

Reward Dysfunction in Depression

Childhood adversity increases the risk for adult psychopathology, but the neurobiological mechanisms underlying this vulnerability remain poorly understood. Using functional magnetic resonance imaging (fMRI), **Dillon et al.** (pages 206–213) found that individuals exposed to childhood adversity were characterized by blunted subjective responses to reward-predicting cues as well as dysfunction in left basal ganglia regions implicated in reward-related learning and motivation.

Hasler et al. (pages 201–205) provide evidence that catecholamine deficits may contribute to anhedonia in depression. The authors found that a catecholamine-depleting drug, alpha-methyl-para-tyrosine (AMPT), impaired performance on a monetary reward task in remitted medication-free depressed patients, but not in healthy subjects. In patients, the extent of compromised reward task performance correlated with the emergence of mood symptoms following administration of AMPT.

Serotonin: Cortical Excitability and Receptor Functioning

Hadjighassem et al. (pages 214–222) describe the properties of a novel protein, Freud-2. Although Freud-2 gene expression did not appear to differ in post-mortem tissue from individuals with and without depression histories, the authors suggest that Freud-2 may downregulate serotonin-1A (5HT_{1A}) receptors on non-serotonergic neurons.

Using positron emission tomography (PET), **Sullivan et al.** (pages 223–230) found higher 5-HT_{1A} receptor binding in depressed bipolar disorder (BD) subjects as compared to controls, with the greatest difference in the brainstem raphe nuclei region. This effect was specific only to the males. The raphe findings may be partly explained by a genetic mechanism, as the number of copies of the G allele of a 5HT_{1A} receptor gene promoter polymorphism was positively associated with 5-HT_{1A} binding.

Using transcranial magnetic stimulation, **Langguth et al.** (pages 283–286) provide further evidence that allelic variation in the serotonin transporter gene (5-HTTLPR) modulates inhibitory measures of motor cortex excitability. This result may provide insight into recent data describing increased cortical excitability in individuals with depression.

Genetic Variations and the Structural Brain in Mood Disorders

The catechol-O-methyltransferase (COMT) gene moderates the predisposition to negative mood and affective disorders. **Mechelli et al.** (pages 231–237) used fMRI and voxel-based morphometry to show that an allele of COMT is associated with increased gray matter volume and heightened emotional reactivity in children. These findings are consistent with the notion that genetic factors affect brain structure and function to moderate vulnerability to affective psychopathology from early age.

Barnea-Goraly et al. (pages 238–244) investigated brain pathways using diffusion tensor imaging (DTI) in adolescents with BD and controls. Adolescents with BD had significant white matter tract alterations in brain regions involved in emotion,

behavior and cognition, suggesting that these abnormalities are present early in the course of disease in BD.

Prior studies identified white matter abnormalities in late life depression (LLD) that include an increased volume of discrete white matter hyperintensities. **Shimony et al.** (pages 245–252) have now examined the integrity of white matter outside of these hyperintensities using DTI. Compared with controls, there were widespread abnormalities in the LLD group, particularly in prefrontal regions. The strongest correlations were observed between cognitive processing speed and DTI abnormalities.

Mirakhor et al. (pages 293–297) report that cortical folding reduces over time in individuals with and without BD. In both groups, the age-related cortical folding patterns were related to brain-derived neurotrophic factor (*BDNF*) genotype.

Antidepressant Response and Treatment

Using tests of retinal function, **Lavoie et al.** (pages 253–258) found that people with seasonal affective disorder (SAD) have differences in retinal sensitivity to light, and that these differences normalize after light therapy and in the summer when they are well. Understanding how light sensitivity is altered in the eyes of individuals with SAD may help explain its causes and how light therapy works.

Smith et al. (pages 259–266) used PET to measure the effect of a single dose of citalopram on brain function. The response of the brain to the antidepressant was greater in the non-depressed compared to depressed older adults in cortical and limbic areas, particularly in the right hemisphere. These results suggest that depressed older adults have a decreased capacity of the brain to respond to serotonin.

The neuroprotective and neurotrophic effects of erythropoietin (EPO) have been used to treat a wide variety of brain insults and damage. **Girgenti et al.** (pages 267–274) have found that peripheral EPO administration produces a robust antidepressant-like effect in behavioral tests. In addition, EPO induces the expression of neurotrophic genes implicated in antidepressant action.

The development of a rapid-acting and sustainable treatment for BD has been a goal for decades. The most widely documented rapid-onset antidepressant therapy is sleep deprivation (SD), which acts within 24–48 hours in 40–60% of patients; however, relapse is common after recovery sleep. **Wu et al.** (pages 298–301) show significant decreases in depression in a chronotherapeutic augmentation (CAT) group versus a medication-only group within 48 hours following SD which was sustained over a 7 week period. In this study, CAT consisted of a combination of three interventions: SD, bright light exposure, and sleep phase advancement.

VGLUT and Depressive Vulnerability

Garcia-Garcia et al. (pages 275–282) provide new insight into the functional implications of decreased vesicular glutamate transporter 1 (VGLUT1) levels as a potential factor that may enhance a depressive-like phenotype in mice. VGLUT1 heterozygous mice exposed to chronic mild stress show specific alterations in neurotransmitter brain levels, in the expression of presynaptic proteins involved in the glutamate/GABA cycle and in behavioral paradigms that could be relevant for clinical depression.

Link Between Interleukin-6 and Suicidal Behavior

Several lines of evidence suggest an association between the immune system and depressive disorders. **Lindqvist et al** (pages 287–292) measured cytokines in cerebrospinal fluid (CSF) of suicide attempters and healthy controls, and found signifi-

cantly elevated levels of interleukin-6 (IL-6) in the suicide attempters. Furthermore, increased CSF IL-6 levels were associated with violent suicide attempts and severity of depressive symptoms, indicating that CSF IL-6 may contribute to the symptomatology of suicidal behavior.