In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Review: Effects of Stress and Depression on Brain Morphology

Major depressive disorder (MDD) is associated with volume reductions in the hippocampus and medial prefrontal cortex. In this review, **Belleau *et al.*** (pages 443–453) examine clinical and preclinical research that highlights the critical role of stress in the development of these neural abnormalities in MDD and a chronic, often treatment-refractory, course of the disorder. The authors propose a model by which stress triggers a set of neurotoxic processes, which include hypothalamic-pituitary-adrenal axis dysregulation, inflammation, oxidative stress, and neurotransmitter disturbances, which in turn lead to brain structural decline and illness progression.

Leveraging Neuroplasticity to Improve Clinical Outcomes in Depression

Neuroplasticity is impaired in depression. Interventions that target neuroplasticity often reduce symptoms, but these effects do not persist past active treatment. This review by **Wilkinson *et al.*** (pages 454–465) examines the potential of combining plasticity-enhancing biological therapies, such as electroconvulsive therapy (ECT), intravenous ketamine, or transcranial magnetic stimulation, with therapies that focus on cognitive and behavioral retraining to improve long-term outcomes for depression. The authors conclude that these treatment modalities could be combined in a synergistic way, but that additional research studies are needed and should be designed specifically to measure the clinical outcomes from these combinations.

ECT induces neuroplasticity in the hippocampus of patients with severe depression, yet how this relates to antidepressant response is unclear. Using arterial spin-labeled functional magnetic resonance imaging, **Leaver *et al.*** (pages 466–476) demonstrate that hippocampal function increased after two treatments of ECT. However, these increases were greater in patients who did not respond to ECT, suggesting that excessive plasticity may not be conducive to antidepressant response. Instead, these results suggest that balanced neuroplasticity in regions relevant to seizure physiology, including thalamocortical networks, may be necessary to achieve a positive ECT outcome.

Abnormal Excitation and Inhibition in MDD

The dorsolateral prefrontal cortex (DLPFC) plays an important role in the pathophysiology of MDD. Here, **Voineskos *et al.*** (pages 477–486) used transcranial magnetic stimulation combined with electroencephalography in healthy participants and patients with MDD to assess DLPFC excitation and inhibition. The MDD group showed larger inhibitory-related (N45 and N100 amplitudes) and excitatory-related (global mean field amplitude and P60 amplitude) measures. Further, the healthy participants displayed a balance between inhibitory and excitatory measures that was not present in the MDD group. These data provide insight into the altered DLPFC physiology associated with MDD.

Hippocampal Substructure in Depression

Hippocampal volume alterations are common in depression. Using automated segmentation of hippocampal substructures, **Roddy *et al.*** (pages 487–497) found differences between patients with first-presentation depression, patients with recurrent depression, and control subjects. Novel assemblies of substructures showed that differences in depression depend on the hippocampal definition used, with the hippocampal core showing the most change. Substructure involvement extended from core regions with chronicity, suggestive of a depressive disease process. Further, CA1 emerged as a potential marker of depression.

Carotid Stiffness and Depressive Symptoms

Age-related arterial stiffness has been associated with late-life depressive symptoms, but prior studies have been cross-sectional. **van Sloten *et al.*** (pages 498–505) conducted a 6-year longitudinal study to evaluate the association between carotid artery stiffness and incident depressive symptoms in older adults from a large community-based cohort. They found that greater carotid artery stiffness is associated with a higher incidence of depressive symptoms, independently of potential confounders, which included lifestyle and cardiovascular risk factors. These data suggest that carotid stiffness may contribute to the development of late-life depression.

Learning and Value-Based Choice in Attempted Suicide

Suicidal behavior can be viewed as the outcome of an altered, suboptimal decision-making process that occurs during the experience of a crisis. Using behavioral experiments and reinforcement learning models in two samples, **Dombrovski *et al.*** (pages 506–516) found that depressed older adults who have attempted suicide display deficits in learning from experience and altered value-based choice processes, compared with suicide ideators, nonsuicidal patients with depression, and healthy control participants. Together, these abnormalities may contribute to the inability to identify alternative solutions and properly consider deterrents during a suicidal crisis.

Dendritic BDNF Transcripts in Depression

MDD is associated with reduced brain-derived neurotrophic factor (BDNF) and reduced somatostatin, an inhibitory neuronal marker, in the brain, but the mechanisms underlying their respective contributions to MDD pathophysiology is unclear. In this study, **Oh *et al.*** (pages 517–526) discovered that *BDNF* transcripts with the long 3′ untranslated region were reduced in prefrontal cortex brain tissue from patients with MDD and in stressed mice. They found correlations between these *BDNF* changes and genes expressed in inhibitory neurons. They then showed that suppression of these specific *Bdnf* transcripts in mice induced MDD-like cellular, molecular, and behavioral changes.

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