In This Issue

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

Review: Pharmacoepidemiology Studies of ADHD Medication

Medication for attention-deficit/hyperactivity disorder (ADHD) is commonly prescribed for both children and adults, but questions and concerns remain regarding the risks and benefits. In this systematic review, **Chang *et al.*** (pages 335–343) examined studies from the last 10 years that investigated the effects of ADHD medication on behavioral and neuropsychiatric outcomes using linked prescription databases. The authors found evidence for short-term protective effects of ADHD medication on injuries, motor vehicle accidents, education, and substance use disorder, and no evidence of increased risks for suicidality and seizures. Evidence was insufficient for other outcomes, such as psychosis, mania, and depression, and evaluation of long-term effects, highlighting the importance of future studies to address gaps in knowledge.

Effects of Nicotine and Morphine on the Dopamine System

Nicotine intake alters neuroplasticity of dopamine-mediated reward circuitry. Here, **Romoli *et al.*** (pages 344–355) investigated the effects of neonatal nicotine exposure on the dopaminergic system and nicotine consumption in adulthood. The authors found that neonatal nicotine exposure enhances drug preference in adult mice through an increase in the number of ventral tegmental area dopamine neurons. These findings identify a mechanism of neuroplasticity by which early nicotine exposure primes the reward system, leading to an increased susceptibility to drug consumption in adulthood.

Animal studies have reported that opioid administration induces dopamine release, but this mechanism remains controversial in humans. Using positron emission tomography, **Spagnolo *et al.*** (pages 356–364) report that an intravenous infusion of morphine induces dopamine release in the ventral striatum of healthy, nondependent opioid–experienced male participants. This finding helps fill the gap between animal and human studies and provides evidence to further investigate the role of dopamine in opioid reward.

Genetics of Habitual Alcohol Intake

Many traits related to habitual alcohol use and alcohol dependence are known to be heritable, and recently, large biobank-based studies have allowed the identification of previously unknown genetic risk factors for these traits. **Gelernter *et al.*** (pages 365–376) conducted a genome-wide association study of maximum habitual alcohol use using a biobank of European American and African American veterans in the United States. Their analyses confirmed previously known risk loci (*ADH1B*) and identified novel loci, most notably *CRHR1*, the gene that codes for corticotropin-releasing hormone receptor 1 and is related to stress-response pathways.

Mechanisms of Cue-Induced Behaviors

Addiction is characterized by drug-associated cues that cause relapse. Drug cues elicit transient changes in reward-related brain areas that mediate the high motivation to seek drugs. Using a rat model of cocaine seeking and relapse, **Garcia-Keller *et al.*** (pages 377–387) identified a molecular signaling cascade that is required for cue-induced drug seeking, which involves signaling from proteins outside of the cell into nucleus accumbens neurons through integrin receptors. Inhibiting this signaling prevented relapse in the rat model, providing a potential new therapeutic target for the treatment of addiction.

Cue-induced motivation for reward-driven behaviors can become dysfunctional, a hallmark of substance use disorders and other psychiatric conditions. Using a behavioral task in rats, **Collins *et al.*** (pages 388–396) showed that cholinergic interneuron activity in the nucleus accumbens critically opposes the motivating influence of reward cues. These data thus suggest that nucleus accumbens cholinergic interneurons may regulate cue-motivated behavior and may serve as a potential therapeutic target for maladaptive motivation.

Losartan and Reinforcement Learning

Animal work suggests that losartan, an angiotensin II receptor antagonist used to treat hypertension, may have the potential to augment exposure therapy for anxiety disorders in humans, but the underlying mechanisms remain unclear. Previous work indicates that successful exposure depends on a shift in learning toward positive, relative to negative, events. In this randomized controlled trial of healthy volunteers, **Pulcu *et al.*** (pages 397–404) report that losartan induced a positive learning bias by reducing learning from negative outcomes, suggesting a neurocognitive mechanism by which losartan could enhance the effect of exposure in clinical populations.

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