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.

Kathryn J Reissner[1]
[1]Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA
E-mail: reissner@musc.edu

DISCLOSURE
The author declares no conflict of interest.

Boudreau AC, Ferrario CR, Glucksman MJ, Wolf ME (2009). Signaling pathway adaptations and novel protein kinase A substrates related to behavioral sensitization to cocaine. *J Neurochem* **110**: 363–377.
Hemby SE (2010). Cocainomics: new insights into the molecular basis of cocaine addiction. *J Neuroimmune Pharmacol* **5**: 70–82.
Reissner KJ, Uys JD, Schwacke JH, Comte-Walters S, Rutherford-Bethard JL, Dunn TE *et al* (2011). AKAP signaling in reinstated cocaine seeking revealed by iTRAQ proteomic analysis. *J Neurosci* **31**: 5648–5658.
Renthal W, Kumar A, Xiao G, Wilkinson M, Covington HE 3rd, Maze I *et al* (2009). Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. *Neuron* **62**: 335–348.
Sanderson JL, Dell'Acqua ML (2011). AKAP signaling complexes in regulation of excitatory synaptic plasticity. *Neuroscientist* **17**: 321–336.

Neuropsychopharmacology Reviews (2013) **38,** 251–252; doi:10.1038/npp.2012.181

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

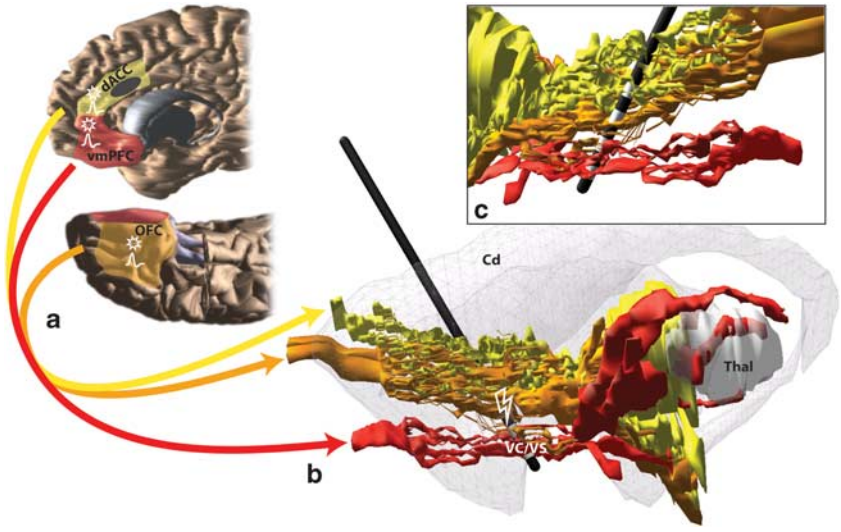

Figure 1. Schematic illustrating key cortical areas involved in obsessive-compulsive disorder (OCD) and their pathways through the internal capsule. (a) Red, orange, and yellow fibers originate in ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and dorsal anterior cingulate (dACC), respectively. The approximate cingulotomy site is depicted as a dark gray oval. (b) Medial view of a sagittal section with vmPFC, OFC, and dACC fibers passing through the internal capsule. The striatum is indicated in gray. A model of the electrode with its four contacts is placed at ventral internal capsule (VC)/ventral striatum (VS) deep brain stimulation (DBS) site. (c) Lateral view of a sagittal section shows the four electrode contact points in the VC/VS. VmPFC and OFC fibers pass through the ventral contacts, and OFC and dACC fibers pass through the dorsal contact points (Lehman *et al*, 2011). Action potential symbols indicate possible regions with changes in firing rates and/or local field potentials following HFS in the VS (McCracken and Grace, 2009); stars indicate regions with possible changes in plasticity following HFS to VS (Rodriguez-Romaguera *et al*, 2012).

in the circuits associated with fear conditioning and OCD dysfunction suggests that these patients may be less flexible in adjusting adverse responses based on new information. Indeed, using a rat model of DBS, with the HFS targeting the VS, a recent study showed that stimulation strengthened fear extinction and retention (Rodriguez-Romaguera *et al*, 2012), while enhancing plasticity in the infralimbic, orbitofrontal, and prelimbic cortices (probable homologs of the vmPFC, OFC, and, perhaps, dACC). Taken together, dysfunction of the vmPFC/OFC/dACC network may lead to an increase in incentive-based fear learning and habit formation.

However, PFC regions associated with OCD pathology are not only involved in aversive behaviors and avoidance; they also mediate reward processing. Indeed, OCD patients are also impaired on tasks using rewarding outcomes (Gillan *et al*, 2011). They underperform when required to flexibly adjust responses based on new or changing reward feedback. These tendencies suggest impairment in goal-directed behaviors and may lead patients to rely too heavily on habit-based responding, even in the positive-incentive domain (Gillan *et al*, 2011). Therefore, rather than being specific to aversive *vs* reward processing, the vmPFC, OFC, and dACC cortices are involved in value representation, stimulus-outcome associations, and action-outcome associations, regardless of valence. Thus, a heuristic approach could posit that OCD symptoms may not be specific to fear learning and habits, but are related to interference in the normal balance between negative and positive-incentive learning based on values attributed to particular stimuli or actions. Probing potential abnormalities in incentive learning strategies and linking them with functional neurocircuitry can be used both as a research tool and to help design innovative therapeutic approaches.

ACKNOWLEDGEMENTS

This work was supported by NIH grants MH7311, MH 086400, and MH045573.

Suzanne N Haber[1] and Sarah R Heilbronner[1]

[1]Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
E-mail: suzanne_haber@urmc.rochester.edu

DISCLOSURE

Dr Haber has received consultation fees from Medtronic, Inc and Pfizer, Inc. Dr Heilbronner declares no conflict of interest.

Gillan CM, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW *et al* (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry* **168**: 718–726.

Greenberg BD, Rauch SL, Haber SN (2010). Invasive Circuitry-Based Neurotherapeutics: Stereotactic Ablation and Deep Brain Stimulation for OCD. *Neuropsychopharmacology* **35**: 317–336.

Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, Haber SN (2011). Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. *J Neurosci* **31**: 10392–10402.

McCracken CB, Grace AA (2009). Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. *J Neurosci* **29**: 5354–5363.

Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* **62**: 446–454.

Rodriguez-Romaguera J, Do Monte FH, Quirk GJ (2012). Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. *Proc Natl Acad Sci USA* **109**: 8764–8769.

Neuropsychopharmacology Reviews (2013) **38,** 252–253; doi:10.1038/npp.2012.182

Brain Serotonin Function in MDMA (Ecstasy) Users: Evidence for Persisting Neurotoxicity

3,4-methylenedioxymethamphetamine (MDMA; ecstasy) is a popular recreational drug, and clinical trials are investigating MDMA as a treatment for anxiety. Animal models suggest that MDMA causes chronic serotonin neurotoxicity, especially in neocortex. Given the role of serotonin in a broad range of brain functions, it is critical to determine whether MDMA is associated with serotonin neurotoxicity in humans. Studies examining the