are at risk for developing opioid use disorder. Urine screening, medication monitoring systems, genetic testing, and smartphone-based apps could be useful in helping clinicians determine the most appropriate treatment strategy for individual patients and in identifying patients at risk for opioid misuse.

3. Devices that would reduce the risk that prescribed opioids would be diverted or misused, such as those that limit the supply of opioid medications or that prevent diversion by limiting access to prescription bottles to the patient for whom the medication is prescribed (i.e., fingerprint locks).

Comer S, Dworkin R, Strain E: Medical devices to prevent opioid use disorder: innovative approaches to addressing the opioid crisis. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4379. From Columbia University Medical Center, New York, NY; and other institutions.

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Beta Coefficient: Used in logistic regression analysis, the β coefficient represents the degree of change in the outcome variable for every 1 unit of change in the predictor variable.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

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.

Population-Attributable Fraction: The proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (e.g., no tobacco use).

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a comparison group.

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