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Neural Circuits Identified in Tourette Syndrome

Functional magnetic resonance imaging (fMRI) studies have identified the neural circuits involved in Tourette syndrome. The tics appear to be caused by a combination of excessive activity in motor pathways and reduced activity of control mechanisms in cortico-striato-thalamo-cortical circuits.

Methods: The investigators compared fMRI scans from 13 individuals with Tourette syndrome and 21 age-matched comparison subjects with no psychiatric disorders or other health problems. The average age of study participants was in the early 30s. Each study group underwent 2 types of MRI scan runs. Those with Tourette syndrome were scanned during the occurrence of spontaneous tics and during a period when they voluntarily produced tics at a rate that eliminated the urge to produce spontaneous tics. The comparison group underwent fMRI during the self-paced production of mimicked tics and during tick production that was paced with an auditory cue. Analysis of the images resulted in identification of 12 sets of independent components and 15 clusters of the components that were reproducible in all participants during all tasks. Activity of the independent components was compared for 4 pairs of conditions. Causal interactions among regions was also analyzed.

Results: Neural activity was stronger in patients with Tourette syndrome during spontaneous tics than in the comparison group during self-paced tics, and it was stronger in the Tourette-syndrome group during voluntary tics than in the controls during cue-paced tics. Increased activity was identified in the patients with Tourette syndrome throughout all portions of the motor pathway, including the sensorimotor cortex, putamen, pallidum, and substantia nigra. In most regions, the strength of activity was correlated with tic severity. In a few regions—parietal operculum, caudate nuclei, and anterior cingulate cortex—activity was weaker in persons with Tourette syndrome and was inversely correlated with tic severity. These circuits, the authors say, exert top-down control over motor pathways, and their relatively low activity suggests faulty top-down circuits may fail to control tic behaviors or the premonitory urges that trigger them. The group differences were not changed

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when adjusting the analysis for medication treatment or the presence of obsessive-compulsive disorder or ADHD in the Tourette-syndrome group.

Among patients with Tourette syndrome, stronger activity was observed in a few regions (i.e., the primary somatosensory cortex, posterior parietal cortex, putamen, and amygdala/hippocampus) during spontaneous tics than during voluntary tics. Activity in these regions may represent features of the premonitory urge that generates tics. Activity in the control group did not differ between the 2 experimental conditions.

Wang Z, Maia T, Marsh R, Colibazzi T, et al: The neural circuits that generate tics in Tourette's syndrome. *American Journal of Psychiatry* 2011; doi 10.1176/appi.ajp.2011.09111692. From Columbia University; and New York State Psychiatric Institute, New York, N.Y. **Funded by the NIMH; and other sources. The authors disclosed no conflicts of interest.**

Long-Term Effects of Caregiver Psychoeducation

Psychoeducation of caregivers was associated with better outcomes in patients with schizophrenia over 5 years, according to an observational study.

Methods: Study participants were 67 patients with schizophrenia or schizophreniform disorder and their caregivers or relatives. The 105 caregivers attended 6 weekly, 90-minute group lectures delivered by health professionals. Group discussions were encouraged, and the emphasis was on dispelling myths. After completion of the course, caregivers' knowledge about psychosis was assessed with a 23-item questionnaire. Clinical outcomes were assessed in the patients after 5 years. A control group consisted of 60 patients with psychosis, from the same geographic area, who experienced an illness episode prior to the time the psychoeducation course was offered. Patients in the psychoeducation group and controls were matched for age, gender, diagnosis, and severity of illness.

Results: The psychoeducation group had a mean of 1.3 relapses during the 5 years of observation, compared with 2.2 relapses in the controls ($p < 0.01$). Caregiver psychoeducation was also associated with a longer average time to first relapse (39 vs 27 months), a shorter length of stay (18 vs 45 days), and fewer bed days (48 vs 102 days; $p < 0.01$ for all comparisons). Among patients in the psychoeducation group, those whose relatives had learned the most about psychosis had better outcomes than those whose caregivers had learned less.

Discussion: Previous studies of brief psychoeducation programs in caregivers of patients with schizophrenia have had differing results. The present study is among those with the longest period of observation. An advantage of brief psychoeducation is its low cost in terms of both time and money. It has been argued that the effects of brief psychoeducation are not lasting, but this study shows long-term effects and evidence of cost-utility.

A weakness of the study is the possibility that self-selection of relatives may have influenced the results; however, patients and controls were well matched for baseline illness severity.

McWilliams S, Hill S, Mannion N, Fetherston A, et al: Schizophrenia: a five-year follow-up of patient outcome following psycho-education for caregivers. *European Psychiatry* 2011; doi 10.1016/j.eurpsy.2010.08.012. From DETECT Early Intervention in Psychosis Service; and other institutions, Dublin, Ireland. **Funded by the Hospitaller Order of St. John of God; and other sources. The authors disclosed no conflicts of interest.**

Alpha-Guided TMS in Schizophrenia

In a controlled study, individualized alpha EEG-guided transcranial magnetic stimulation (alpha-TMS) resulted in reduced overall symptoms of schizophrenia but did not produce the expected effects on negative symptoms.

Background: Preliminary research suggests high-frequency repetitive TMS (rTMS) may increase activation of the prefrontal cortex, reducing negative symptoms in patients with chronic schizo-

phrenia. A TMS protocol was developed that allowed investigators to individualize stimulation by linking the frequency to the patient's intrinsic peak alpha EEG frequency. Researchers hypothesized that alpha-TMS would entrain and normalize the patient's alpha EEG frequency by reducing frontoparietal disparities, resulting in improvement of negative symptoms.

Methods: Study participants were 78 patients with chronic schizophrenia (mean illness duration, 15 years) who had been stabilized with an antipsychotic but had persistent symptoms. Patients were randomly assigned to 1 of 4 parallel treatment groups: alpha-TMS using bilateral frontal or parietal electrodes and sham treatment at each anatomic location. Treatment consisted of 10 daily sessions over a 2-week period. Peak alpha frequency was averaged over 3 central EEG leads. Clinical outcomes were measured with the Positive and Negative Syndrome Scale (PANSS).

Results: Treatment outcomes did not differ as a function of electrode placement. Patients who received active alpha-TMS showed greater alpha peak frequency coherence between midfrontal and parietal areas. Active treatment was associated with significant improvement in the PANSS total score ($p=0.02$) and in positive but not negative subscale scores. When response was classified as a $\geq 30\%$ reduction in PANSS total score, 17 of 41 patients responded to active treatment and 3 of 24 responded to sham treatment (42% vs 12%; $p=0.01$). A positive correlation was demonstrated between the increase in frontoparietal alpha coherence and both positive and negative symptom improvement.

Patients receiving first-generation antipsychotics showed greater clinical improvement than those taking second-generation antipsychotics. Alpha-TMS was also associated with improvement of depression and of extrapyramidal symptoms.

A total of 14 patients dropped out of the study for reasons unrelated to treatment. Other than mild tension headaches during the first week ($n=9$), no adverse effects were reported.

Discussion: These study results must be considered preliminary because the nature of the sham treatment may not have been adequately concealed. The study failed to confirm the results of an earlier study that indicated negative symptom improvement, perhaps because the prior study selectively enrolled patients with prominent negative symptoms. The finding of a differential effect for different antipsychotic drug classes suggests a possible ceiling effect for atypicals; previous research indicates atypicals may help normalize EEG power density in patients with schizophrenia.

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

Jin Y, Kemp A, Huang Y, Thai T, et al: Alpha EEG guided TMS in schizophrenia. *Brain Stimulation* 2011; doi 10.1016/j.brs.2011.09.005. From NeoSync, Inc., Newport Beach, Calif.; Peking University, Beijing, China; and the University of California Irvine, Orange, Calif. **Funded by the Stanley Medical Research Institute. The primary study author holds patents regarding the use of EEG-guided TMS and disclosed a financial relationship with NeoSync, a company exploring the commercial viability of EEG-guide TMS. The remaining study authors disclosed no competing interests.**

*See Reference Guide.

Long-Term Results of Anorexia Psychotherapies

In a group of women with anorexia nervosa, long-term effects of 3 distinct psychotherapies were indistinguishable, although the temporal patterns of response differed significantly.¹ Incorporating a stepped approach and elements from multiple types of therapy may improve anorexia outcomes.

Methods: Study participants were women, aged 17–40 years, with broadly defined anorexia nervosa (i.e., body mass index of 14.5–19.0, with or without amenorrhea). The women were

randomly assigned to 1 of 3 psychotherapies: cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), or a control therapy called specialist supported clinical management (SSCM) designed to resemble usual clinical practice. SSCM consisted of clinical management with supportive psychotherapy, with a strong focus on abnormal nutritional status, normalization of eating patterns, and restoration of weight. CBT focused on restructuring abnormal eating behaviors, and IPT focused on the relationship between eating behaviors and interpersonal events. Results of acute treatment were previously published; contrary to expectations, short-term results of SSCM were superior to the other treatments.²

Of 56 women initially randomized, 35 completed treatment and 40 were assessed at post-treatment. For the present study, subjects were recontacted ≥ 5 years later, interviewed in person, and weighed if possible; otherwise they were interviewed by telephone. The primary outcome measure was a 4-point global anorexia nervosa measure, with scores of 1 or 2 (no or few features of anorexia nervosa) representing good outcome. Additional outcome measures were various clinical features of anorexia, weight and other body measurements, and general psychopathology and function.

Results: A total of 43 women participated in the long-term assessment, which took place an average of 6.7 years following treatment. Long-term results of the 3 psychotherapies were indistinguishable with regard to the primary outcome and all secondary outcomes, and regardless of whether the analysis included all women followed, all women randomized (intent-to-treat), or only those who completed treatment. Long-term global anorexia outcome was good in 7 of 17 women after CBT (41%), 9 of 14 after IPT (64%), and 5 of 12 after SSCM (42%).

Differences emerged when the investigators examined the temporal pattern of response. Of women who received SSCM, three-fourths had a good initial outcome but only 42% met criteria for good outcome at follow-up. Results of CBT were relatively stable over time (33–41% with good outcome), and response rates for IPT increased from an early 15% to 64%.

Discussion: About half of women in this study had a good outcome with these 3 forms of psychotherapy. Although the sample was too small to detect effect sizes reliably, the results suggest the effects of psychotherapy are in the small-to-moderate range. Many of the women continued to have significant anorexia symptoms during follow-up, but few received additional treatment.

¹Carter F, Jordan J, McIntosh V, Luty S, et al: The long-term efficacy of three psychotherapies for anorexia nervosa: a randomized, controlled trial. *International Journal of Eating Disorders* 2011;44 (November):647–654. From the University of Otago, Christchurch, New Zealand; and other institutions. **Funded by the Health Research Council of New Zealand. Two study authors disclosed financial relationships with commercial sources.**

²McIntosh V, Jordan J, Carter F, et al: Three psychotherapies for anorexia nervosa: a randomized controlled trial. *American Journal of Psychiatry* 2005;162:741–747.

Melatonin and Nocturnal Blood Pressure

Controlled-release melatonin, but not the fast-release formulation, can produce reductions in nocturnal blood pressure, according to a meta-analysis.

Background: Several studies have evaluated the effects of exogenous melatonin—often used to treat insomnia—on nocturnal blood pressure, but results have been mixed. The inconsistent results may have been related to differing melatonin formulations. A meta-analysis was undertaken to assess the overall effects of melatonin on nocturnal blood pressure and to evaluate potential differential effects of fast-release and controlled-release formulations.

Methods: Researchers identified randomized placebo-controlled trials (n=7) in which the effects of melatonin were measured with 24-hour ambulatory blood pressure monitoring: 6 studies

evaluated a total of 200 adults, and 1 study included 21 adolescents. In 3 adult studies, participants were randomly assigned to parallel-group treatment with melatonin or placebo; the remaining studies were crossover in design. A total of 99 study participants were hypertensive. Four studies with a total of 149 subjects used fast-release melatonin at a dosage of 5 mg/day, and 3 studies used controlled-release melatonin at dosages of 2–3 mg/day in a total of 72 subjects.

Results: Overall, melatonin had no significant effect on nocturnal blood pressure. However, in the studies that used controlled-release melatonin, mean nocturnal systolic blood pressure decreased by 6.1 mm Hg and diastolic pressure by 3.5 mm Hg ($p=0.009$ for both results). Most of the reduction in blood pressure was observed during the late night and early morning, when blood pressure is normally on the rise. Production of endogenous melatonin normally starts soon after dark and peaks in the middle of the night. The fast metabolism of melatonin may explain the lack of effect for rapid-release formulations. Adverse events were reported in 3 studies and included headache, drowsiness, weakness, and nightmares.

Editor's Note: Because melatonin is so widely used to treat insomnia, its potential to affect blood pressure could have important cardiovascular implications for patients with and without hypertension. Benzodiazepines and similar hypnotics do not reduce blood pressure; in fact the most widely prescribed hypnotic—zolpidem (*Ambien*)—may increase nocturnal blood pressure. The reductions in nocturnal blood pressure found in this study appear to be directly related to the mechanism of action of controlled-release melatonin rather than the hypnotic effects of treatment.

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

Grossman E, Laudon M, Zisapel N: Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vascular Health and Risk Management* 2011;7:577–584. From the Chaim Sheba Medical Center, Tel Hashomer, Israel; and other institutions. **Two authors are employees of Neurim Pharmaceuticals, Tel Aviv, which manufactures a controlled-release melatonin.**

*See Reference Guide.

Seasonality, Premenstrual Symptoms, and Bipolar Disorder

Women with bipolar disorder commonly report seasonal mood fluctuations and premenstrual symptoms. A review was conducted with the purpose of updating the available information on this subject. Because most existing studies are based on designs likely to have overestimated the frequency of cyclic mood symptoms, the possible association requires investigation with prospective study designs.

Seasonal affective disorder (SAD) can affect up to 20–25% of patients with bipolar disorder and appears to be more common in type II than in type I. A few cross-sectional studies have advanced the descriptive epidemiology of bipolar disorder and SAD. In a mixed population of 105 patients with bipolar disorder, seasonal variations in mood symptoms were reported by 64% of those with type II and by 41% of those with type I disorder. Another cross-sectional study showed that patients with bipolar disorder had a greater degree of seasonal mood symptoms than healthy controls, and 15% of patients with the disorder had a comorbid diagnosis of SAD. In a third study, patients with bipolar disorder had a nearly 4-fold increase in self-reported SAD compared with primary-care patients, as well as greater self-reported seasonal fluctuations in mood, socializing, sleep, and weight.

Some authors have suggested light therapy for patients with bipolar disorder who consistently experience depression during the fall and winter. This treatment is likely to be safe, but results of efficacy studies are preliminary. Light therapy should be used cautiously, with monitoring for mania or hypomania.

The association of bipolar disorder with premenstrual symptoms is less consistent. About two-thirds of women with bipolar disorder report premenstrual exacerbation of their bipolar symptoms. Data from a longitudinal study suggest premenstrual exacerbation is associated with a worse course of bipolar disorder. In another cross-sectional study, a diagnosis of premenstrual dysphoric disorder (PMDD) was associated with type II bipolar disorder and with a history of postpartum depression, but not with rapid cycling or seasonal depression.

The hormone melatonin may be the biological link among the different types of cyclic mood fluctuation. Synthesis of melatonin from serotonin is responsive to external light cues. External light suppresses melatonin to a greater degree in patients with bipolar disorder, regardless of their mood state, than in controls. Increased sensitivity to light-induced melatonin suppression is also a feature of SAD and of PMDD.

Kim D, Czarkowski K, Epperson C: The relationship between bipolar disorder, seasonality, and premenstrual symptoms. *Current Psychiatry Reports* 2011; doi 10.1007/s11920-011-1233-z. From the University of Pennsylvania, Philadelphia. **Two study authors disclosed financial relationships with commercial sources.**

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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 have been posted at www.alertpubs.com.

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