2020 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.

Reproducible Genetic Risk Loci for Anxiety

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

Anxiety disorders are among the most common psychiatric disorders, are highly comorbid with other disorders, and frequently begin in childhood. In addition, anxiety symptoms accompany most other psychiatric disorders, and their presence frequently is associated with poorer treatment outcomes. While DSM-5 categorically defines anxiety disorders, anxiety can be viewed as a dimensional trait ranging from adaptive to pathological. The data presented by Levey et al. (1) are from the largest GWAS study to date examining genetic alterations related to anxiety in a cohort of approximately 200,000 individuals from the Million Veteran Program. Importantly, the analysis separately examined African American and European American cohorts. In the smaller African American cohort (N=24,448), one genome-wide significant locus was found near the *TRPV6* gene (Transient Receptor Potential Cation Channel Subfamily V Member 6). This gene encodes a calcium selective membrane cation channel, and the SNP found to be associated with anxiety is rare in the European-American population and much more common in African-American individuals. Exciting leads found in the larger European-American cohort (N=175,163) included a site near the *SATB1* gene (Special AT-Rich Sequence Binding 1), a locus in the *ESR1* gene (Estrogen Receptor 1) as well as an association between the *CRHR1* gene (Corticotropin Releasing Hormone Receptor 1) and anxiety. Potential involvement of the *SATB1* gene is interesting as this gene affects the regulation of numerous genes associated with neuronal development as well as the corticotropin-releasing hormone (CRH) gene, which is critical for integrating the hormonal, behavioral, and emotional components of the stress response. CRH functions by activating CRH receptors and mediates its effects in part via activation of the CRHR1 receptor. The ESR1 finding is intriguing as estrogen influences neuronal development, brain function, and mood regulation. Taken together, these data begin to elaborate genetic variation that is related to the heritable component of anxiety. This study highlights the importance of including individuals from diverse populations in GWAS studies as the variant identified to be potentially important in the African-American population would not have been found if the sample was entirely constituted of individuals of European descent. We look forward to the availability of additional data from the Million Veterans Program, as larger GWAS studies will reveal additional genetic leads related to the risk of developing pathological anxiety.

Ambient Air Pollution and Daily Hospital Admissions for Depression

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

Gu et al. (2) examine the association between ambient air pollution and daily hospital admissions for depression. In addition to genetic factors, depression is strongly driven by environmental risk factors. An in-depth understanding and characterization of such environmental risk factors and their interplay—ranging from individual specific adversities to large-scale environmental factors such as societal factors but also effects of climate change and air pollution—could be key for elucidating important pathophysiological mechanisms and in identifying clinically relevant prevention strategies. The authors combined data from daily measurements of standard air pollutants with daily hospital admission data for depression collected over 5 years from the beginning of 2013 to the end of 2017 in 75 cities from both northern and southern China. From these extensive records, the authors conclude that short-term exposure to increased levels of most of the measured pollutants was associated with increased hospital admissions for depression. Effects for nitrogen dioxide (NO_2) were most robust and consistent across different geographical regions and demographic characteristics, with increases of 10$\mu g/m^3$ NO_2 associated with over 1.7% more hospital admissions/day. Air pollution has previously been linked not only to increased respiratory disease but also a systemic inflammatory response and increased oxidative stress, both also reported in patients with depression. Findings from this study support the idea that even short-term exposures to increased air pollutants may trigger a worsening of depressive episodes. This effect may be particularly relevant in patients with pre-existing vulnerabilities (genetic or environmental) in convergent pathways, such as inflammation and oxidative stress. Gu et al. highlight the importance of detailed investigations of environmental risk

factors, both on the micro- and the macro-level, as well as their interactions and the need to map their effects on convergent or divergent functional pathways for a better understanding of the pathophysiological mechanisms contributing to depression.

Vulnerability of U.S. Adults With Pain to Nonmedical Cannabis Use and Cannabis Use Disorder

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

Two of the most challenging areas in addictions in the United States today are the opioid crisis and the medicalization/legalization of cannabinoids across the country. Hasin and colleagues (3) look at both, examining differences in the prevalence of nonmedical cannabis use and cannabis use disorder in U.S. adults with and without pain. Using data from the National Household Survey on Drug Abuse, they found a disproportionate increase in cannabis use in individuals with pain between 2000 and 2013, suggesting an increase in cannabis use to treat pain. During this same period, state regulations on cannabinoid use changed dramatically: medical marijuana is legal in 34 states, in spite of the fact that the FDA has not approved marijuana or cannabis for any disease or condition. Chronic pain impacts more than 20% of the U.S. population, and treatment options are limited. The ongoing opioid overdose epidemic was largely initiated because many Americans seeking treatment for chronic pain were too frequently prescribed opioids. While cannabinoids have shown promise in the treatment of chronic pain, the evidence is flawed and inconclusive, and there are risks involved with the chronic use of cannabinoids that need to be explored. So this article emphasized the fact that Americans seeking new treatments for pain are likely turning to options for which the efficacy, risks, and benefits are unknown. We clearly need a greater investment in research focused on the treatment of chronic pain and better data on potential medicinal uses for cannabinoids, including risk/benefit assessment.

Enduring Effects of an Early Parenting Intervention on Brain Responses to Maternal Cues Among High-Risk Children

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

Six decades ago, David Hubel and Torsten Wiesel discovered the presence of a critical period for visual experience in the normal development of the visual cortex. Since that discovery, a variety of sensitive periods, maturational stages during which the brain is especially sensitive to certain environmental exposures or experiences, have been the focus of studies seeking to understand the developmental origins of a range of psychiatric conditions, with the hope that knowledge of such processes would guide innovative strategies for preemptive therapeutic interventions. The study by Valadez and colleagues (4) provides an important next step in that pursuit. These investigators studied high-risk infants whose parents received an early parenting intervention (Attachment and Biobehavioral Catch-Up [ABC]) or a control intervention. Ten years later, children in the ABC group showed greater activation in brain regions associated with social cognition in response to maternal cues and fewer total behavior problems relative to the control intervention group. These findings provide compelling evidence of enduring effects of an early environmental intervention on later brain function and behavior and set the stage for future studies examining the neural mechanisms underlying such effects. The results also serve to motivate additional studies examining when, and for whom, such preemptive interventions will have the greatest positive impact.

Common Neural Circuit Disruptions in Emotional Processing Across Psychiatric Disorders

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

Recent brain imaging research suggests that the neural correlates of mental illnesses fail to respect boundaries highlighted in current nosology. Quantitative meta-analysis provides an important avenue for appreciating this disconnect between neural and clinical profiles. This form of investigation also provides important clues for refining nosology. McTeague and colleagues (5) provide such a meta-analysis in more than 10,000 individuals, approximately half affected by a mental illness. They relate psychopathology to neural responses evoked by emotional stimuli, a particularly common theme in imaging research on mental illness. One important aspect of their findings illuminates yet another instance where brain function fails to align with nosology. This suggests that emotionally evocative imaging paradigms, much like executive function and still other approaches, yield correlates of mental illness that span current clinical boundaries. The second important aspect is to illustrate the circuitry-level nature of these correlates. Correlates of mental illness revealed by emotionally evocative paradigms do not manifest randomly across the brain. Rather, these correlates cluster in regions that basic science implicates in aspects of emotion among a wide array of mammals. This suggests that imaging paradigms systematically detect core circuitry-level disruptions in conserved functions, thereby generating hope for such paradigms to inform future nosology. Progress in nosology may follow if brain function on imaging paradigms consistently can be related to clinical outcome, response to treatment, genetics, or environmental risk factors. Readers might anticipate future meta-analyses focused on such relations.

Translational Neuroscience: Mitochondrial Pathways Shed Light on Therapeutic Targets

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

Identification of the mechanisms underlying mental illness is foundational to the development of new methods to prevent,

diagnose, and treat illness that can be tested in clinical trials. The elegant study by Glausier et al. (6) captured my interest for three reasons. First, it highlights a promising pathway for treating schizophrenia and bipolar disorder identified through a rigorous translational neuroscience approach (e.g., mitochondrial-related gene expression in postmortem human cortex). Second, the study's targeted analysis highlighted that the severity and nature of the mitochondrial alterations found in both schizophrenia and bipolar disorder, including their cell-type specificity, differ across these diagnoses. Third, these analyses were repeated in primate model to assess the effect of antipsychotic administration on mitochondrial-related gene expression. Mitochondria perform many different functions integral to neuronal functioning, including adenosine triphosphate (ATP) synthesis, Ca2+ buffering, regulating apoptosis, and generating reactive oxygen species. Although alterations in mitochondrial functional pathways have been described in both schizophrenia and bipolar disorder, Dr. Glausier and colleagues analyzed multiple datasets and cohorts of subjects of a gene set reflective of a range of mitochondrial functions in the dorsolateral prefrontal cortex and discovered a robust effect on energy production pathways selectively in schizophrenia subjects. Specifically, they found lower measures of mitochondrial ATP production in schizophrenia. They additionally report that chronic administration of first- or second-generation antipsychotic drugs had no significant effect on alterations in mitochondrial gene expression, suggesting that antipsychotics' role in altering dorsolateral prefrontal cortex functioning is unlikely to be mediated via changes in mitochondria. This study provides a neuroscience-informed rationale for therapeutics targeting enhancement of synaptic excitation as a novel approach to improve cognitive dysfunction.

Ketamine Shows Promise for Reducing Alcohol Use

Madhukar H. Trivedi, M.D., Deputy Editor

Alcohol and substance use disorders continue to be on the rise, and in the midst of the COVID-19 pandemic, we anticipate ever-increasing morbidity and mortality due to high rates of alcohol and substance use. Yet, despite the public health concerns of alcohol and substance use disorders, treatment options remain limited, and there is a paucity of novel pharmacologic treatments that have demonstrated robust enough results to warrant FDA approval. Dakwar and colleagues (7) found that a single infusion of ketamine during the second week of a 5-week motivational enhancement therapy intervention significantly increased abstinence, reduced the number of heavy drinking days, and delayed the time to relapse compared with the midazolam control condition. Although this study employed a relatively small sample size (N=40), the results are very exciting. Ketamine has been shown to be effective in treating depressive disorders, and it makes theoretical sense that the modulatory effects may lead to improvements in the stress reactivity and dysphoria vulnerabilities that are common in alcohol use disorder. Furthermore, ketamine's properties may help to address clinical presentations common during alcohol withdrawal, which contribute to negative reinforcement, ultimately leading to relapse. Even more exciting is the potential utility of ketamine on other substance use disorders, such as stimulant use disorder. Clearly more research is needed to further elucidate the mechanisms associated with these clinical phenomena.

From the AJP Residents' Journal: Involuntary Hospitalization During COVID-19

Matthew L. Edwards, M.D., Editor-in-Chief

Now in its 16th volume, *The American Journal of Psychiatry Residents' Journal* (AJP-RJ) continues its tradition of supporting the scholarship of medical students, residents, and fellows across the United States and Canada. Indeed, the AJP-RJ has benefited from tremendous growth over the past year, with greater reach and influence across residency programs, a record number of applications to its expanded board, and more robust social media and podcast initiatives. The AJP-RJ's unique role for trainees has become all the more significant as our community continues to respond to perhaps the most significant public health threat of our lifetimes. The COVID-19 pandemic has caused an unprecedented disruption in both psychiatric training and the administration of psychiatric services. As Editor-in-Chief, I have tasked the editorial board to keep pace with the rapidly evolving literature on COVID-19 and its impact on mental health services. In a particularly noteworthy article published in our December issue, Drs. Nathaniel Morris and Robert Kleinman analyze how the ethical calculus involved in hospitalizing patients against their will has shifted during the pandemic (8). They discuss strategies—from admission to discharge—to minimize the risk of transmission of infectious disease. Clinicians and policymakers alike must continue to weigh the ethics of the civil commitment statutes and involuntary hospitalization as the COVID-19 pandemic continues to affect our communities.

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