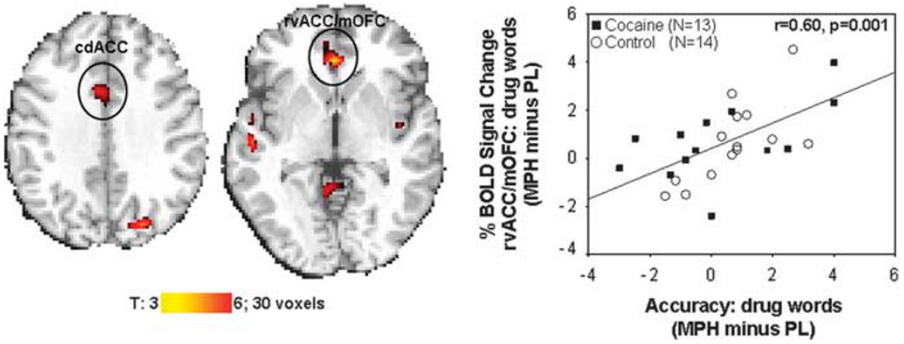

Figure 1. Methylphenidate (MPH) enhances functional magnetic resonance imaging (fMRI) cingulate responses and reduces commission errors on a salient (cue reactivity) cognitive task in individuals with cocaine addiction. On the left are axial maps depicting caudal–dorsal anterior cingulate (cdACC, BA 24, 32) and rostroventromedial anterior cingulate (extending to the medial orbitofrontal cortex, rvACC/mOFC, BA 10, 32) cortical regions that showed enhanced responses to MPH as compared with placebo (PL) in cocaine-addicted individuals. On the right is a graph showing the correlation between % blood oxygenation level-dependent (BOLD) signal change from a fixation baseline as a function of drug words in the rvACC/mOFC ($x = -9$, $y = 42$, $z = -6$, BA 10, 32) and the respective change in accuracy on the fMRI task (both are delta scores: MPH minus placebo). Subjects are 13 individuals with cocaine use disorders and 14 healthy controls.

task performance in CUD consistent with the cognitive benefits of MPH in other psychopathologies. In CUD, we speculate that these effects reflect MPH-induced increases in dopamine neurotransmission in these dopamine-deficient individuals. Specifically, we postulate (based on preclinical electrophysiological studies) that MPH increased SNR by enhancing dopamine (perhaps also noradrenergic) neurotransmission, thereby enhancing the activation of regions involved in the task (ACC). Although clinical trials with MPH have not been effective in decreasing cocaine use in CUD, these results suggest that MPH may have therapeutic benefits in facilitating behavioral modification (eg, impulse control) when combined with specific cognitive interventions.

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DISCLOSURE

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Failures in Learning-Dependent Predictive Perception as the Key Cognitive Vulnerability to Psychosis in Schizophrenia

Cognitive deficits present in almost all patients with schizophrenia, and account for considerable functional disability, but as typically measured in schizophrenia are unrelated to hallucinations and delusions. The absence of this relationship may be caused in part by the lack of an organizing principle of psychosis-related cognitive impairment. Most studies of cognition in schizophrenia involve standard neuropsychological tests that were devised for measuring brain injury in patients with no previous relevant illness. Human perception, thought and action—the basic elements of maintaining reality—are based upon a hierarchical process that conjoins memory and external stimuli, which we refer to as learning-dependent predictive perception. We

propose that impairments in this elemental process lead to psychosis in patients with schizophrenia.

The hierarchical model posits that the nature of the output from a given area of cortex depends on temporal coincidence with the patterns of the bottom-up input it receives. If an individual experiences stimuli that do not clearly fit any top-down hypotheses derived from previous experience, a given area of cortex relays the details of the patterns it receives to higher cortical areas; the signals are passed on to the next highest layer and this pattern extends until a match is achieved. As a situation becomes more familiar, the representations of a given level of analysis are shifted to lower cortical areas, freeing higher areas for the detection of high-level patterns. The correct identification of objects, sensations, and processes in the environment is thus based upon probabilistic prediction determined by the accumulation of memories of how the perceptual world is organized and how it operates (Hawkins and Blakeslee, 2004; Purves *et al*, 2001).

We hypothesize that in schizophrenia, the formation and storage of invariant representations at higher hierarchical levels is insufficient. The higher levels do not provide enough input to lower levels for solving the nature of stimuli, and the lower levels do not provide adequate perceptual details to enable a sufficient establishment of perceptual context (Kraus *et al*, 2009). Thus, simple information must be sent repeatedly to higher levels for more effortful interpretation. Reduction in the correct identification of percepts in the context of real-world information-processing demands, affords the opportunity for arbitrary internally generated interpretations of reality to intrude upon perception and thought, leading to an accumulation of inaccurate but internally meaningful perceptions that may build upon one another into incorrect beliefs. This failed process may be at the core of the development of hallucinations and delusions. Context-based perceptions of real objects and real events are reduced in favor of an interpretation of reality that is individually determined and disconnected from the experiences and beliefs shared by others. This, we hypothesize, is the mechanism behind the development of delusions and hallucinations in patients with schizophrenia.

Recent work supports this concept (Javitt, 2009). Patients with schizophrenia have great difficulty in perceiving visual objects among noise and are unable to identify incongruous events in a virtual reality context. Although few studies have addressed whether these cognitive impairments precede the onset of psychosis, there have been some confirming data. Individuals who are soon to develop psychosis experience the perception of more elaborate sequences of verbal stimuli in auditory noise conditions (Hoffman *et al*, 2007). Cognitive paradigms that measure an individual's ability to distinguish percepts from noise based upon context have particular promise for identifying impairments in learning-dependent predictive perception (Koethe *et al*, 2009).

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New Insights into the Mechanisms Underlying the Effects of BDNF on Eating Behavior

Food intake is a complex behavior resulting from interactions between homeostatic and hedonic regulatory mechanisms acting in the energy balance and reward centers of the brain. Alterations in feeding behavior are often pervasive and can lead to obesity and its associated medical complications, including metabolic and cardiovascular disorders and psychological distress. A compelling body of evidence emerged recently, indicating a pivotal role of brain-derived neurotrophic factor (BDNF) in pathological processes leading to abnormal food intake and excessive weight gain. BDNF signals through the TrkB receptor to promote neuronal survival, differentiation, and synaptic plasticity. Perturbing central BDNF signaling in mice results in hyperphagic behavior and obesity (Xu *et al*, 2003; Unger *et al*, 2007). In humans, BDNF haploinsufficiency was linked to elevated food intake and severe weight gain (Han *et al*, 2008). These findings have significant clinical implications, as the *Bdnf*Val66Met allele, which impedes regulated BDNF secretion, is highly prevalent in humans (Shimizu *et al*, 2004).