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

Inflammation, "Sickness," and Depression

People with medical illnesses associated with inflammation are at increased risk of depression. Using functional magnetic resonance imaging (fMRI), **Harrison *et al.*** (pages 407–414) show that experimentally-induced peripheral inflammation is associated with acute deterioration in mood, the magnitude of which is predicted by activity change in the subgenual anterior cingulate cortex, a brain region recognized to coordinate emotional processing and strongly implicated in the etiology of depression. These observations suggest that brain circuits supporting motivational reorientation during sickness may be maladaptively 'hijacked' during clinical depression.

Infections induce psychological, emotional and behavioral changes known as "sickness behaviors." Circulating inflammatory cytokines are implicated in initiating sickness behavior in rodents, but data in humans are lacking. Using fMRI, **Harrison *et al.*** (pages 415–422) show that experimentally-induced peripheral inflammation in healthy volunteers modulates activity within brain regions representing internal bodily state. Activation of these regions correlates with experienced fatigue and confusion, suggesting specific targeting for development of therapies to alleviate sickness-related symptoms across medical specialties.

In their meta-analysis comparing depressed with non-depressed individuals, **Yirmiya and Bab** (pages 423–432) report that depression is associated with low bone mineral density (BMD). Pre-menopausal women formally diagnosed with major depressive disorder (MDD) are particularly at high-risk for depression-associated low BMD. These findings indicate that depression should be regarded as an official risk factor for osteoporosis, suggesting a need for close follow-up of depressed individuals for changes in BMD and other osteoporotic markers.

Neuropeptide Y (NPY) is involved in counteracting stress-related processes to maintain emotional homeostasis. **Frisch *et al.*** (pages 433–440) found that the number of NPY-positive neurons in the amygdala of temporal lobe epilepsy patients is positively correlated with parameters of anxiety and depression. The results point to a role of NPY in negative emotion and might reflect emotional adaptation processes in epilepsy patients.

Neural Mechanisms and Circuits Associated with Depression

Roiser *et al.* (pages 441–450) combined acute tryptophan depletion (ATD) with fMRI while remitted MDD patients and healthy controls performed an emotional processing task. They found ATD differentially affected the thalamus, caudate and anterior cingulate in the two groups, and increased blood flow in the habenula in the patients following ATD. These findings provide new insight into the mechanisms underpinning resilience to temporarily lowering serotonin synthesis in patients recovered from depression.

Distinguishing bipolar disorder (BD) from MDD is a major clinical challenge. **Almeida *et al.*** (pages 451–459) show that bipolar and MDD patients exhibit different types of abnormal functional relationships in emotion regulation brain circuitry when viewing happy and sad faces. This finding suggests different biological mechanisms for these two disorders, and is a promising step toward identifying biological markers to distinguish bipolar and major depression.

Wang *et al.* (pages 516–521) utilized complementary MRI methodologies, functional connectivity analysis and diffusion tensor imaging to investigate connectivity between the perigenual anterior cingulate cortex (pACC) and amygdala in BD. The findings provide novel evidence of abnormalities in pACC-amygdala coordinated responding to emotional stimuli and an association with abnormalities in the white matter structural connections between the two brain regions in BD.

Risk Genes for Suicide and Depression

Fiori *et al.* (pages 460–467) identified and functionally characterized a number of variants in the promoter region of the gene coding for spermidine/spermine N1-acetyltransferase, *SAT1,* in suicide completers, and found several polymorphisms to be associated with differential gene expression both in the brain and *in vitro*. These results provide insight into the mechanisms responsible for variation in *SAT1* expression, and provide functional evidence to support previous findings of decreased *SAT1* expression in the brains of suicide completers. The *SAT1* haplotype would be predicted to influence the level of the polyamines, spermidine and spermine. These polyamines modulate the activity of *N*-methyl-D-aspartate (NMDA) glutamate receptors. In light of evidence that NMDA glutamate receptor antagonists may have clinically relevant antidepressant effects, the findings with *SAT1* may help to bridge risk genes and novel therapeutics for depression.

Wray *et al.* (pages 468–476) report a large scale genotyping effort to study the serotonin transporter length repeat polymorphism (5HTTLPR). By genotyping 13 single nucleotide polymorphisms (SNPs) in a 38kb region around the 5HTTLPR, they identified a two SNP haplotype proxy for 5HTTLPR. These two SNPs are in linkage disequilibrium with the previously reported variable number tandem repeat polymorphism. Association analysis for major depression and/or anxiety disorder in unrelated cases and controls provided evidence for association with SNPs positioned about 15.5kb from 5HTTLPR.

Serotonergic neurotransmission is vital to the etiology and pathophysiology of psychiatric disorders. **Henningsson *et al.*** (pages 477–485) show that, in men but not in women, variation in the gene encoding brain-derived neurotrophic factor (BDNF) influences the availability of the serotonin transporter, one of the major regulators of serotonergic transmission. Carriers of variants associated with increased BDNF secretion displayed higher transporter availability.

Neurodevelopment and Neuroplasticity in Psychiatric Disease

Connor *et al.* (pages 486–493) found that neuronal numbers and densities are increased in the white matter beneath the cingulate cortex of subjects diagnosed with BD or schizophrenia. Furthermore, they show that white matter neuron densities decline steeply during the first postnatal year, but then remain stable thereafter, suggesting that processes regulating rates of neurogenesis that occur relatively early in life might have a significant impact on the subsequent risk for cognitive, emotional, and behavioral function later in life.

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Neurogenesis, the production of new neurons in adult brains, may be impaired in psychiatric diseases, such as major depression, BD, and schizophrenia. **Eom and Jope** (pages 494–502) report that increased activity of glycogen synthase kinase-3 (GSK-3), an enzyme already implicated in these diseases, impairs neurogenesis and the neurogenesis-promoting actions of therapeutic drugs. Thus, normalizing GSK-3 with inhibitors of this enzyme may bolster neurogenesis and contribute to the treatment of psychiatric disorders.

Serotonin-dependent modulation of neuroplasticity is proposed as an underlying mechanism for depression. In healthy subjects, **Nitsche *et al.*** (pages 503–508) found that citalopram, a serotonin reuptake blocker, facilitated neuroplasticity induced by transcranial direct current stimulation. These data support the hypothesis that novel treatments for depression might exert their beneficial effects by enhancing neuroplasticity.

Progress in Antidepressant Treatment

The prefrontal cortex is the most common target for transcranial magnetic stimulation (TMS) in the treatment of depression. But where should one stimulate the brain? For the past 15 years, the most common practice was to locate an area on the scalp that, when stimulated, activated a particular muscle in the contralateral hand. TMS would then be delivered 5 cm anterior to that point in the sagittal plane. The "5-cm rule" used to target delivery may be sub-optimal, as it does not account for differences in skull size, or variations in prefrontal anatomy relative to motor cortex location. **Herbsman *et al.*** (pages 509–515) now demonstrate the variability of coil placement following the 5-cm rule method and how more lateral and anterior placement can improve response rates.

Intravenous ketamine has shown rapid antidepressant effects in early trials. **Price *et al.*** (pages 522–526) explored ketamine's effects on suicidality in patients with treatment-resistant depression. Ketamine acutely reduced suicidal thoughts when patients were assessed 24-hours after a single infusion. A performance-based measure of implicit suicidal cognition also showed changes following ketamine. Rapid, initial reductions in suicidality were sustained by repeated-dose ketamine infusions given every other day for 2 weeks.