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R RAWSON AND T CONDON SUPPLEMENT (special issue of *Addiction*)

Corticolimbic dysregulation and chronic methamphetamine abuse

Short title: Cortical Control and Methamphetamine Abuse

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ABSTRACT

Aims. This review aims to present and interpret evidence that methamphetamine dependence is associated with disorder of brain function that is required for top-down control of behavior.

Approach. Presented here are findings from brain imaging studies of human research participants with histories of chronic methamphetamine abuse in the context of functional consequences and implications for treatment of their dependence on methamphetamine. **Findings.** Brain imaging

studies have revealed differences in the brains of research participants who have used methamphetamine chronically and then abstained from taking the drug, compared with healthy control subjects. These abnormalities are prominent in cortical and limbic systems, and include deficits in markers of dopaminergic and serotonergic neurotransmitter systems, differences in glucose metabolism, and deficits in gray matter. These abnormalities accompany cognitive deficits, including evidence of impaired inhibitory control. **Conclusion.** Cortical deficits in

abstinent methamphetamine abusers can affect a wide range of functions that can be important for success in maintaining drug abstinence. These include but are not limited to modulation of responses to environmental stimuli as well as internal triggers that can lead to craving and relapse.

Potential therapies may combine behavioral approaches with medications that can improve cognitive control.

KEYWORDS: Methamphetamine, brain imaging, inhibitory control, cognition, emotion.

INTRODUCTION

An individual's response to environmental stimuli often involves a complex interplay of cortical and subcortical interactions. Although rapid responses, governed primarily by subcortical activity, can be vital to an organism's survival, advantages can be provided by cortical involvement in the evaluation and interpretation of stimuli to guide behavior. Such cortical influence can apply to the control of motor responses of cognitive functions (e.g., the focusing of attention) and of emotional responses.

Current findings from brain imaging and behavioral assessments of human volunteers with histories of chronic methamphetamine (MA) abuse demonstrate prominent functional and/or structural abnormalities within the limbic and paralimbic cortices and subcortical areas that are normally under cortical control. As described below, these deficits accompany behavioral impairments, including diminished capacity for cognitive control, that are likely to be core manifestations of this disturbance. Impairments in the ability to control responses to environmental stimuli may compromise treatment outcomes and can contribute directly to adverse life consequences for MA-dependent individuals. Understanding their basis and considering them as therapeutic targets may lead to incremental progress in the treatment of MA dependence. This review presents findings from brain imaging studies, and discusses deficits observed in research participants with histories of chronic MA abuse in the context of impaired inhibitory control.

FUNCTIONAL AND STRUCTURAL DEFICITS OF CORTICOLIMBIC BRAIN REGIONS IN METHAMPHETAMINE-DEPENDENT HUMAN SUBJECTS

Studies of brain chemistry, function and structure in individuals who abused MA chronically have taken the form of postmortem assay and noninvasive imaging using nuclear medicine procedures for functional assessments and magnetic resonance imaging (MRI) for structural analyses. What

has emerged is a picture of long-term deficits that can partially explain the problems that MA-dependent individuals experience in mood, cognition and social interactions. These deficits can reflect targets for therapy, and they at least must be considered in designing treatment interventions.

Relative to other drugs of abuse, MA is highly neurotoxic (1-3). Neurochemical as well as anatomical evidence from animal studies indicates that this drug adversely affects dopaminergic, serotonergic, and non-monoaminergic systems (4-6) [for review, see (7)]. Consistent with these findings, postmortem brain tissue from human subjects who abused MA exhibited deficits in striatal dopaminergic markers and in orbitofrontal cortical serotonin (8). *In vivo* positron emission tomographic (PET) studies extended this work to show that, compared with healthy comparison subjects, individuals who have engaged in chronic MA abuse exhibit lower levels of dopamine transporters in the striatum (9-11)