In this Issue

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

Anxiety Disorders: Genes, Environment, and Their Interactions

In general, the more traumatic events a person experiences ('traumatic load'), the higher their likelihood of developing posttraumatic stress disorder (PTSD). In their study of Rwandan genocide survivors, **Kolassa *et al.*** (pages 304–308) show that genetic factors can influence this relationship. Homozygous methionine allele carriers of the catechol-*O*-methyltransferase (COMT) $Val^{158}Met$ polymorphism exhibited a high risk for PTSD independent of the severity of their traumatic load, indicating a gene-environment interaction in the risk of developing PTSD.

Dysfunction of neuronal pathways during early stages of brain maturation could predispose an organism to affective dysfunction later in life. **Vinkers *et al.*** (pages 309–316) show that by blocking the serotonin 1A receptor in young mice, long-lasting increases in benzodiazepine sensitivity and anxiety levels emerge. Thus, early-life serotonergic disruption has a long-lasting influence on anxiety and benzodiazepine responsivity in adulthood, which may have clinical implications for psychoactive drug prescription during pregnancy.

The serotonin transporter length repeat polymorphism (5-HTTLPR) has been associated with changes in basal perfusion levels in the limbic system and ventral prefrontal areas of the brain in healthy subjects. These regions are involved in the pathophysiology of depression and anxiety, suggesting the existence of a neurobiological trait predisposing to these disorders. Using advanced perfusion imaging techniques in a large European cohort, **Viviani *et al.*** (pages 317–322) reassessed these findings and report a lack of association, indicating that this biological marker may not apply broadly.

Schwandt *et al.* (pages 323–330) show that sex may be an important mediating factor in the gene-environment interaction of risk for psychopathology. They found that in the context of social threat, only male rhesus macaques carrying the s allele of 5-HTTLPR exhibit increased levels of high risk aggression if they were also exposed to early adversity in the form of peer rearing.

Dysregulation of the serotonin transporter has been implicated in the biological basis of mood and anxiety disorders. Using quantitative polymerase chain reaction, **Gyawali *et al.*** (pages 331–338) found that a common variant located in 5-HTTLPR alters the strength of the signal and is associated with panic disorder. This functional variant in the serotonin transporter gene seems to add to the link between variation in this gene and the risk for developing panic disorder.

The expression of anxiety-like behavior after a traumatic stressor depends on a number of environmental and genetic factors. **Christianson *et al.*** (pages 339–345) found that rats exposed to uncontrollable stress reduced their investigation of another juvenile rat, suggestive of social anxiety, whereas exposure to controllable stress had no effect. The reduction in social investigation was correlated with serotonin release in the basolateral amygdala and dependent upon the serotonin 2C receptor in that structure. These data further implicate the serotonin 2C receptor in stress-related changes in social function and in anxiety.

McTeague *et al.* (pages 346–356) recorded heart rate acceleration, sweat gland activity, facial muscle action, and startle reflex reactions in PTSD patients and healthy controls during unpleasant imagery. Patients who suffered a single severe trauma were markedly more reactive than controls, as expected. However, patients who had experienced multiple traumas, with more symptomatic and chronic PTSD, showed a paradoxical, blunted physiological reaction. This response may represent a shift from heightened emotional reactivity to blunted emotional reactivity and emotional numbing in severe or chronic PTSD.

Adverse experiences during early childhood are associated with a higher risk for depression in later life. Animal studies show that the hippocampus, a brain region involved in memory, is highly susceptible to stress. **Rao *et al.*** (pages 357–364) found smaller hippocampal size in healthy adolescents at high-risk for depression by virtue of parental history. Smaller hippocampal size partly accounted for the relationship between early-life stress and susceptibility to depression during longitudinal follow-up in the high-risk and depressed youth.

Treating Anxiety: Focus on Learning Processes and Attention Biases

Kim and Richardson (pages 297–303) review recent studies conducted in rodents that highlight differences between the phenomenology, neurobiology, and pharmacology of extinction learning early in life (before weaning) and later in life. They point out that early in life, extinction learning essentially eliminates the learned fear response (i.e., it cannot be reinstated), is based entirely in the amygdala, and is sensitive to opiate function. In contrast, later in life, fear learning cannot be completely eliminated. The extinction of fear learning involves both prefrontal cortex and amygdala, and it is dependent on *N*-methyl-D-aspartate glutamate receptor and γ-aminobutyric acid-A receptor function. These development-related changes may hold clues to the development and treatment of anxiety disorders.

Otto *et al.* (pages 365–370) provide evidence of the efficacy of d-cycloserine (DCS) for augmenting the benefit of exposure-based cognitive behavior therapy for panic disorder. In this randomized double-blind study, patients with panic disorder received DCS or placebo before undergoing brief cognitive behavior therapy. Those who received DCS had better outcomes and were more likely to achieve clinically significant change. These findings lend support for the role of DCS in enhancing therapeutic learning.

Persistent biases to selectively process negative, relative to positive or neutral, information may contribute to the development of anxiety vulnerability. In a prospective study with nonclinical participants, **Fox *et al.*** (pages 371–377) found that a preconscious bias to process threat was a stronger predictor of stress reactivity than self-reported neuroticism up to 8 months after the initial assessment. Biased attention may provide an early marker of anxiety vulnerability and be a potential marker of treatment response.

Coronary Heart Disease and Dimensions of Anxiety

In this report from the Health and Social Support (HeSSup) study, **Nabi *et al.*** (pages 378–385) used prospective data from a large sample of the Finnish population to examine the extent to which psychological and somatic symptoms of anxiety are predictive of coronary heart disease. They found that somatic symptoms of anxiety were robustly associated with an increased risk of coronary heart disease in women. This finding lends support to the physiological pathway for the association between psychological factors, anxiety in particular, and heart disease.

Immune Challenge in Animal Model of Schizophrenia

Feleder *et al.* (pages 386–392) studied the effect of an immune challenge localized to the ventral hippocampus of neonatal rats on prepulse inhibition and dopamine modulation of prefrontal cortical interneurons in adult rats. In particular, the authors report that injection of lipopolysaccharide, which stimulates an immune reaction similar to that associated with an infection, disrupted prepulse inhibition and minimized the adult profile in the D2 dopamine modulation of fast-spiking interneurons. This pattern of alterations is also seen with neonatal ventral hippocampal lesion, a paradigm that may model aspects of schizophrenia. These findings suggest possible convergent neural system changes in these two models.