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Differential roles of medial prefrontal subregions in the regulation of drug seeking

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ABSTRACT

The prefrontal cortex plays an important role in shaping cognition and behavior. Many studies have shown that medial prefrontal cortex (mPFC) plays a key role in seeking, extinction, and reinstatement of cocaine seeking in rodent models of relapse. Subregions of mPFC appear to play distinct roles in these behaviors, such that the prelimbic cortex (PL) is proposed to drive cocaine seeking and the infralimbic cortex (IL) is proposed to suppress cocaine seeking after extinction. This dichotomy of mPFC function may be a general attribute, as similar dorsal–ventral distinctions exist for expression vs. extinction of fear conditioning. However, other results indicate that the role of mPFC neurons in reward processing is more complex than a simple PL-seek vs. IL-extinguish dichotomy. Both PL and IL have been shown to drive and inhibit drug seeking (and other types of behaviors) depending on a range of factors including the behavioral context, the drug-history of the animal, and the type of drug investigated. This heterogeneity of findings may reflect multiple subcircuits within each of these PFC areas supporting unique functions. It may also reflect the fact that the mPFC plays a multifaceted role in shaping cognition and behavior, including those overlapping with cocaine seeking and extinction. Here we discuss research leading to the hypothesis that dorsal and ventral mPFC differentially control drug seeking and extinction. We also present recent results calling the absolute nature of a PL vs. IL dichotomy into question. Finally, we consider alternate functions for mPFC that correspond less to response execution and inhibition and instead incorporate the complex cognitive behavior for which the mPFC is broadly appreciated.

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1. Introduction

The prefrontal cortex (PFC) includes a collection of brain regions intimately associated with the regulation of cognitive, emotional, and motivational processes. Included among these functions are those related to control of behavior: attention, response inhibition, planning, and decision-making (Balleine and Dickinson, 1998; Dalley et al., 2004; Euston et al., 2012; Miller and Cohen, 2001). Dysregulaton of these functions is at the core of addiction, and, ultimately related to the balance between execution and inhibition of behavior (Goldstein and Volkow, 2011). Although considerable research has focused on the role of motivational processes in addiction, it is ultimately a disorder of the balance between motivation and self-regulation, where self-regulation is underpinned by behavioral control functions described above. Given the primacy that deficits in self-control play in driving compulsive drug use and addiction, it is no surprise that there is substantial interest in understanding how PFC both moderates reward or drug seeking behaviors as well as in how its dysfunction can result in diseases such as addiction.

There have been a number of reviews relating PFC function to reward seeking-related behaviors and its dysfunction to addiction (Goldstein and Volkow, 2011; Kalivas, 2008; Peters et al., 2013). The goals of the current review are to (1) summarize the preclinical findings associating the PFC with drug seeking, particularly seeking of cocaine and related psychostimulants, (2) discuss models relating PFC subdivision function to drug seeking and addiction, and (3) provide a discussion of future directions necessary to provide a comprehensive understanding of how best to study the PFC in relation to drug seeking and addiction. Given the widespread use and powerfully predictive outcomes of rodent models (Bentzley et al., 2013; Crombag et al., 2008; Epstein et al., 2006; Mahler et al., 2012), we will focus on these for the majority of the review. However, we do so knowing that there are significant differences between rodent and primate (including human) PFC (Kesner and Churchwell, 2011; Uylings et al., 2003; Wise, 2008) and that there have been substantial advances in understanding how the human PFC functions in relation to drug abuse and addiction as described in a number of comprehensive reviews (Goldstein and Volkow, 2011; Moeller and Goldstein, 2014). We first briefly discuss the role of the human PFC in drug abuse and addiction before turning to a more comprehensive discussion of rodent models.

2. PFC in drug abuse and addiction in humans

There are a number of reasons why a consideration of human PFC function in drug abuse and addiction is worth briefly discussing in this review that focuses on rodent models of drug seeking. First, addiction is exclusively a human disease. Second, the prefrontal cortex plays an important role in the regulation of behaviors disrupted in addiction such as impulse control, response inhibition and executive function, and this area is massively expanded in human and non-human primates relative to rodents (Wise, 2008). Although it is difficult to make precise relationships between human and rodent PFC, it is clear that these overlapping areas are critically important as potential targets for understanding how prolonged drug use results in a loss of control over behavior.

2.1. *Response to direct effects of drug*

Intravenous cocaine delivery in short-term abstinent cocaine-addicted patients is associated with positive blood oxygen level-dependent (BOLD) responses in multiple prefrontal cortical regions, including dorsolateral prefrontal cortex (dlPFC), anterior cingulate (ACC), anterior orbital gyrus, orbitofrontal cortex (OFC), medial orbital gyrus, and frontopolar cortex (FPC) (Breiter et al., 1997; Kufahl et al., 2008, 2005; Risinger et al., 2005). These prefrontal responses may be enhanced in cocaine addicts, as intravenous methylphenidate (which cocaine addicts report as being similar to cocaine) increases metabolic responses in right medial orbital prefrontal cortex in addicted subjects, but decreases metabolism in control subjects (Volkow et al., 2005). Prefrontal responses to cocaine appear to be mediated, at least in part, by expectation of drug, as BOLD signals are significantly enhanced in lateral OFC, FPC, and ACC after expected vs. unexpected cocaine delivery (Kufahl et al., 2008). In contrast, expectation has little effect on the activation of subcortical regions, with responses in these regions mainly associated with the pharmacological effects of cocaine (Goldstein and Volkow, 2011; Kufahl et al., 2008). Prefrontal activity also appears to be associated with the perceived pleasurable effects of intravenous cocaine delivery, as BOLD signals in most regions are positively correlated with 'rush' ratings (Breiter et al., 1997). These data indicate that the effects of cocaine on PFC function in humans are related to both the liking as well as the wanting of delivered cocaine, perhaps differentiated by subregional activation.

2.2. *Effects of drug-associated cues*

Studies investigating patterns of activation in response to drug-associated stimuli typically involve exposing participants to either video or pictures of people using drugs or handling drug-associated paraphernalia. These studies have generally demonstrated that relative to controls, cocaine-addicted individuals exhibit enhanced activation in prefrontal regions following exposure to drug-associated stimuli, particularly in cingulate cortex (Kilts et al., 2004; Kuhn and Gallinat, 2011; Marhe et al., 2013; Wexler et al., 2001), left lateral OFC and right dlPFC (Bonson et al., 2002). Activation of prefrontal regions following exposure to drug cues has also been reported in nicotine (Brody et al., 2002, 2007; Kober et al., 2010b; Yalachkov et al., 2009), alcohol (Grusser et al., 2004; Heinz et al., 2007) and heroin (Li et al., 2012, 2013, 2014; Xiao et al., 2006) addicted individuals. Importantly, measures of PFC activity following cue exposure appear to have some clinical relevance (Goldstein and Volkow, 2011). For example, cue-induced PFC activity is generally positively correlated with self-reported craving in cocaine, nicotine and alcohol addicts (Bonson et al., 2002; Heinz et al., 2004; Yalachkov et al., 2009). Anterior cingulate activity during a cocaine Stroop task can predict cocaine use three months later (Marhe et al., 2013). Similarly, PFC responses to alcohol related imagery can predict drinking behavior at a three-month follow up (Grusser et al., 2004).