

2019 Articles of Import and Impact

The Editors are pleased to offer personal selections of the articles they found particularly interesting and important from the past year.

Linking Neural Circuits to Symptoms to Inform New Interventions

Ned H. Kalin, M.D., Editor-in-Chief

The article by Brady et al. (1), “Cerebellar-Prefrontal Network Connectivity and Negative Symptoms in Schizophrenia,” is an outstanding example of how understanding the relation between neural circuit dysfunction and symptoms can inform new treatment development. Using a data-driven approach to probe functional MRI data, the investigators demonstrated that decreased levels of cerebellar-dorsolateral prefrontal cortical network connectivity were predictive of negative symptoms among patients with schizophrenia. To test the extent to which this relation was causal, the authors used repetitive transcranial magnetic stimulation (rTMS) targeted at the midline cerebellar region, which increased functional connectivity between the cerebellum and the dorsolateral prefrontal cortex and was accompanied by a reduction in negative symptoms. The results from this study highlight the significance of the cerebellum in schizophrenia and in understanding the expression of negative symptoms. More importantly, the findings emphasize that the integrative function between the dorsolateral prefrontal cortex and the cerebellum is critical. The strategy to use cerebellar-directed rTMS to increase cerebellar-dorsolateral prefrontal connectivity was a direct outgrowth of the authors’ discovery-based analytic approach. Although the rTMS intervention was performed in a very small sample, the results are promising because cerebellar-targeted rTMS appears to reduce negative symptoms in association with an increase in cerebellar-dorsolateral prefrontal cortical connectivity. The research highlighted in this article is an excellent example of how modern neuroimaging, data analytic, and neuromodulation strategies can be combined to further our understanding of illness mechanisms and demonstrate how this knowledge can be used to conceptualize and test novel neuroscientifically informed treatment approaches.

Advancing Understanding of the Choroid Plexus

Elisabeth Binder, M.D., Ph.D., Deputy Editor

In their article, “Association of Choroid Plexus Enlargement With Cognitive, Inflammatory, and Structural Phenotypes

Across the Psychosis Spectrum,” Lizano et al. (2) focused on the choroid plexus in psychosis. The choroid plexus produces cerebrospinal fluid (CSF); forms a filtrating, protective barrier between blood and the CSF; secretes biologically active molecules, including chemokines and growth factors; and is important for neurogenesis and immune surveillance of the brain. The choroid plexus is thus a key structure in controlling brain microenvironments and regulating the interaction of the brain and the periphery. Choroid plexus dysfunction could be highly relevant in psychiatric disorders. However, so far very few studies have investigated this organ in psychiatric patients. The study by Lizano et al. bridges an important knowledge gap and assesses differences in choroid plexus volume in patients with psychosis, their first-degree relatives, and healthy control subjects by using structural MRI in a large, very well-characterized sample of over 1,400 subjects. The authors observed increased choroid plexus volumes in patients and their first-degree relatives, independent of diagnosis. Choroid plexus volume was also shown to be heritable and to inversely correlate with cognition, total gray matter and amygdala volume, and structural connectivity measures. Finally, in a subsample, larger choroid plexus volume was positively correlated with serum interleukin-6 levels. This carefully executed study encourages further investigations in the burgeoning field of choroid plexus research in psychiatry and inspires a series of clinical and basic research follow-up experiments, ranging from analyses in longitudinal cohorts to mechanistic studies in animal and cell models.

Progress in Cocaine Use Disorder Treatment

Kathleen T. Brady, M.D., Ph.D., Deputy Editor

Progress in innovative treatments for substance use disorders is a particularly exciting advancement in psychiatry. However, for some substance use disorders, such as cocaine use disorder, little progress has been made despite the extraordinary public health toll that cocaine use has extracted. For this reason, one article, “A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial,” by Dakwar and colleagues (3), stands out. This well-designed study explored the impact of a single infusion of ketamine, a glutamate-modulating drug that has demonstrated efficacy

in the acute treatment of depression among individuals with cocaine use disorder. Participants also received 5 weeks of mindfulness-based relapse prevention. Individuals treated with ketamine, as compared with those in an active control group who received an infusion of midazolam, had significantly more abstinence in the final 2 weeks of treatment, significantly less relapse, and significantly less craving. However, like many early studies in a research area, findings from the Dakwar et al. study are not ready for implementation, but they are provocative and lead to more questions that need to be addressed. Because ketamine has abuse potential and may work through opioid-related mechanisms, caution must be exercised in its use in the treatment of any substance use disorder. The role that mindfulness-based relapse prevention played is also not clear. However, the fact that this study showed robustly positive results in decreasing cocaine use and craving across a number of different outcomes is reason for optimism in the treatment of a disorder for which hundreds of agents have been tested, yet no treatments have been approved by the U.S. Food and Drug Administration.

Treating Insomnia Among Patients With Major Depressive Disorder to Reduce Suicidal Ideation

David A. Lewis, M.D., Deputy Editor

The epidemic of suicide in the United States continues unabated, with mortality rates due to suicide continuing to rise. Although the causes of suicide are multifactorial, insomnia has been associated with suicidal ideation, suicide attempts, and death by suicide in both cross-sectional and longitudinal studies. On the basis of these findings, McCall and colleagues (4) sought to test the hypothesis that pharmacotherapy targeted at treating insomnia would reduce suicidal ideation. In a robust and rigorously conducted 8-week randomized controlled trial, described in their article “Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT): A Randomized Clinical Trial,” they compared zolpidem controlled-release (CR) hypnotic therapy and placebo in conjunction with open-label fluoxetine among individuals with major depressive disorder and suicidal ideation. They found that zolpidem-CR was effective in improving insomnia and that the magnitude of improvement in insomnia was positively related to improvement in suicidal ideation. The authors were quick to caution that their findings do not support the routine prescription of hypnotic agents for the treatment of suicidal ideation, but their findings do suggest that a judicious, time-limited prescription of small quantities of a hypnotic agent may reduce suicidal ideation in individuals with major depressive disorder and marked insomnia. More generally, their findings support the idea that insomnia serves as a risk factor for suicidal ideation and thus that reducing insomnia, perhaps through behavioral as well as pharmacological strategies, might help stem the rising tide of suicide in our country.

Long-Term Efficacy of a Psychostimulant in Treating Attention-Deficit Hyperactivity Disorder

Daniel S. Pine, M.D., Deputy Editor

Articles that answer a pressing question are particularly worthy of close readings, and in their article, “Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized Placebo-Controlled Discontinuation Study,” Matthijssen and colleagues (5) report data regarding just such a question. The article described a randomized controlled trial examining the long-term efficacy of a psychostimulant for treating attention-deficit hyperactivity disorder (ADHD). The authors compared the efficacy of continued methylphenidate treatment versus placebo substitution among patients who had been treated successfully for more than 2 years. Two features are exciting about this report. First, questions about long-term efficacy have lingered for years, at least partly because of the difficulty of properly evaluating this measure. Against this backdrop, the new study possessed very strong methods and provided clear results. At least in some children and for some aspects of ADHD, methylphenidate produced lasting improvement. It is reassuring to discuss such findings with parents. Second, the article identified sources of heterogeneity in this response. Continued treatment with the medication appeared to have the greatest effect among younger children and on behaviors expressed in school settings. Again, these findings provide clinicians with valuable information to communicate to families.

Toward Novel Addiction Therapeutics

Carolyn Rodriguez, M.D., Ph.D., Deputy Editor

The devastating consequences of the opioid crisis underscore the urgent need for novel therapeutics to break the cycle of addiction. The article “Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial” by Hurd et al. (6) highlights a promising pathway for treating opioid use disorders, identified through a bench-to-bedside approach to drug development. In addition, the study’s rigorous research design was informed by clinically meaningful therapeutic targets, including environmental cue-induced drug craving. Alleviating craving is an important goal because craving, a core component of opioid use disorders, contributes to relapse. Dr. Hurd and colleagues established the foundation for their study through several lines of research. Their earlier animal-model work on cannabidiol (CBD), a nonintoxicating cannabinoid, showed that CBD reduced cue-induced drug-seeking behavior for weeks after administration. They then translated these preclinical findings to humans, reporting that CBD was safe, was tolerable, and did not elicit adverse effects when opioid agonists were coadministered. Building on these findings in this year’s article, Hurd et al. used a double-blind, randomized, placebo-controlled design to explore

the effects of acute and short-term CBD administration on craving and anxiety among individuals addicted to heroin. They found that acute CBD administration significantly reduced cue-induced craving and anxiety and showed effects 7 days after short-term CBD administration. There were no serious adverse effects. This exciting study provides a strong, neuroscience-informed rationale for further clinical research and may yield a novel treatment for patients suffering from opioid use disorders.

Effects of Maternal Depression on Brain Development in Children

Madhukar Trivedi, M.D., Deputy Editor

Extensive research has been conducted linking maternal depressive symptoms to negative cognitive, emotional, and behavioral outcomes in children. Over the past 10 years, neuroimaging studies have demonstrated adverse outcomes in brain development in children of mothers with depression. Yet, to date we still do not know what underlying biological mechanisms link maternal depression and brain development in children, nor do we know if there are specific key developmental periods leading to adverse outcomes in brain development. The article by Zou and colleagues (7), “Exposure to Maternal Depressive Symptoms in Fetal Life or Childhood and Offspring Brain Development: A Population-Based Imaging Study,” reports on whether maternal depressive symptoms during various developmental periods (perinatal and ages 2 months, 3 years, and 10 years) were associated with child brain development outcomes at preadolescence (age 10 years). The study also examined whether depressive symptom trajectories in mothers were associated with brain development. The study found that maternal depressive symptoms during the child’s infancy (age 2 months) were associated with smaller total gray matter volume and lower global fractional anisotropy at 10 years of age, after adjusting for potential confounding variables. Of interest, maternal depressive symptoms during pregnancy or later childhood (ages 3 years and 10 years) were not associated with brain development outcomes at 10 years of age. Children of mothers with consistently high levels of depression symptoms across all time points had smaller gray- and white-matter volumes than did children whose mothers reported no depressive symptoms. Unlike prior studies, the study by Zou and colleagues did not find any associations between maternal depressive symptoms and volumes of the thalamus, amygdala, or hippocampus. This study is pivotal, as it is the largest study to date (3,469 mother-child dyads) to examine the impact of maternal depressive symptoms on brain development in children. Further elucidation of the exact mechanism of long-term effects on brain development is essential in order to develop prevention efforts.

From *The AJP Residents’ Journal*: Becoming a Psychiatrist

Shapir Rosenberg, M.D., Editor-in-Chief

The American Journal of Psychiatry Residents’ Journal continues its mission to connect, inform, and inspire psychiatric trainees.

The journal underwent a major transformation in Fall 2019 as it converted to volume years that correspond with academic years (and thus the tenure of each Editorial Board member) and a quarterly publication schedule to allow for larger issues with longer, more reflective pieces. The recent expansion of podcasting and social media efforts contributes to the journal’s already broad geographic reach to psychiatric residency and fellowship programs across the United States and Canada. The talented all-trainee editorial board continues its tradition of supporting authors from initial idea proposal through to manuscript publication in a manner that fosters the personal and professional development of all involved. High-quality general articles as well as guest-edited theme sections—this year devoted to neuropsychiatry, visual arts, and military psychiatry—lend variety to the journal’s subject areas. Of these, I wish to highlight Dr. Brent Schnipke’s September commentary (8) entitled “Becoming a Psychiatrist” as an exemplary model of powerful, sincere, and humanistic writing. His piece connects with readers at all stages of medical and psychiatric training as they strive to better understand patients and themselves, amidst illness and uncertainty, and to offer hope for the suffering.

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