to relapse—even in the face of an expressed desire to remain abstinent. There is, however, considerable individual variation in the ability of reward cues to gain motivational control over behavior. Emerging evidence from preclinical studies suggests that such variation is due, at least in part, to intrinsic differences in the extent to which reward cues are attributed with incentive salience, thereby acquiring the properties of incentive stimuli. When a Pavlovian conditional stimulus (CS) reliably predicts delivery of a food reward, for some rats (sign-trackers; STs), the CS itself becomes attractive, in that these rats approach and interact with the CS, and becomes 'wanted', in that these rats will work just to obtain the CS. For other rats (goal-trackers; GTs), the CS itself is not attractive, but instead evokes conditioned approach towards the location of food delivery (rather than the CS), and GTs will not work avidly to get the CS (Meyer *et al*, 2012). Importantly, variation in the propensity to attribute incentive salience to a food cue predicts the extent to which drug cues gain motivational control over behavior. For example, a cocaine-associated cue is more effective in maintaining self-administration behavior, and instigates more robust relapse behavior, in STs than GTs (Saunders and Robinson, 2010). Additionally, STs will exert more effort to self-administer cocaine, and are more likely to relapse when 'primed' with drugs themselves (Saunders and Robinson, 2011). Therefore, it is possible to predict, *before any drug experience*, which rats will find drug cues more desirable, will exhibit greater motivation to take drugs, and will be more likely to relapse. Thus, the extent to which drugs cues acquire motivational properties may not only influence their ability to control normal behavior but to also tempt maladaptive behavior, thereby contributing to addiction vulnerability.

Several lines of evidence suggest that the propensity to attribute incentive salience to reward cues represents a complex psychological trait (Meyer *et al*, 2012). First, there are neurobiological differences between STs and GTs, including differences in dopaminergic systems (Flagel *et al*, 2011; Flagel *et al*, 2010). Second, the variation is heritable (Flagel *et al*, 2010), indicating that some unknown genetic differences contribute to variation in reward cue processing. Third, the extent to which rats become STs or GTs is influenced by early life experiences (Lomanowska *et al*, 2011), suggesting that environmental factors also contribute to how individuals process and respond to reward cues in adulthood. In conclusion, this line of research provides a novel approach to understanding the interplay between genetic, epigenetic, environmental, and neural-systems-level factors that confer susceptibility (and resilience) to impulse-control disorders, such as addiction. Implications for the development of clinical intervention strategies include: (1) greater attention to individual differences in the psychological factors that control pathological motivation for drugs, and (2) greater recognition that, in susceptible individuals, drug cues may be especially insidious in instigating and maintaining drug-seeking behavior.

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DISCLOSURE

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Fractionating the Impulsivity Construct in Adolescence

The teenage years are often associated with 'impulsive' behavior; that is, behavior with diminished regard to potential negative consequences. Adolescent impulsivity, while often adaptive, can manifest itself in a range of sub-optimal behaviors, including use of nicotine, alcohol, or illicit substances, symptoms associated with attention deficit hyperactivity disorder (ADHD), or poorer performance on laboratory assays of impulse control. Although these maladaptive behaviors are often co-morbid, their correlation is not perfect. It is therefore increasingly recognized that impulsivity is multi-dimensional, with some predicting that 'what is generally denoted as impulsivity will be fractionated into distinct forms that may, however, often coexist in the same individual' (Dalley *et al*, 2011, page 691).

Fractionating impulsivity is challenging, not least because of the large sample size needed to ensure an adequate number of participants in each phenotypic group, although recently the 'population neuroscience' (Paus, 2010) approach has provided these large samples. Data from the IMAGEN (Schumann *et al*, 2010) project permitted the data-driven identification of impulsivity subtypes by Whelan *et al* (2012). Nearly 1900

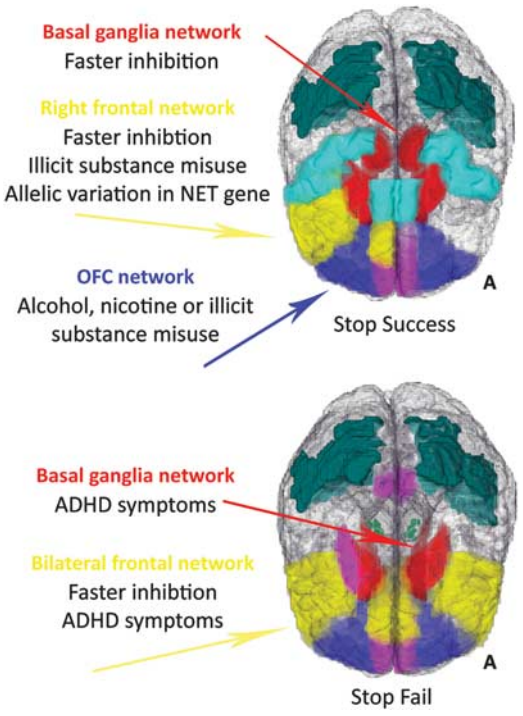

Figure 1. The impulsivity networks and associated phenotypes described in Whelan *et al* (2012), for both trials on which subjects successfully inhibited an already initiated motor response (Stop Success) and trials on which subjects failed to inhibit (Stop Fail). A, anterior; ADHD, attention deficit hyperactivity disorder; OFC, orbitofrontal cortex; NET, norepinephrine transporter.

14-year-olds completed a test of motor inhibition—the Stop Signal Task (SST)—while undergoing functional magnetic resonance imaging (fMRI). The large sample size allowed functional brain activity to be decomposed into a smaller number of distinct networks using factor analysis (a data-reduction method). Next, these networks were tested for relationships with various phenotypes. Adolescents who had experimented with either alcohol, cigarettes, or illicit substances showed reduced activity in an orbitofrontal cortex network on successful stop trials, even those with only 1–4 total lifetime alcohol uses. For adolescents who had used illicit substances, there was hyperactivity in a right frontal network (inferior frontal gyrus, cingulate, and insula), an effect that remained even after controlling for nicotine and alcohol effects. In contrast, ADHD symptoms were associated with bilateral frontal (inferior frontal gyri, anterior cingulate, and anterior insula) and basal ganglia networks only on unsuccessful stop trials. Individual differences in the speed of the inhibition process on the SST were associated with activity in the right frontal network and in the basal ganglia. Finally, the right frontal network was also associated with allelic variation in a single-nucleotide polymorphism located in the *SLC6A2* gene, which codes for the norepinephrine transporter (see Figure 1).

Understanding the neural correlates of impulsivity subtypes is important because it yields insights into the etiology of maladaptive impulsive behaviors. Disentangling the biological basis of substance misuse and ADHD symptoms has proven difficult previously because, for example, adult substance misusers are more likely to retrospectively endorse childhood ADHD symptoms (Ivanov *et al*, 2008). However, the results of Whelan *et al* (2012) suggest that ADHD symptoms and adolescent substance misuse can be separated, at least in terms of brain activity during a test of inhibitory control. Furthermore, these results support the role of norepinephrine in modulating impulse control, with implications for treatment of ADHD (Chamberlain *et al*, 2007). A goal of future research will be to shed more light on the structural, functional, neurochemical, and genetic underpinnings of the various impulsivity brain networks.

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Proteomic Analyses of PKA and AKAP Signaling in Cocaine Addiction

The development and application of proteomics techniques allows for *ab initio* identification of changes in protein expression and modifications which drive cellular processes. In the case of behavioral neuroscience, these techniques may be applied toward identification of candidate proteins and cellular pathways within specific nuclei that are affected by experience or training, and testing of subsequent hypotheses in behavioral models. Accordingly, proteomic techniques have been applied to identify protein