Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

In this Issue-September 15th

Serotonin, Temperament, and Depression

Lenzenweger *et al.* (pages 553–564) used the National Comorbidity Study-Replication to show that approximately 9% of the United States general population has a diagnosable DSM-IV personality disorder (PD). Borderline personality disorder was found to have a prevalence of 1.4%, occurring equally often in men and women. DSM-IV Axis-I disorders were frequently found among those with a PD and it appeared that functional impairments associated with a PD were largely accounted for by Axis-I comorbidity.

Behavioral disinhibition (BD) is the temperamental tendency to respond to novelty with boldness, approach, and talkativeness. **Hirshfeld-Becker *et al.*** (pages 565–572) found that high levels of BD, assessed at 2-6 years of age, was associated with increased risk for mood disorders and disruptive behavior disorders, particularly oppositional defiant disorder, over the subsequent 5 years.

Maternal nurturance promotes the ability of infants to attenuate their reactivity to usual daily stresses. **Azar *et al.*** (pages 573–579) found that, among teenage mothers, lifetime history of major depression and a maternal pattern of intrusive and overstimulating behavior toward their infant ("maternal overcontrol") was associated with a persisting pattern of increased release of cortisol following mild stress exposure in the infants.

Borderline personality disorder (BPD) is associated with mood instability and increased risk for depression. **Soloff *et al.*** (pages 580–587) report increased densities of the serotonin-2A ($5HT_{2A}$) receptors in the hippocampus of females with BPD compared with healthy females, as assessed with [^{18}F] altanserin and positron emission tomography (PET).

Using PET imaging, **Takano *et al.*** (pages 588–592) linked the tendency to feel depressed to the density of the serotonin transporters (5-HTT) in the thalamus, a part of the limbic system. 5HTT's are the sites where many antidepressant drugs increase brain serotonin function. In their study, the authors linked 5HTT density with the depressive component of the neuroticism trait.

There appear to be important sex differences in the way that men and women react to reductions in serotonin function. **Walderhaug *et al.*** (pages 593–599) found that men became more impulsive, while women became more cautious and more dysphoric after consuming an amino acid drink that lowered serotonin levels. The mood lowering effect in women was also influenced by the serotonin transporter gene (*5-HTTLPR*).

Using perfusion imaging, **Rao *et al.*** (pages 600–606) provide evidence that variation in the gene that codes for the serotonin transporter (*5-HTTLPR*) might contribute to the risk for a mood disorder by influencing the resting activity of limbic and cortical structures. The authors found that the short allele of *5HTTLPR* was associated with increased resting cerebral blood flow (CBF) in the amygdala and decreased resting CBF in ventromedial prefrontal cortex, a pattern of activity associated with anxiety and depression.

Heritable Factors Influencing the Risk for Alcoholism and Response to Alcoholism Treatment

Using T1-weighted magnetic resonance imaging (MRI), **Gilman *et al.*** (pages 607–615) evaluated whether, among alcohol dependent patients, reduced brain volume was related to family history of alcoholism or alcoholism-related toxicity. The authors report that, among these patients, a family history of alcoholism was associated with smaller intracranial volume but not greater brain shrinkage. These data suggest that family history of alcoholism influenced brain volume primarily by affecting brain development rather than by influencing the toxicity associated with alcoholism.

Human cannabinoid receptor 1 protein, encoded by the *CNR1* gene, is hypothesized to play a role in the development of drug dependence (DD) and/or alcohol dependence (AD). **Zuo *et al.*** (pages 616–626) demonstrated that, in their study of 10 markers in a case-control sample, *CNR1* variation is in fact important for both DD and AD risk, even after controlling for possible confounding effects.

One mechanism through which naltrexone might reduce heavy drinking is by blocking the rewarding effects of ethanol. **Job *et al.*** (pages 627–634) show that interventions that reduce μ opiate receptor function reduce the ability of ethanol to stimulate the release of dopamine, a transmitter implicated in the rewarding effects of ethanol. The authors found that the effects of knocking out the gene for the μ opiate receptor were generally similar to the effects of a drug that blocks the μ opiate receptor, naltrexone.

Krishnan-Sarin *et al.* (pages 694–697) report human laboratory data suggesting that naltrexone may be particularly effective in reducing alcohol consumption in individuals with a family history of alcoholism. The authors reported that as one increased the dose of naltrexone, individuals with a family history of alcoholism consumed less alcohol in the laboratory, but individuals without a family history of alcoholism actually drank more ethanol.

Neural Mechanisms of Smoking Urges and the Treatment for Smoking

The CYP2B6 enzyme metabolizes the anti-smoking drug, bupropion (Zyban), and nicotine. **Lee *et al.*** (pages 635–641)

0006-3223/07/$32.00

found that individuals with the CYP2B6*6 allele of the gene that codes for this enzyme benefited from bupropion treatment and maintained abstinence for a longer period while doing poorly on placebo. In contrast, those in the CYP2B6*1 wild-type group did well on both bupropion and placebo. This report indicates that genetic variation in CYP2B6 can affect smoking cessation treatment outcome.

Using functional MRI (fMRI), **Brody *et al.*** (pages 642–651) studied cigarette smokers who were presented with cigarette-related cues under conditions where they were instructed to suppress the desire for a cigarette and where they did not depress craving. While resisting smoking urges, smokers had greater activation of brain regions associated with decision-making and attentional motivation, and greater deactivation of primary sensory and motor areas than when they allowed themselves to crave.

N-acetyl-cysteine Treatment for Pathological Gambling

Grant *et al.* (pages 652–657) report preliminary evidence that a commonly used amino acid treatment for acetaminophen (Tylenol) overdose, N-acetyl-cysteine (NAC), reduces the severity of pathological gambling. In this open-label study, 16 of 27 patients met criteria for a clinically significant response to NAC. NAC is presumed to increase glutamate levels in the extrasynaptic space. Thus, these preliminary data support the further exploration of the role of glutamate systems in the neurobiology and treatment of pathological gambling.

Toward a Neural Circuitry of Pedophilia

Using fMRI, **Walter *et al.*** (pages 698–701) report that pedophilic patients showed reduced activation of the hypothalamus, a brain region involved in regulating physiologic arousal and hormone release, compared to healthy individuals when they were viewing sexually arousing pictures of adults. Deficits of activation in the frontal cortex were associated with the extent of pedophilic behavior.

Neuro-Immune Insights into Opiate Addiction

Niwa *et al.* (pages 658–668) report that tumor necrosis factor-α (TNF-α) and Leu-Ile, a TNF-α inducer, reduced the rewarding effects of morphine and the development and expression of sensitization to the effects of morphine. The effects of Leu-Ile were not observed in TNF-α knockout mice. These findings raise the possibility that Leu-Ile might attenuate the severity of morphine addiction.

Mechanisms Underlying MDMA Effects in the Brain

Methylene deoxy-methamphetamine (MDMA; "ecstasy") has effects on several brain neurotransmitter systems. In their study, **Trigo *et al.*** (pages 669–679) show that MDMA self-administration is substantially reduced in animals without a functional version of the gene for the serotonin transporter, one of the targets for MDMA in the brain. These findings highlight the importance of the serotonin transporter for the effects of MDMA.

Federici *et al.* (pages 680–686) also highlight the diversity of MDMA effects in the brain. Their data suggest that MDMA has effects mediated by the blockade of the dopamine transporter, the serotonin-1B receptor, and the $GABA_B$ receptor. These diverse targets for MDMA in the brain may provide future targets for the treatment of MDMA abuse.

Advancing the Development of a Screening Paradigm for Drugs Modulating Attention

Attentional deficits accompany many psychiatric disorders, underscoring the need for rodent models of attention to screen novel therapeutic agents and characterize the biological basis of attention. **Paine *et al.*** (pages 687–693) found that Sprague-Dawley rats demonstrate that 4 psychotropic drugs (methylphenidate, MK-801, desipramine and U69593) with distinct pharmacological profiles have dissociable effects on performance in the 5-choice serial reaction time task, a rodent version of the continuous performance task used to quantify attention in humans.