

2023 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.

Achieving Long Term Physical and Mental Health Improvements in Socially Deprived Children

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

There is no question that early adversity, especially trauma and deprivation, can have profound effects on children's development. However, there is little controlled data that addresses whether early interventions can mitigate the negative consequences of early social neglect. The Bucharest Early Intervention Project that began in 2001 is a unique study that directly addresses this issue. The data reported by King and co-authors (1) in the August issue of the *Journal* convincingly demonstrates the long-term positive impacts of good foster care on orphaned Romanian children. Importantly, the study employed a rigorous experimental design that involved randomly selecting young children from orphanages to be placed into quality foster care while comparing their outcomes to a group of randomly selected orphaned children that received standard institutional care. The children were followed longitudinally for up to 18 years of age and the findings demonstrated that living with foster families facilitated increases in IQ and physical growth compared to the children that did not have the intervention. As significantly, the children placed in foster families also had fewer symptoms associated with attachment-related disorders and internalizing disorders. This study is remarkable. It is likely the first scientific demonstration of an intervention that promotes healthy physical and brain development in neglected children and the data from this study were used to support public policy changes related to the care of orphaned children. This is a great demonstration of how effective science can promote societal change; identifying a very relevant need, making discoveries with the potential to promote health, and using the new data to help change policies—in this case related to children's well-being.

The Power of Single Cell Resolution Analyzes

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

My favorite *Journal* article is by Chatzinakos et al. (2), the first to report on single nucleus RNA sequencing (snRNA-seq) in postmortem brain tissue in PTSD.

In the same month, 21 articles were published by the National Institute of Health's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative—Cell

Census Network (BICCN), highlighting the strength of single-cell resolution to understand brain complexity and how these analyzes can help unravel pathomechanisms in psychiatry (3).

This paper gives a taste of the power of single cell resolution analyzes. While previous large-scale RNA sequencing studies in postmortem brain have indicated the relevance of inhibitory neurons in the biology of PTSD (4), this manuscript can now pinpoint that excitatory and inhibitory neurons show most changes in gene expression, as well as differentiate which transcripts and pathways are regulated in which cell type. Bulk sequencing studies had to rely on more global analyzes that revealed enrichment of cell-type-specific transcripts among the regulated ones. Using glucocorticoid-induced gene expression changes in neurons, the authors could not only show correlation of disease-associated transcripts with those changes, but also pinpoint cell-type specific differences in directionality for transcripts associated with PTSD versus major depression. Finally, these snRNAseq data were also informative in refining findings from large-scale data integration, including genome-wide association studies for PTSD and related traits, such as neuroimaging phenotypes. For example, genetic associations with a locus on chromosome 17, corroborated by different levels of analyzes and including the gene encoding corticotropin releasing hormone receptor 1 (CRHR1) could now be related to up-regulation of CRHR1 and a linked non-coding RNA in PTSD, specifically in excitatory neurons.

While certainly not definitive, this article is an example of the type of resolution of analyses and novel insights we can look forward to with more single cell studies forthcoming.

The Relationship Between Self-Reported Race and Ethnicity and the Diagnosis of Alcohol Use Disorder

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

Vickers-Smith and colleagues (5) used data from the Million Veteran Program to investigate the relationship between self-reported race and ethnicity and the diagnosis of alcohol use disorder (AUD). Importantly, the authors had access to self-reports of alcohol use as well as information about alcohol-related disorders and other potentially confounding factors. They found a large discrepancy in the prevalence of an AUD diagnosis in spite of similar distribution of alcohol consumption levels, suggesting racial and ethnic bias in diagnosis. Black and Hispanic veterans were more likely to

receive a diagnosis of AUD as compared to White veterans. There have been other studies demonstrating racial and ethnic differences in the diagnosis of substance use disorders, conduct, and externalizing disorders (6, 7), but none have data from alternate sources to support or refute the diagnosis. It is the availability of information about the level of alcohol consumption and alcohol-related disorders that makes this study so powerful. While over-diagnosis of a stigmatized disorder like AUD might be considered a disadvantage, if it leads to more aggressive treatment of the disorder in question for some racial and ethnic groups, it might improve health outcomes in a preferential manner. However, a number of studies have demonstrated that Blacks and Hispanics are less likely to receive FDA-approved medications to treat AUD (8) and opioid use disorder (9, 10) as compared to Whites. The reasons behind this disconnect between diagnosis and treatment which leads to a compounding of disadvantage for racial subgroups within the health system are not clear, but it is an area that clearly warrants further investigation in the quest for health equity.

Inequalities in the Incidence of Psychotic Disorders Among Different Racial and Ethnic Groups

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

Differences among racial and ethnic groups in the incidence of psychiatric disorders have been shown to be particularly pronounced for psychosis, but most large-scale studies have been conducted among people living in Europe. Understanding the presence and magnitude of such differences in the U.S. population is essential for determining the extent to which these differences reflect bias in clinical assessment and assignment of diagnoses, variability in access to health care, disparities in social and economic factors, and/or other effects of systemic and interpersonal racism. Toward this goal, Chung and colleagues (11) analyzed the incidence over a 10-year period of non-affective psychotic disorders among six racial/ethnic groups in nearly 6 million members of Kaiser Permanente Northern California. They found that the risk of a non-affective psychosis diagnosis was higher among Black and American Indian/Alaskan Native members and lower among Asian and Hispanic members relative to White members. They also found that a psychotic disorder diagnosis was associated with a greater burden of other health problems, such as risk of suicide, stroke, and premature death, as well as a lower likelihood of utilizing health care. These findings highlight the need for research focused on understanding and changing the clinical and social factors that contribute to these disparities in diagnosis and health outcomes; the *Journal* encourages and welcomes the submission of reports of such studies.

Targeting TMS

William M. McDonald, M.D., Deputy Editor

The target for most repetitive transcranial magnetic stimulation (rTMS) protocols is the dorsolateral prefrontal

cortex (DLPFC). The traditional method of locating DLPFC is to identify the area on the motor strip that stimulates the abductor pollicis on the thumb and target 5 centimeters anterior on the scalp (the “5-centimeter rule”). About a third of the time the 5-centimeter rule misses the DLPFC. Other methods such as the BeamF3 which locates the DLPFC via EEG coordinates on the scalp are more accurate, although not without discrepancies when compared to MRI-guided positioning. Thus, investigational protocols and the recent FDA approved SAINT Neuromodulation System have moved to targeting the DLPFC using functional MRI (fMRI) guided neuronavigation, a process which is both expensive and difficult to employ for TMS practitioners not located in a university setting.

Elbau et al. (12) take a practical look at targeting treatment using an individual’s subgenual anterior cingulate cortex (sgACC) negative functional connectivity to the DLPFC in order to downregulate a hyperactive SgACC. They added electric field modeling to analyze the association between the SgACC and stimulation site. These investigators found that treatment response was “weakly but robustly” negatively correlated with the identified treatment site ($r = -0.16$) explaining only 3% of the variance in outcomes. They also found a significant artifact related to the patient’s breathing pattern. This paper highlights the importance and potential of personalized targeting, but also the need for more research in this area which has implications for access and affordability of targeted TMS.

Investigating Distinctions Between MDD Remission in Pharmacotherapy Versus Psychotherapy Treatment

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

Recent failures to replicate key brain imaging findings highlight the need for new approaches. One promising avenue that embeds imaging into a randomized controlled trial infrequently appears in the literature. This reflects the inherent difficulties in pursuing such research. Executing an imaging or treatment study each poses unique problems for researchers, and these problems can magnify when scientists combine these approaches. Dunlop and colleagues (13) overcome these difficulties and report an important new study concerning the treatment of major depressive disorder (MDD). The authors examine 35 health volunteers and 131 affected patients who were randomly assigned to receive either antidepressant medication or cognitive behavioral therapy. All subjects underwent resting-state functional magnetic resonance imaging (rsfMRI).

The findings are important both because they illustrate the feasibility of following this difficult approach and because they illustrate the complexity of brain-behavior relations in MDD. Findings reveal more pervasive differences than similarities in the relations that brain function shows with response to the two treatments. Thus, medications and therapy may produce overall similar levels of response through distinct neural pathways. Moreover, among brain areas related to treatment response, few areas also differentiate patients with MDD from healthy volunteers. This

highlights the marked degree of heterogeneity in MDD as the condition relates to both treatment response and brain function as well as their overlap.

Visualizing OCD Psychotherapy Treatment Response

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

Obsessive-compulsive disorder (OCD) is a chronic illness that is often debilitating when left untreated. Individuals with OCD are plagued by recurrent, intrusive, and unwanted thoughts, images, or urges (obsessions) that trigger distressing feelings as well as repetitive behaviors (compulsions) that serve to neutralize or decrease the distress generated by obsessions. The most effective and evidence-based OCD psychotherapy is cognitive behavioral therapy with exposure and response prevention (ERP). In ERP, individuals practice facing obsession-inducing situations, while resisting urges to perform compulsions. The pioneering study by Russman Block et al. (14) drew my attention for three reasons. First, it sought to answer the question of why some OCD patients respond better to ERP than others. Second, it studied both adolescents and adults, gathering data on whether treatment response might vary by age. Third, the team used a network connectivity approach, studying resting-state functional connectivity of cognitive control and subcortical networks.

OCD study participants (N=116; 54 adolescents and 62 adults) were randomized to ERP (active condition) or stress-management therapy (SMT; control condition). As expected, those randomized to the ERP group had significant reductions in OCD symptoms compared to SMT in both adolescent and adult groups. Greater baseline functional connectivity of cognitive control and subcortical network regions was associated with symptom reduction in both ERP and SMT groups. However, treatment-specific associations were also observed, with lower connectivity between the ventromedial prefrontal cortex and subcortical regions linked to positive treatment responses in the ERP group only. Of note, associations involving ventral striatal connectivity differed by age group. Taken together, the findings indicate that it may be possible to improve the effectiveness of ERP via novel cognitive training or neuromodulation interventions targeting baseline connectivity between cognitive control and subcortical regions. However, such approaches should be tailored to consider the maturation of underlying brain networks and how their associations with symptom reduction may change with age.

From the *AJP Residents' Journal*: Visualizing Psychiatry

Syeda Razia "Ray" Haider, M.D., Editor-in-Chief

The first issue of the 19th volume of the *American Journal of Psychiatry Residents' Journal* (AJP-RJ) features seven manuscripts authored by talented medical students, residents, and fellows from across the United States and

Canada. This issue includes topics of immediate relevance to psychiatry trainees such as a literature review on psychedelics. Our all-trainee editorial board members have tirelessly worked over the past year to compile this issue, despite ongoing challenges from the COVID-19 pandemic. As we move into a "post-pandemic" world and adapt to meeting in person, I encourage readers to reflect on the ways different media platforms have shaped our perception over the past couple of years. Hence, I would like to highlight "Visual Media: An Aperture Into the Past and Future of Psychiatry" by Dr. Can Misel Kilciksiz and colleagues (15). In this timely manuscript, the authors describe visual media's close connection with the field of psychiatry. They discuss our field's portrayal in popular visual media (movies, TV shows) and explore the role of social media in public perception of psychiatry. They report on concerning trends related to the popularity of mental health discussions on social media such as the creation of echo chambers and social contagion phenomena. The manuscript also provides strategies for improving visual media literacy in psychiatry training. In summary, this aptly titled "history of psychiatry" manuscript provides a succinct overview of visual media in psychiatry and encourages psychiatry trainees to examine the world at large.

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