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**Reply to Dakis and O'Brien**

# Reply: Clinical Implications of Cocaine-Induced Cortical Depression

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Sir

We concur with Dackis and O'Brien's view that prefrontal cortex dysfunction represents a cardinal feature of cocaine abuse. Although *in vivo* recordings from our and others laboratories (Chang *et al*, 1997, 1998, 2000) implicate a common set of changes in electrophysiological indices in prefrontal cortex neurons after acute and chronic stimulant exposure, the precise synaptic mechanisms mediating these alterations remain unknown. We therefore emphasize the probable dependence of complex psychopathologic features of addiction on the canonical cortico-striatal-pallido-thalamo-cortical loops that are clearly implicated in many aspects of cognitive, motor, and affective function (Haber, 2003), and that are direct mediators of recidivism-like phenomena (Kalivas and Volkow, 2005).

Elegant work by Steriade and colleagues (Steriade and Deschenes, 1984; Steriade and Timofeev, 2003) indicates that thalamic inputs to the neocortex as well as cortico-cortical connections (Timofeev *et al*, 2000) are important regulators of spike activity, as well as of the bistable membrane potentials recorded from prefrontal neurons *in vivo*. When taken together with the growing evidence for direct actions of stimulant drugs on pallidal and thalamic neurons (Lavin and Grace, 1998), it becomes apparent that subcortical actions of addictive agents could disrupt cortical neuron function either directly or through complex multi-synaptic actions. Indeed, Jentsch and Taylor (1999) have emphasized how drug effects on multiple cortical and subcortical brain regions may be required to sustain the compulsive aspects of drug addiction. We therefore additionally stress these larger circuit actions of stimulant drugs in the key psychological features of addiction noted by Dackis and O'Brien.

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Much remains unknown about the subcellular causes of dysfunction of these neuronal loops. New work has emphasized mechanism implicating LTP (Borgland *et al*, 2004; Saal *et al*, 2003; Ungless *et al*, 2001), intracellular signaling proteins (Szumlinski *et al*, 2004; Bowers *et al*, 2004; Nestler, 2004), and monoamine neurotransmitters (Volkow *et al*, 2004). *In vivo* recordings will be but part of the experimental repertoire required to reveal these changes.

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