In This Issue

Volume 3, Number 1, January 2023

A brief summary of the articles in this issue of *Biological Psychiatry: Global Open Science*.

Review of NODDI in Psychiatric Disorders

Microstructural abnormalities are a key pathophysiological finding across multiple psychiatric disorders, and advanced neuroimaging techniques are being used to further expand our mechanistic understanding of disease processes. Here, **Kraguljac *et al.*** (pages 10–21) performed a systematic review of studies using NODDI (neurite orientation dispersion and density imaging) to map cellular tissue architecture and assess brain microstructure abnormalities in patients with psychiatric disorders. The authors also discuss principles and technical considerations for the use of NODDI in future psychiatric research.

Building Animal Models of the Prodrome

Schizophrenia has a prodrome, a period during which symptoms do not yet meet a clinical diagnosis. Considerable effort has been directed at this prodromal period to diminish severity or prevent onset, but current attempts have largely been unsuccessful. Much has been learned about the neurochemistry and brain structure/connectivity associated with schizophrenia using animal models, but our limited understanding of the neurobiology of schizophrenia onset hampers progress. In this review, **Petty *et al.*** (pages 22–32) discuss what is required to build an appropriate animal model of the schizophrenia prodrome to develop better interventions.

Salience and Reward Processing in Psychosis

Salience and reward processing is impaired in psychosis. Here, **Kesby *et al.*** (pages 33–46) summarize the current knowledge of behavioral and functional neuroimaging in salience, prediction error, and reward. These specific processes contribute to multiple feedback and feedforward systems integral to decision making and cognition in general. The authors argue that the origin of salience and reward processing dysfunction may be centered in the subcortex during the earliest stages of psychosis, with cortical abnormalities being initially more spared but becoming more prominent in established psychotic illness. The neural circuits underpinning salience and reward processing may provide targets for delaying, or preventing, progressive behavioral and neurobiological decline.

Reward processing in the striatum is altered in individuals with schizophrenia and in their unaffected relatives. In this reward task functional magnetic resonance imaging study of twin pairs, **Nielsen *et al.*** (pages 47–55) report that predisposed but unaffected twins showed no differences from control twins in striatal activity during anticipation, contrary to previous findings in patients, suggesting that this may not be a stable vulnerability indicator of psychosis. However, unaffected twins did show differences in brain activity during evaluation of unexpected negative outcome, which may reflect a compensatory resilience mechanism.

Psychiatric Disorders and COVID-19 Deaths

Evidence has suggested a link between psychiatric disorders and increased mortality from COVID-19, but it is unclear whether this association is explained by comorbid medical risk factors. Here, **Hoertel *et al.*** (pages 56–67) conducted a multicenter retrospective observational study of patients hospitalized for laboratory-confirmed COVID-19. The authors found a 6-fold higher risk of mortality in individuals diagnosed with a psychiatric disorder than in those without a psychiatric diagnosis, but this increased risk was explained by higher rates of medical risk factors, including greater number of medical conditions and higher prevalence of obesity, in this population.

Psychopharmacology: Effects and Mechanisms

The cognitive-enhancing drug donepezil, used for patients with Alzheimer's disease, increases acetylcholine broadly across the brain, but brain regions involved in distinct cognitive functions are differentially sensitive to acetylcholine. In this study of nonhuman primates, **Hassani *et al.*** (pages 68–77) show that donepezil enhanced cognitive flexibility at a low dose and selective attention at a high dose. Bioavailability of donepezil was confirmed at low and high doses in the frontostriatal network. These results suggest that finding the most optimal therapeutic dose may require the use of multiple cognitive outcomes measures.

Psychosis is linked to alterations in dopamine activity, which evidence suggests may be mediated by the hippocampus. α5-$GABA_A$ receptors are highly expressed in the hippocampus. Studying selective α5-$GABA_A$ receptor allosteric modulators in a rat model of schizophrenia, **Perez *et al.*** (pages 78–86) demonstrate that negative allosteric modulators augment dopamine neuron activity, whereas positive allosteric modulators reverse aberrant dopamine signaling. These data suggest that selective pharmacological manipulation of hippocampal activity may differentially modulate dopamine neuron activity.

A key challenge in the understanding and treatment of depression is identifying cell types and molecular mechanisms that may mediate behavioral responses to antidepressant drugs. Using a mouse model and multiple classes of antidepressant drugs, **Funayama *et al.*** (pages 87–98) found that *Cartpt* was consistently upregulated in responders and that increased CART peptide signaling in inhibitory neurons in the anterior cingulate cortex promoted stress resilience. These results suggest fundamental differences in the molecular signatures between responders and nonresponders and implicate specific molecules in the development of antidepressant drugs.

ISSN: 2667-1743

Effects of Early-Life Adversity

Exposure to early-life adversity is associated with long-lasting effects, including increased risk for stress-related disorders into adulthood, but the underlying mechanisms are not completely understood. Here, **Short *et al.*** (pages 99–109) studied early-life adversity–induced gene expression changes in hypothalamic corticotropin-releasing factor–expressing neurons in mice. The authors identified distinct subpopulations of these stress-regulating cell types, which showed selective changes in genes linked to stress and inflammation that were associated with increased vulnerability to stress.

Depression, Trauma, and Inflammation

Inflammation is associated with depression, trauma, and body mass index (BMI), but the interrelationships between these factors are not clear. Analyzing data from a large cohort, **Palmos *et al.*** (pages 110–118) found no association between C-reactive protein and major depressive disorder, but did find associations between trauma, BMI, and major depressive disorder, and also between trauma, BMI, and C-reactive protein. These data highlight the importance of controlling for both BMI and trauma in studies of depression and inflammation.

Self-referential Processing in Depression

Self-referential processing biases to negative information are linked to depression, but whether this risk factor persists into remission is unclear. Using electroencephalography, **Allison *et al.*** (pages 119–129) report that compared with healthy individuals, individuals with remitted depression showed slower drift rate to negative stimuli, which was associated with greater symptom severity and also greater interpersonal stress over time. These data suggest that brain-behavior markers related to depressogenic self-referential processing are present in remitted individuals and could increase risk for the re-emergence of depressive symptoms.

Mindfulness and Alzheimer's Disease

Mindfulness is a practice that can reduce stress and improve health. Here, **Strikwerda-Brown *et al.*** (pages 130–138) examined longitudinal data in older adults at familial risk for Alzheimer's disease and found that higher levels of mindfulness in daily life were associated with less amyloid, less tau, and less cognitive decline over time. These data suggest that trait mindfulness may have potential protective effects against Alzheimer's disease and should be further investigated.

Childhood Sleep and Brain Size

Childhood sleep disturbances are common and often comorbid with psychiatric disorders. However, little is known about potential shared genetic influences underlying childhood sleep and psychiatric symptoms. Using data from a large study in children, **Hernandez *et al.*** (pages 139–148) report that childhood insomnia is heritable, demonstrates shared genetic etiology with externalizing traits, and has a distinct genetic architecture from childhood brain size. These findings highlight potential shared genetic mechanisms that may be underlying sleep quality and externalizing traits in children.

Cerebellar Connectivity in Autism

Cerebellar functional connectivity (FC), important for error-based learning, is disrupted in autism spectrum disorder (ASD). **Hawks *et al.*** (pages 149–161) examined infant cerebellar FC as an early-emerging risk factor for ASD, but contrary to hypotheses, no associations were found between infant cerebellar FC and later ASD-associated behaviors and outcomes. However, results did reveal clusters of brain-behavior relationships between infant networks implicated in error signaling and ASD. These findings indicate that cerebellar alterations in ASD may not manifest until after the development of symptoms.