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How does early puberty contribute to the risk for substance abuse disorders among boys? **Reynolds *et al.*** (pages 1223–1227) show that increased testosterone levels in 12-14 year old boys, by producing early sexual maturation, contributes to the affiliation with deviant peer groups and the endorsing of antisocial behaviors by age 16 and substance abuse disorders by age 22. These data speak to a complex interplay of genetic vulnerability, hormonal effects during adolescence, and social processes that shape the risk for addictive behaviors.

Kaufman *et al.* (pages 1228–1234) shed new light on how genetic and environmental factors interact to increase the risk for early alcohol use. Childhood maltreatment increased the risk for early alcohol use seven-fold and this effect was particularly prominent among those children with the short version in the promoter region of the serotonin transporter gene.

Methamphetamine is an emerging drug abuse epidemic in the U.S. The long-term impact of this epidemic is not yet understood. **Deng *et al.*** (pages 1235–1243) report that, in rodents, methamphetamine kills dopamine neurons in a brain region involved in emotion regulation, the olfactory bulb.

The initial reactions to drugs of abuse may shape the propensity of individuals to abuse these substances. Many people, for example, dislike their initial exposure to heroin. In this issue, **Zhang *et al.*** (pages 1244–1251) show that variation in the gene coding for the μ opioid receptor (*OPRM1*), the principal target for heroin in the brain, influences the initial response to heroin.

Yasuno *et al.* (pages 1252–1259) implicate the dopamine D1 receptor (D1R) in nicotine addiction and nicotine craving. The authors report that D1R density, measured with positron emission tomography (PET), was reduced in smokers compared to non-smokers in the ventral striatum, a brain region implicated in reward and motivation. They also showed that D1R density was negatively correlated with the activation of the ventral striatum and the level of craving, i.e., the lower the receptor density, the higher the craving for nicotine.

Rilling *et al.* (pages 1260–1271) use functional neuroimaging to describe brain circuitry underlying deficits in emotional and social functions among individuals with psychopathic traits. In a game that tests the propensity to cooperate, the Prisoner's Dilemma Game, psychopathic individuals tend to try to benefit by looking out for themselves rather than cooperating. The brain imaging showed that they experienced reduced activation in the orbital frontal cortex, a reward and motivation center, when they successfully cooperated and reduced activity in executive cortical regions when they "cheated" on their partner.

There is growing concern that methamphetamine (MA) may have neurotoxic properties. In this report, **Salo *et al.*** (pages 1272–1280) report that MA dependent individuals show reduced levels of a marker of neuronal viability, *N*-acetyl aspartate (NAA), in a brain region involved in attention and emotion, the anterior cingulate cortex. NAA/creatine levels, measured with magnetic resonance spectroscopy (MRS) also correlated with attention function. Although this study design does not rule out the possibility that risk factors underlying the propensity for MA abuse contribute to the findings, it adds to the growing concern about potential neurotoxic effects of MA.

In another MRS study of substance abuse, **Hermann *et al.*** (pages 1281–1289) describe reductions in NAA/creatine ratios in the dorsolateral prefrontal cortex among cannabis users relative to a group of comparison subjects. As with the prior study, this study was not designed to distinguish risk factors that contribute to the risk for cannabis abuse from the possible neurotoxic impact of cannabis ingestion.

When a clinical trial fails, is there an empirical strategy for evaluating whether the medication worked in a subgroup of patients? **Gueorguieva *et al.*** (pages 1290–1295) illustrate the power of trajectory-based analysis to evaluate a medication in two clinical trials that had reported negative findings. Using data from the VA Cooperative Study #425 and the Women's Naltrexone Study of naltrexone for alcohol dependence, the authors identified three distinct trajectories of "any drinking" and "heavy drinking" over time: "abstainers", "sporadic drinkers" and "consistent drinkers". Although the traditional analytic methods failed to show efficacy, naltrexone was found to have a significant effect that was limited to reducing the likelihood of belonging to the "consistent drinker" trajectory.

Dlugos *et al.* (pages 1296–1305) implicate variation in the norepinephrine transporter gene in the euphoric response to amphetamine. The norepinephrine transporter plays a role in the metabolism of the catecholamine neurotransmitters, norepinephrine and dopamine. Thus, genetic factors that influence catecholamine metabolism deserve further exploration with regard to addiction risk.

Glahn *et al.* (pages 1306–1309) demonstrated that healthy young adults who have a family history of alcoholism and who score low on a test of adherence to social rules have reduced amygdala activity when shown emotional faces, compared to a group of rule-abiding healthy comparison subjects. These data suggest that deficient limbic system activation to social cues may contribute to the heritable comorbidity of alcoholism and psychopathic traits.

Kalayasiri *et al.* (pages 1310–1313) implicate a genetic propensity for increased dopamine activity in the risk for cocaine-induced paranoia. Dopamine beta-hydroxylase (DBH) is an enzyme that converts dopamine to norepinephrine. The "T" version (C-1021T) of this has lower activity, i.e., is associated with higher dopamine levels. The authors report that, among 31 cocaine users self-administering cocaine in the laboratory setting, individuals who were homozygous, i.e., had two T versions of the DBH gene, were more likely to show signs of cocaine-induced paranoia.

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