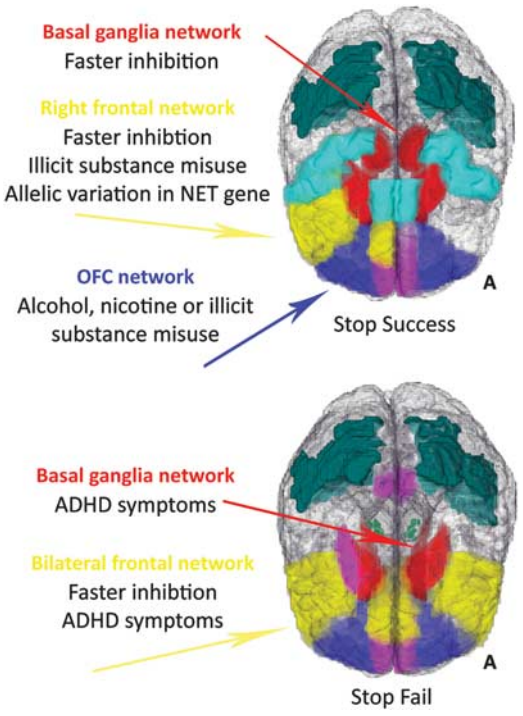

Figure 1. The impulsivity networks and associated phenotypes described in Whelan *et al* (2012), for both trials on which subjects successfully inhibited an already initiated motor response (Stop Success) and trials on which subjects failed to inhibit (Stop Fail). A, anterior; ADHD, attention deficit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

changes following chronic cocaine abuse. These studies have examined changes in the nucleus accumbens (NAc) from human overdose victims, as well as non-human primates and rodents (for review, see Hemby (2010)). From these, a number of important themes have emerged; for example, changes in cellular metabolism, cytoskeletal dynamics, and signal transduction were highly represented. Of particular note, elements of the cAMP, adenylate cyclase, and PKA signaling pathway have been identified by traditional biochemical methods and genomic analyses, as well as proteomic methods (Hemby, 2010).

For example, ChIP-chip microarray analysis of genes influenced by cocaine exposure has indicated increased histone acetylation at the promoters of the PKA catalytic and RII regulatory subunits, as well as A kinase anchoring protein 9 (AKAP9) (also known as Yotiao) and AKAP8 (AKAP95) (Renthal *et al*, 2009). Moreover, increased binding of transcription factor ΔFosB was identified at the promoters for PKA RIIα, as well as AKAP8 following cocaine *vs* saline exposure. AKAPs constitute a family of more than 50 proteins across vertebrates and invertebrates, which mediate scaffolding and localization of PKA and other signaling molecules within specific cellular subcompartments (Sanderson and Dell'Acqua, 2011).

An isobaric tag for relative and absolute quantitation proteomic analysis of a rat postsynaptic density-enriched subfraction following cocaine self-administration and extinction identified upregulation of AKAP5 (also known as AKAP79/150) (Reissner *et al*, 2011). AKAP150 serves to complex PKA and other signaling molecules with ionotropic glutamate receptors (Sanderson and Dell'Acqua, 2011). Disruption of AKAP scaffolding by microinjection of a cell permeable inhibitor peptide in the NAc (*vs* control peptide) led to decreased reinstatement of cocaine seeking, indicating a functional role for AKAPs in the neuropathology of drug abuse (Reissner *et al*, 2011).

Downstream of PKA, Boudreau *et al* (2009) observed increased AMPA surface expression, as well as PKA (and pERK2) activation over time during withdrawal in cocaine sensitized rats. They went on to use a mass spectrometry approach to identify PKA substrates whose phosphorylation increased over time of withdrawal, employing proteomics to analyze effector proteins downstream of PKA.

The repeated identification of the PKA signaling pathway in the cellular adaptations induced by cocaine underscores the importance of this pathway in the addiction process. However, the ubiquitous nature of AKAP and PKA signaling in cellular pathways and subcompartments (eg, synapse *vs* nucleus, organelles, etc) complicates application of this pathway toward candidate pharmacotherapeutic targets for psychostimulant abuse. In the specific case of AKAP150, however, proteomic and functional studies indicate that synaptic upregulation promotes reinstatement behavior; thus, development of a structurally specific inhibitor targeting this member of the AKAP family may aid inhibition of craving and drug seeking, as a pharmacological adjuvant to cognitive therapy and counseling.

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Translational Research in OCD: Circuitry and Mechanisms

Although the pathophysiology of obsessive-compulsive disorder (OCD) remains unknown, converging lines of evidence point to abnormalities in the orbital (OFC), ventromedial (vmPFC-subgenual cingulate and medial OFC), and dorsal anterior cingulate (dACC) cortical-basal ganglia circuits. OCD-linked patterns of activity in these PFC regions are accentuated during provocation of symptoms and can predict treatment response; they tend to normalize following successful treatment (Greenberg *et al*, 2010). Moreover, neurosurgical interventions (lesions or deep brain stimulation-DBS) within the ventral internal capsule (VC), ventral striatum (VS), or dACC (treatments for intractable OCD) all act on subcomponents of the vmPFC/OFC/dACC-basal ganglia network (Greenberg *et al*, 2010). Indeed, DBS interventions specifically affect vmPFC, OFC, and possibly dACC connections with striatum, thalamus, and/or brainstem (Figure 1) (Lehman *et al*, 2011). The efficacy of VC/VS DBS (or lesions) for OCD likely requires modulating the OFC/vmPFC/dACC-basal ganglia circuit. Interestingly, high frequency stimulation (HFS) in a rat homolog of the VC/VS DBS target reduces OFC activity, enhances local field potential delta band activity in OFC, and enhances synchrony between specific regions within this prefrontal network (McCracken and Grace, 2009). Thus, OCD pathophysiology likely represents dysfunctional network interactions rather than only disruption within specific structures.

OCD is often characterized by abnormal risk assessment and unrealistic fears leading to excessive avoidance. Changes in vmPFC/OFC/dACC activity have been linked to fear conditioning and recall in normal subjects (Milad *et al*, 2007), with vmPFC activity and structure particularly relevant for fear extinction recall. Overlap