In this Issue

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

Review: The Future of Ketamine Research for Depression

Several studies evaluating ketamine's effects have consistently described its rapid antidepressant effects and confirmed its potential utility as a treatment for major depressive episodes. In an effort to identify which patients might be more likely to respond to ketamine treatment, how it should be administered, and how long the response may last, **aan het Rot *et al.*** (pages 537–547) reviewed all available published findings on the antidepressant effects of ketamine, resulting in data from 163 patients, primarily with treatment-resistant depression. They conclude that further research of ketamine for individuals with severe mood disorders is recommended, although not outside of the hospital setting.

Antidepressant Effects and Mechanisms

Cyclic adenosine monophosphate response element binding protein (CREB)-regulated transcription coactivator 1 (CRTC1) is required for the expression of brain-derived neurotrophic factor. Here, **Breuillaud *et al.*** (pages 528–536) show that mice lacking CRTC1 are socially impaired, more aggressive, and have depressive-like symptoms. Their blunted response to the antidepressant fluoxetine in tests assessing behavioral despair suggests that CRTC1 might be required for certain antidepressant effects.

Using ^{11}C-(*R*)-rolipram positron emission tomography, **Fujita *et al.*** (pages 548–554) report a significant reduction in phosphodiesterase type IV, an enzyme that serves as an important component of the cyclic adenosine monophosphate cascade, in unmedicated patients with major depressive disorder (MDD) compared to healthy controls. This finding is consistent with previous animal experiments and human postmortem studies and indicates that stimulation of the downregulated signal transduction system may show antidepressant effects.

Using magnetoencephalography in drug-free treatment-resistant patients with MDD, **Cornwell *et al.*** (pages 555–561) show that increased cortical excitability selectively occurs in patients showing a robust alleviation of depressive symptoms within 4 hours after a single infusion of ketamine. This finding is consistent with animal studies that suggest ketamine's antidepressant action involves cortical plasticity mechanisms.

Boldrini *et al.* (pages 562–571) examined the relationship between amount of vascularization and number of neural progenitor cells (NPCs) in the dentate gyrus using postmortem tissue from antidepressant-treated individuals with MDD, untreated individuals with MDD and non-psychiatric controls. They report that antidepressant treatment is associated with more NPCs and capillaries, suggesting that NPC proliferation and angiogenesis may be co-regulated and enhanced by antidepressants in the adult human brain.

Cognitive Vaccine? Attention Bias Modification to Prevent Depression

Negative biases in the processing of affective information are believed to increase the risk of recurrence in depression. **Browning *et al.*** (pages 572–579) examined residual depressive symptoms and cortisol waking response in previously depressed patients who received active or placebo computerized attention bias modification (ABM). Active face-based ABM, but not word-based or placebo ABM, reduced both measures of recurrence risk, with the protective effect developing over the month following its completion. These results provide evidence that modification of affective processing bias may form the basis of a secondary preventative strategy for depression.

Vocal Acoustic Measures as Depression Biomarkers

In a double-blind, randomized (sertraline or placebo), multisite clinical trial, **Mundt *et al.*** (pages 580–587) analyzed acoustic characteristics of speech produced by MDD patients as objective biomarkers of depression severity and response to treatment. They report that speech production patterns are related to depression severity and treatment response, with depressed patients showing generally lengthened recorded speech, which shortens with clinical improvement. The results replicate findings from a prior pilot study and support generalizability of the physiologically-based measurement method across different clinical outcome measures and study designs.

Neural Processing and Network Connectivity in Depression

McCabe *et al.* (pages 588–594) used functional magnetic resonance imaging (fMRI) to investigate reward and punishment processing in young people with familial risk of depression. Compared to healthy controls, they found that at-risk individuals had decreased neural activation to reward in the orbitofrontal cortex and increased processing of aversive stimuli in the lateral orbitofrontal cortex and insula. The at-risk group also showed blunted neural responses to both rewarding and aversive stimuli in anterior cingulate cortex. These findings suggest that young people at-risk for depression have altered neural representation of reward and punishment, particularly in cortical regions linked to the use of positive and negative feedback to guide adaptive behavior.

Therapeutic efficacy for treatment of depression using transcranial magnetic stimulation remains limited, partially due to the poorly understood underlying mechanisms and optimal stimulation targets. Using fMRI in healthy subjects, **Fox *et al.*** (pages 595–603) show that the efficacy of different stimulation targets in the left dorsolateral prefrontal cortex is related to their connectivity to the subgenual cingulate, a limbic region known to be critical in mediating antidepressant response. They then translated this information into a technique for identifying an optimized stimulation target, and reproduced the results in patients with depression.

Using fMRI, **Goulden *et al.*** (pages 604–611) evaluated network connectivity associated with emotional face processing in unmedicated patients remitted from MDD. They found that the patterns of connectivity associated with sad and happy faces were abnormal in patients compared to healthy controls, with a reversal of normal patterns of emotion-specific connectivity between the amygdala, fusiform gyrus and orbitofrontal cortex. These results suggest that connectivity abnormalities, in the absence of abnormalities of region-specific brain response, persist into remission from MDD.

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