movement'' (Llinás, 2002), then one might expect so. In this view the cortical extent of the motor system extends beyond primary motor areas. Behavior, after all, is essentially synonymous with the activity of the motor system. Indeed, a compelling case can be made for the viewpoint that 'layer 5 is motor everywhere' (Diamond, 1979); in other words, layer 5B is 'motor cortex'. Should we regard layer 2/3 as 'premotor cortex'?

We expect that as research on motor/frontal cortex goes forward, a general framework for understanding behavioral 'control' mechanisms at the level of cortical circuits will emerge, which will link multiple levels of neural organization and have useful roles both in assimilating the rapidly accruing new information and in inspiring testable hypotheses. New opportunities for the neuropsychopharmacology of movement disorders are also likely to arise. For example, many cognitive disorders have a motor component, and vice versa; apraxias are classic examples. Also, the expression patterns of ion channel and intracellular signaling molecules is highly diverse in layer 5B (Allen Brain Atlas). This diversity presents a fertile substrate for exploring pharmacological strategies to selectively target pathological mechanisms in specific subclasses of cortical projection neurons involved in different aspects of voluntary movement.

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Oral Methylphenidate Normalizes Cingulate Activity and Decreases Impulsivity in Cocaine Addiction During an Emotionally Salient Cognitive Task

Deficits in dopaminergically modulated striato-thalamo-prefrontal circuits contribute to compromises in self-control and motivation in cocaine addiction (Goldstein and Volkow, 2002). Methylphenidate (MPH), a dopaminergic agonist, has been successfully used to enhance inhibitory control and salience attribution in attention-deficit hyperactivity disorder and other prefrontal psychopathologies (eg, frontotemporal dementia); indeed MPH has been suggested to improve signal-to-noise ratio (SNR) and optimize activity (eg, processing efficiency) in brain regions that modulate executive functions (Mehta *et al*, 2000; Volkow *et al*, 2008). However, in clinical trials on cocaine addiction, MPH did not reduce cocaine consumption (Volkow *et al*, 2004). We hypothesized that oral MPH would improve executive function in individuals with cocaine use disorders (CUDs), an effect that, when coupled with cognitive or behavioral interventions, may improve the clinical outcome.

In the current functional magnetic resonance imaging (fMRI) study, 13 CUDs (12 male subjects, mean age = 46.2 years, mean duration of cocaine use, predominantly smoked = 17.9 years, all meeting the current cocaine dependence criteria) matched on education and intellectual functioning with 14 healthy controls (all male, mean age = 38.8, group differences statistically controlled) received 20 mg oral MPH or placebo in a randomized and counterbalanced order over two consecutive MRI sessions (separated by a mean of 14 days, MRI performed on a 4-T whole-body Varian/Siemens scanner). During peak MPH effects (60–90 min post administration), subjects performed an emotional variant of the color-word Stroop task: subjects were monetary remunerated for correct pressing for color of drug-related and matched neutral words. This task engages the prefrontal cortex in CUD (Goldstein *et al*, 2007). Importantly, despite lack of group differences in task engagement or performance, compared with healthy controls, CUD showed robust anterior cingulate cortex (ACC) hypoactivations, encompassing the rostroventral ACC (rvACC) (extending to the medial orbitofrontal cortex (mOFC)) and the caudal–dorsal ACC (cdACC) (Goldstein *et al*, 2009).

Results showed that MPH did not increase task-related cocaine craving in CUD. Importantly, the current results demonstrated that compared with placebo, MPH during a salient cognitive task (1) enhanced the cdACC (Brodmann area (BA) 24, 32) and rvACC/mOFC (BA 10, 32) task response in the CUD; (2) the larger the signal increases in rvACC/mOFC (BA 10, 32), the greater the improvement in task accuracy; and (3) MPH decreased response impulsivity (errors of commission) in all subjects (see Figure 1).

These fMRI results are the first to show that oral MPH improved the response of the ACC and associated

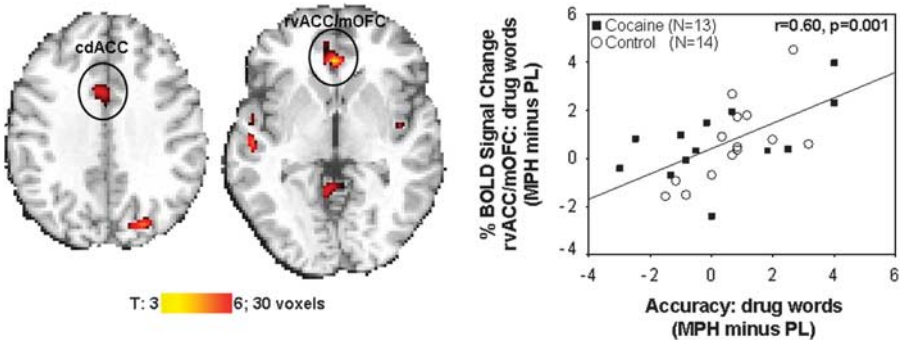

Figure 1. Methylphenidate (MPH) enhances functional magnetic resonance imaging (fMRI) cingulate responses and reduces commission errors on a salient (cue reactivity) cognitive task in individuals with cocaine addiction. On the left are axial maps depicting caudal–dorsal anterior cingulate (cdACC, BA 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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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