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Review

Recovering from cocaine: Insights from clinical and preclinical investigations

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ABSTRACT

Cocaine remains one of the most addictive substances of abuse and one of the most difficult to treat. Although increasingly sophisticated experimental and technologic advancements in the last several decades have yielded a large body of clinical and preclinical knowledge on the direct effects of cocaine on the brain, we still have a relatively incomplete understanding of the neurobiological processes that occur when drug use is discontinued. The goal of this manuscript is to review both clinical and preclinical data related to abstinence from cocaine and discuss the complementary conclusions that emerge from these different levels of inquiry. This commentary will address observed alterations in neural function, neural structure, and neurotransmitter system regulation that are present in both animal models of cocaine abstinence and data from recovering clinical populations. Although these different levels of inquiry are often challenging to integrate, emerging data discussed in this commentary suggest that from a structural and functional perspective, the preservation of cortical function that is perhaps the most important biomarker associated with extended abstinence from cocaine.

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1. Introduction

Chronic cocaine use is a seemingly intractable public health problem worldwide. Whether cocaine is snorted, injected, or smoked as crack, users often suffer serious negative consequences to their health, social relationships, as well as severe economic hardships. Although there have been many efforts to develop effective treatments, whether pharmacological or cognitive and behavioral, rates of relapse continue to be alarmingly high. Moreover, these relapse rates continue to be among the highest of all illegal drugs (Vocci, 2007). One substantial obstacle to the discovery of successful treatment approaches has been our rather incomplete understanding of the neurobiological processes that naturally occur when drug use is discontinued (likely best modeled in animals) as well as any unique features of the small population of addicts that are able to successfully abstain from cocaine for extended periods of time. Without a more complete picture of these structural and functional neuroadaptations, it is difficult to direct effective strategies

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toward targets with the greatest potential for promoting abstinence and reducing harm.

To understand the natural neural adaptations that follow discontinuation of drug use as well as neurological features that promote successful abstinence in humans, it is first necessary to understand the changes that directly result from cocaine exposure. Decades of robust molecular, genetic, cellular, and neural systems level studies have provided important insights in this area. One important approach that has been used in both human and animal models of chronic cocaine use is neuroimaging. This approach encompasses a wide range of in vivo and in vitro techniques capable of assessing neural function and structure, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), diffusion tensor imaging, tissue morphometry, metabolic mapping, and receptor autoradiography, among others. Not only do these approaches have the advantage of being able to sample multiple brain regions simultaneously, but many in vivo approaches can be applied to human drug users and animal models alike providing for substantial translation and cross-validation of findings. Here, we focus on the insights and perspectives that imaging approaches have contributed to the issues that surround the long-term neural adaptations that follow discontinuation of cocaine use after chronic abuse and dependence.

Although there are many unanswered questions, this brief commentary will consider two fundamental questions about abstinence from continued cocaine use that we believe neuroimaging studies can in part address:

(1) To what extent do the neurostructural and functional abnormalities that accompany chronic cocaine use either improve or persist following discontinuation of cocaine?
(2) Are there patterns of neural function or structure that can be used as predictors of successful abstinence when given the choice to use?

A broad perspective is required in order to address these questions. In this commentary we examine complementary insights from clinical addiction research and preclinical animal models of drug use. When considered together these data give us a deeper understanding of the neurofunctional and structural adaptations that are present in both early and extended periods of abstinence.

2. Imaging the brain of cocaine abstainers: clinical research

As with many psychiatric diseases, the neuropathology present in cocaine-dependent individuals is not restricted to a single brain region, a single cell type, or a single neurotransmitter system. Rather substance dependence is frequently associated with disruptions in at least three major systems that contribute to behavior – limbic processing, cognition, and basic motor control. These systems span both cortical and subcortical regions of the brain and therefore are vulnerable not only to pathology in a local population of cells, but also in the white matter tracts that connect these regions.

Additionally, just as addiction is not limited to one spatially distinct disruption, there is also an important temporal component to the addiction process. That is, addiction exists on a continuum that likely extends from a vulnerable, drug-naïve individual that casually uses a drug, to an individual that becomes dependent, attempts abstinence and, typically, relapses. While several research groups have isolated traits that predict better than average treatment outcomes in cocaine users (Kampman et al., 2002; Poling et al., 2007; Sinha et al., 2007) there are still no FDA approved medications for cocaine dependence. Moreover, relapse rates are among the highest of all illegal drugs (Vocci, 2007).

Longitudinal studies of neural activity during this continuum are very difficult to perform in substance-dependent individuals for pragmatic reasons (e.g. identifying vulnerable individuals, loss to follow-up due to frequent changes in phone numbers, living arrangements, lack of transportation). There is, however, a growing body of research that has tried to address these questions. In this review we will discuss several studies which have investigated individuals at each stage of this continuum. In order to determine whether patterns of brain activity predict treatment success or relapse, however, it is important to first understand common structural and functional abnormalities present in the brain of a cocaine dependent individual.

2.1. Beyond the striatum: altered activity in the prefrontal cortex of users and abstainers

Cocaine's primary mechanism of action in the brain involves binding to the dopamine transporter which is highly concentrated in the basal ganglia (or striatum). Dopamine disruption in the striatum has been robustly studied in animal models of cocaine use and in several human imaging studies. Additionally however, many highly-cited human neuroimaging studies have revealed significantly lower rates of functional activity in the frontal cortex of cocaine users relative to non-drug using controls. This 'hypofrontality' was first documented in PET imaging studies which measured baseline glucose metabolism throughout the brain of cocaine users (Goldstein et al., 2004; Goldstein and Volkow, 2002; Volkow et al., 1991a, 1992, 2005).

Volkow and colleagues were also among the first to demonstrate that, in addition to a lower metabolic rate of glucose utilization, both currently active and recently abstinent cocaine users have lower levels of dopamine D2 receptors in both frontal and limbic regions of the cortex (Volkow et al., 1993). Baseline cerebral blood flow (CBF) is also significantly lower in chronic cocaine users compared with non-drug using controls, in the prefrontal and temporal cortices (Goldstein and Volkow, 2002; Holman et al., 1993; Strickland et al., 1993; Volkow et al., 1988).

Although many studies have assessed alterations in cognitive function of cocaine abusers after the cessation of drug use (Bolla et al., 2004, 2003; Gottschalk et al., 2001), few studies have directly addressed the question of the persistence or potential changes in these abnormalities over the course of abstinence. One of the first and only longitudinal studies in this field was done by Volkow et al. (1991a,b). They demonstrated that cerebral metabolism in the basal ganglia and ventral prefrontal cortex of cocaine abusers was elevated above control levels during the first week of abstinence (Volkow et al., 1991b). After 1–6 weeks of abstinence however, these acutely elevated cerebral metabolic rates had decreased. These decreases persisted in a subset of subjects tested again after 3 months, suggesting that many neurofunctional abnormalities persist after extended abstinence from cocaine.

It is yet unclear however, if more protracted periods of abstinence (greater than 6 months) are associated with better affective and neurofunctional outcomes. As demonstrated in methamphetamine abstainers (Wang et al., 2004), significant neocortical recovery may not occur until several months after abstinence begins. Emerging data from several laboratories, including our own, suggests that individuals who are able to maintain abstinence for a long period of time may in fact have higher levels of frontal cortex activity. A recent functional MRI study by Connolly et al. (2012) demonstrated that during a response inhibition task, individuals that had been abstinent from cocaine for 10–25 months (long term) had significantly higher blood oxygen level dependent (BOLD) signal in the prefrontal cortex during a response inhibition task than shorter term abstainers (1–5 weeks). Furthermore, whereas current cocaine users typically have lower prefrontal activity than controls