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Dorsal MPFC circuitry in rodent models of cocaine use: Implications for drug-addiction therapies

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Abstract

While the importance of the medial prefrontal cortex (MPFC) in cocaine addiction is well established, its precise contribution to cocaine seeking, taking, and relapse remains incompletely understood. In particular, across two different models of cocaine self-administration, pharmacological or optogenetic activation of the dorsal MPFC has been reported to sometimes *promote* and sometimes *inhibit* cocaine seeking. We highlight important methodological differences between the two experimental paradigms, and propose a framework to potentially reconcile the apparent discrepancy. We also draw parallels between these preclinical models of cocaine self-administration and human neuroimaging studies in cocaine users, and argue that both lines of evidence point to dynamic interactions between cue-reactivity processes and control processes within the dorsal MPFC circuitry. From a translational perspective, these findings underscore the importance of interventions and therapeutics targeting not just a brain region, but a specific *computational process* within that brain region, and may have implications for the design and implementation of more effective treatments for human cocaine addiction.

Keywords

Addiction; Cocaine; Medial Prefrontal Cortex; Prelimbic Cortex

Introduction

Drug addiction is a chronic and relapsing neuropsychiatric disease with staggering costs to the individual and society, for which effective, long-lasting treatments are still lacking. According to one prominent line of thinking (Bechara, 2005; Goldstein and Volkow, 2002, 2011; Jentsch and Taylor, 1999), chronic drug use produces increased reactivity to the enhanced salient drug-related cues as well as impaired ability to inhibit conditioned drug

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craving and seeking in response to such cues, both of which lead to escalated use, an inability to quit despite negative consequences, and relapse (Bechara, 2005; Goldstein and Volkow, 2002, 2011; Jentsch and Taylor, 1999). These accounts typically attribute the increased drug cue reactivity to hyperactive subcortical regions such as the ventral striatum and/or the amygdala, and the decreased control over drug use to hypoactivity in prefrontal cortical regions. Thus, addiction is postulated to stem from—and reflect—impaired prefrontal cortical control over hyperactive subcortical centers.

However, recent evidence paints a more complex and nuanced picture and suggests that both drug-cue reactivity and control over cue-induced craving and drug seeking involve the prefrontal cortex as well as extended subcortical circuits. Specifically, instead of a cortical-subcortical dissociation, growing evidence points to a central role of a dynamic functional dissociation between the dorsal and ventral portions of the medial prefrontal cortex (MPFC) in drug addiction (for reviews, see (Gass and Chandler, 2013; Peters et al., 2009)).

The aim of this review is to summarize the current understanding of the role of the dorsal MPFC in drug addiction, drawing predominantly upon the extant cocaine literature, to examine parallels between the preclinical and human research where possible, and to highlight some outstanding questions and the translational relevance of this area of research. We believe that by elucidating the contribution of the dorsal MPFC circuitry, including the cue-reactivity and control processes computed within the dorsal MPFC, these findings may ultimately inform the design and implementation of novel, more effective treatments for drug-addicted individuals. While inclusion of the structure and function of the ventral MPFC would be desirable, space limitations preclude a complete parallel analysis at this time. We do, however, include discussion of this region at various points in the review.

Molecular and cellular mechanisms of cocaine addiction

The molecular mechanism of action of cocaine is to block monoamine transporters, thus increasing extracellular transmitter levels within the synaptic cleft (Ritz et al., 1990). Although cocaine can bind to and block all three monoamine transporters, dopamine (DA) transporters are most strongly implicated in cocaine's behavioral and reinforcing effects, including cocaine self-administration (Povlock and Schenk, 1997; Ritz et al., 1987). In fact, drug-induced increases in DA neurotransmission have been postulated to be one of the shared mechanisms by which most drugs of abuse, each with distinct primary molecular targets, produce addicted behaviors (Nestler, 2005). In the mammalian brain, midbrain dopaminergic cells project widely to both cortical and subcortical regions, forming the mesocortical, mesolimbic, and nigrostriatal DA systems. These widespread dopaminergic projections provide the primary source of DA to the brain and the dynamic shift from tonic to phasic DA cell firing and transmitter release is thought to modulate brain function to signal stimulus salience of both artificial and natural reinforcers, and to enhance learning of behavioral responses towards such reinforcers (Schultz, 2010; Wise, 2006). To signal salience, DA neurons switch from an irregular single-spike firing to phasic burst-like firing, which results in increased extracellular DA in the target regions (Phillips et al., 2003; Schultz, 1998). This shift in firing mode can be modulated by descending, excitatory glutamatergic afferents (Mathon et al., 2003; White, 1996) originating from various cortical

regions ((Geisler et al., 2007); for review see (Fields et al., 2007)). Importantly, these excitatory synapses undergo different forms of synaptic plasticity. For example, reward learning (Stuber et al., 2008) and exposure to drugs of abuse (Saal et al., 2003), including cocaine (Chen et al., 2008; Ungless et al., 2001), have been shown to increase glutamate action on DA neurons. Thus, by increasing excitatory drive to dopaminergic neurons, exposure to drugs of abuse can increase DA-neuron firing and extracellular DA release, which in turn promotes drug-seeking behaviors. Adding to the complexity is the recent discovery that glutamate is also co-released (Hnasko et al., 2010) by dopaminergic projections to the nucleus accumbens (Stuber et al., 2010), although the role of this co-released glutamate remains unknown.

Drugs of abuse are postulated to hijack these DA-dependent reward-related learning processes (Hyman et al., 2006; Kalivas and O'Brien, 2008; Kelley, 2004). Indeed, studies have shown common synaptic glutamate plasticity in nucleus accumbens medium spiny neurons (Martin et al., 2006) and VTA DA neurons (Chen et al., 2008) in animals trained to self-administer either cocaine or natural rewards. In animals trained to self-administer natural rewards, these neuroadaptations were transient, lasting less than 21 days; whereas in animals trained to self-administer cocaine, changes in synaptic plasticity persisted for up to 3 months of abstinence. Moreover, in the VTA, synaptic alterations induced by cocaine use were unaffected even after drug-seeking behavior was extinguished (Chen et al 2008). This long-lasting change in synaptic glutamate plasticity supports the hypothesis that neuroadaptations induced by cocaine self-administration persist, even in the absence of drug-seeking behaviors, and may serve as powerful memories to trigger relapse.

In line with studies in the VTA, the effects of cocaine exposure on neuroplasticity in dorsal MPFC have been revealed in recent studies. In animals receiving non-contingent cocaine injections, various neuroadaptations have been observed. A significant increase in membrane excitability was observed in dissociated deep-layer PFC neurons following five daily cocaine injections (Dong et al., 2005); this increase in neuronal excitability was due in part to a reduction in voltage gated K^+ -conductance. In addition, non-contingent cocaine injections also resulted in the promotion of long-term potentiation in deep-layer PFC neurons following a brief abstinence period (Huang et al., 2007). In contrast, abstinence from cocaine injections can also lead to the loss of mGluR5-receptor mediated depolarization (Sidiropoulou et al., 2009).

Extending these studies where animals received non-contingent cocaine injections, recent studies have examined neuronal changes in dorsal MPFC neurons from animals trained to self-administer cocaine. Forced abstinence from daily cocaine self-administration induced an increase in PKA-mediated phosphorylation of cAMP response element binding protein and GluA1 in dorsal MPFC neurons (Sun et al., 2014). Moreover, by inhibiting the PKA-mediated phosphorylation during the abstinence period, the authors were able to suppress cue-induced relapse, suggesting that PKA activation may be critical in promoting cue-induced reinstatement following an abstinence period. To determine which of the many cocaine-induced neuroadaptations in the PFC that may be specifically associated with the escalation to addiction-like behaviors, two recent studies have incorporated fear-conditioning into self-administration training (see below for details of this protocol). Chen et

al. (2013) showed that in comparison to cocaine naïve rats and rats that did not exhibit addiction-like behaviors (i.e. continue to self-administer cocaine despite negative consequences), deep-layer dorsal MPFC neurons from “addictive” rats exhibited significant decreased neuronal excitability. In addition, studies from Kasanetz et al. (2013) also revealed that mGluR2/3-mediated long-term depression was suppressed exclusively in addictive-like rats. These studies highlight some of the neuroadaptations in the dorsal MPFC that are brought on by prolonged cocaine self-administration and may serve to promote compulsive addiction-like behaviors.

Thus, with repeated cocaine use, drug-induced neuroadaptations involving dopaminergic and glutamatergic signaling pathways produce a particularly robust and persistent form of learning. Through the process of Pavlovian conditioning, this heightened dopaminergic and glutamatergic response to the drug itself also generalizes to external and internal cues associated with cocaine administration (Volkow et al., 2006; Wong et al., 2006), such that, over time, cocaine-related cues acquire high motivational salience and become robust triggers of drug-seeking and drug-taking behaviors (Robinson and Berridge, 1993). In addition to conditioned discrete and contextual drug-related cues, acute re-exposure to the drug and exposure to various stressors (Sinha, 2008; Sinha et al., 2011) also induce subjective craving and the enhanced urge to use. Simultaneous with the drug-induced changes that heighten salience and motivation processes, chronic cocaine use is also believed to impair inhibitory control over cocaine seeking and taking ((e.g., (Kaufman et al., 2003); for reviews, see (Goldstein and Volkow, 2002, 2011)).

Animal models of cocaine addiction

The two defining features of cocaine addiction—propensity for relapse, and persistent use despite aversive consequences—have been studied in preclinical models using two largely distinct experimental paradigms. Propensity to relapse is typically modeled with paradigms that involve drug self-administration, followed by extinction training and a test of drug-, cue-, or stress-induced reinstatement; whereas persistent use despite negative consequences is typically modeled with paradigms that combine drug self-administration with fear conditioning. We briefly describe the main features of both paradigms below.

In animal models of reinstatement of cocaine use following extinction ((de Wit and Stewart, 1981; McFarland and Kalivas, 2001; McLaughlin and See, 2003), for a recent review, see (Bossert et al., 2013)), animals are first trained to self-administer cocaine, typically via lever presses or nose pokes for drug infusions paired with drug-associated cues. Once stable self-administration is established, animals undergo extinction training, wherein the operant response to previously cocaine-associated cues no longer results in cocaine delivery. Following extinction training, cocaine seeking is restored in the reinstatement phase by means of drug priming, drug-associated cues, or by exposure to certain stressors (e.g., an intermittent footshock or yohimbine administration).

In contrast, persistent-use animal models assess cocaine self-administration in the face of aversive consequences (Chen et al., 2013; Kasanetz et al., 2012). As in the reinstatement model, laboratory animals are trained to self-administer cocaine, typically via lever presses

or nose pokes for drug infusions in conjunction with drug-associated cues, until stable cocaine self-administration is established. But instead of extinction training, this paradigm employs fear-conditioning techniques, such as a delivery of a footshock, to identify and characterize those animals that persist in drug-seeking behaviors despite aversive consequences, as opposed to those animals that cease drug-taking. Such individual differences in rodents are thought analogous to those seen in human users demonstrating high vs. low risk of developing drug dependence following use.

Of note, there are critical methodological differences between these two paradigms, which may modify the neurobiological processes of interest. As such, we next briefly outline the MPFC circuitry in the rodent brain and then summarize the evidence for the postulated distinct roles of the dorsal and ventral MPFC circuits in cocaine seeking. We then re-examine the respective findings from the two paradigms in light of their methodological differences—in particular, the differential impact of extinction training and cocaine abstinence vis-à-vis that of cocaine self-administration paired with fear conditioning on monoaminergic neurotransmission, on the involvement of the MPFC circuitry, and on the resulting cocaine-seeking behavior.

Dorsal and ventral MPFC circuits in the rodent brain

Both dorsal and ventral MPFC circuits in the rodent brain have been implicated in cocaine addiction, but their interactions and respective contributions remain incompletely understood. A comparison of anatomical connectivity may offer some insight. Of note, the dorsal MPFC is centered on the prelimbic cortex, while the ventral MPFC is centered on the infralimbic cortex. We will use the terms “dorsal MPFC” and “ventral MPFC” when discussing animal studies (Heidbreder and Groenewegen, 2003), for consistency and for ease of comparison with human neuroimaging research. However, we acknowledge that we have simplified a more nuanced distinction made by Heidbreder and Groenewegen (2003), who group together the dorsal anterior cingulate cortex (ACC) and the *dorsal* prelimbic cortex into the dorsal MPFC, and the *ventral* prelimbic cortex and the infralimbic cortex into the ventral MPFC. In this review, the dorsal MPFC denotes the dorsal prelimbic cortex, and the ventral MPFC the infralimbic cortex.

Although reciprocally interconnected, the dorsal and ventral portions of the rodent MPFC have dissociable connectivity with a number of key regions implicated in addiction, including the nucleus accumbens (NAc), amygdala and monoaminergic brainstem nuclei (for review, see (Heidbreder and Groenewegen, 2003)). The dorsal MPFC preferentially projects to the NAc core, whereas the ventral MPFC innervates primarily the NAc shell (Brog et al., 1993; Sesack et al., 1989). Although the entire MPFC is reciprocally connected with the amygdaloid complex, the distribution and volume of each subdivision projections differs, with the ventral MPFC projecting heavily to the medial, basomedial, central, and cortical nuclei of amygdala, whereas the amygdala projections from the dorsal MPFC are sparse and target primarily the basal and lateral nuclei (Vertes, 2004). The two subregions of the MPFC also differ in their patterns of cortico-cortical connectivity. The dorsal MPFC has stronger connections with sensory and motor cortical areas, whereas the ventral MPFC is preferentially connected with association and limbic cortices. And while both subregions are

connected with the agranular insular cortex, the dorsal MPFC targets primarily the dorsal subdivision of the insula, while the ventral MPFC targets primarily the ventral subdivision of the insula.

The dorsal and ventral MPFC also differ in their connectivity and interactions with the DA, norepinephrine and serotonin brainstem monoaminergic systems (for review, see (Heidbreder and Groenewegen, 2003)). The entire MPFC is innervated by dopaminergic fibers originating from the VTA and to a lesser degree from the substantia nigra, although the ventral division receives a much denser innervation than does the dorsal MPFC. In addition, relative to the ventral MPFC, the dorsal MPFC has higher levels of expression of the DA transporter, a primary molecular target of cocaine. Similarly, although both MPFC subregions project back to the dopaminergic brainstem nuclei, the ventral MPFC projections are denser than those of the dorsal MPFC. Further, the ventral MPFC may also have stronger connectivity with the serotonergic dorsal raphe brainstem nuclei. Thus, given the profound impact of monoamines on synaptic-plasticity processes at glutamatergic synapses, such differential sensitivity to monoaminergic modulation suggests that the dorsal and ventral MPFC circuits may fundamentally differ in their response to cocaine and in the degree to which cocaine alters the learning processes within each circuit.

Taken together, these anatomical and neurochemical differences support the view that the dorsal and ventral MPFC circuits serve different functions in cocaine seeking and in reinforcement learning and goal-directed behavior more generally. We next review the behavioral evidence of the complex contribution of the dorsal MPFC to cocaine seeking in rats; the critical contribution of the ventral MPFC is briefly addressed in the final section of the review.

Role of dorsal MPFC in cocaine seeking in rats

A number of studies using drug self-administration reinstatement paradigms have suggested that the dorsal (or prelimbic) MPFC activity *promotes* cocaine seeking (e.g., (Di Pietro et al., 2006; Fuchs et al., 2005; McFarland and Kalivas, 2001; McLaughlin and See, 2003)). McFarland and Kalivas (2001) used a series of pharmacological manipulations to examine the role of the dorsal MPFC in drug-induced reinstatement to cocaine seeking following extinction training. Inactivation of the dorsal MPFC with bilateral injections of the GABA-A and GABA-B agonists (muscimol and baclofen, respectively) prior to reinstatement testing effectively blocked drug-induced reinstatement of cocaine seeking, with no change in lever presses from extinction levels of responding, compared to saline pre-treatment. Furthermore, the same pharmacological inactivation of the ventral MPFC had no effect on reinstatement to cocaine seeking, suggesting that the effects were specific to the dorsal MPFC circuitry. The authors further tested the role of DA transmission in the dorsal MPFC on reinstatement to cocaine seeking following extinction, reasoning that acute cocaine-induced increases in extracellular DA would serve to trigger reinstatement. Indeed, a blockade of DA release in the dorsal MPFC via GABA-agonist-induced inactivation of the VTA decreased the intensity of reinstatement of cocaine-seeking behaviors, whereas microinjection of DA into the dorsal MPFC was sufficient to induce reinstatement even in the absence of systemic cocaine. Convergent results were obtained with bilateral infusion of tetrodotoxin (TTX), a

sodium channel blocker, into the two MPFC subregions on cue-induced reinstatement (Fuchs et al., 2005; McLaughlin and See, 2003). TTX inactivation of the dorsal MPFC attenuated both discrete-cue-induced (McLaughlin and See, 2003) and context-induced (Fuchs et al., 2005) reinstatement of lever-pressing, whereas TTX inactivation of the ventral MPFC had no effect on reinstatement behavior. These studies support the idea that the dorsal MPFC *promotes* relapse to cocaine-seeking following extinction, although null effects of dorsal MPFC manipulation have also been reported (Peters et al., 2008b).

Cocaine-reinstatement studies also support the involvement of the ventral (infralimbic) MPFC in regulating cocaine seeking (e.g., (Peters et al., 2008a; Peters et al., 2008b)), although again null effects have also been reported (e.g., (Fuchs et al., 2005; McLaughlin and See, 2003)). In particular, a series of studies from the Kalivas lab showed that inactivation of the ventral MPFC with GABA agonists following extinction abolished extinction learning and reinstated cocaine seeking in response to small doses of cocaine (Peters et al., 2008a) and to contextual cues (Peters et al., 2008b), whereas activation of this region with glutamate agonist following extinction suppressed cocaine-induced reinstatement (Peters et al., 2008a). Extending the analyses to the circuit level, the authors showed that the reinstatement of cocaine seeking induced by ventral MPFC inactivation required activity in the dorsal MPFC, such that inactivation of the dorsal MPFC prior to the inactivation of the ventral MPFC reduced level-pressing for cocaine relative to the inactivation of the dorsal MPFC alone (Peters et al., 2008a). Based on these findings, Peters and colleagues (Peters et al., 2009) proposed a model whereby the ventral MPFC exerts inhibitory control over drug seeking following extinction in part by inhibiting the dorsal MPFC, which would also indirectly modulate the activity in specific subregions of the amygdala and NAc. According to this model, the dorsal MPFC *promotes* cocaine seeking, whereas the ventral MPFC *inhibits* cocaine seeking, following extinction of cocaine self-administration (Peters et al., 2009).

However, equally compelling evidence suggests that the dorsal MPFC can *suppress* cocaine seeking in rats, at least under some conditions. For example, Chen and colleagues (Chen et al., 2013) employed a paradigm in which rats first underwent extended cocaine self-administration training, followed by aversive footshock on approximately one-third of drug-infusion trials. A subgroup of animals that continued to compulsively self-administer cocaine despite the punishment were considered “shock-resistant” or addicted-like; whereas lever-pressing for cocaine was virtually eliminated by fear conditioning in the majority of the animals (considered “shock-sensitive” or non-addicted-like). Thus, in contrast to reinstatement paradigms, this fear-conditioning paradigm involved no extinction training and no period of cocaine abstinence. Chen and colleagues (2013) then employed electrophysiology and optogenetic manipulations to assess the role of the dorsal MPFC in the maintenance of cocaine seeking despite punishment. These experiments demonstrated that prolonged cocaine self-administration was associated with reduced excitability in dorsal MPFC pyramidal neurons, that this reduction was more profound in shock-resistant (or addicted-like) rats than in shock-sensitive rats, and that it positively correlated with cocaine intake under shock. In an attempt to rescue this reduced excitability, channel-rhodopsin and photostimulation delivered via optic fiber was used to stimulate the dorsal MPFC before and

after the shock sessions. While the optogenetic stimulation of the dorsal MPFC *prior to* fear conditioning did not alter baseline cocaine seeking, stimulation *after* fear conditioning significantly reduced cocaine seeking in shock-resistant animals. In contrast, the opposite manipulation of optogenetic inhibition of bilateral dorsal MPFC with halo-rhodopsin induced cocaine seeking in shock-sensitive rats that were otherwise deterred by the punishment—again only *after* the shock treatment, with no effect on baseline cocaine seeking *prior to* fear conditioning (Chen et al., 2013).

Apparent conflicting findings of MPFC involvement in cocaine addiction

The evidence reviewed above points to an outstanding question: How to account for these apparently contradictory findings about the role of the dorsal MPFC in cocaine seeking? In particular, why does the dorsal MPFC appear to promote cocaine seeking in some studies and to suppress cocaine seeking in others? We argue below that key methodological differences between the two main experimental paradigms can lend insight into the question.

Reinstatement models involve extinction training as well as cocaine abstinence, and the MPFC manipulations are typically performed following such manipulations, generally after the effects of cocaine have ceased. This timing has potentially important consequences for neural activity in dorsal MPFC circuits, because subsequent MPFC manipulations in these protocols occur when DA neurotransmission is at normal or even reduced levels. Of note, extinction training appears to be a more decisive causal factor than simple abstinence, since rats that undergo abstinence without extinction do not demonstrate the same effects of dorsal MPFC manipulations on cocaine seeking (Fuchs et al., 2006). In contrast, in studies that combine cocaine self-administration with fear conditioning, MPFC function is manipulated in the course of cocaine delivery when DA neurotransmission is augmented to supra-physiological levels by the continued action of cocaine. In addition, the anticipation and delivery of aversive shocks also engages other modulatory neurotransmitters, further altering the activity and interactions of the dorsal and ventral MPFC circuitry.

One recent study using a hybrid design that combines features of both paradigms provides at least partial support for this hypothesis. Mihindou and colleagues (Mihindou et al., 2013) trained rats to self-administer cocaine and then delivered a discriminative stimulus signaling the absence of cocaine reinforcement (DS-) instead of the more traditional extinction training. One feature that made it a hybrid paradigm was that the DS- consisted of turning on the house lights in the otherwise dark operant chamber (all the behavioral testing was conducted during the dark phase), which would be expected to act as at least a mild stressor, perhaps akin to a low-intensity but nevertheless aversive footshock. Another critical hybrid feature was that lever responding continued to be reinforced with cocaine infusions at the beginning of each daily session—before the onset of the non-reinforced DS- period, which served as inhibitory-control training (equivalent to extinction training). In consequence, and critically, the DS- training occurred *in the presence of cocaine*. Thus, in contrast to reinstatement paradigms—but akin to fear-conditioning paradigms—the extinction-like inhibitory training to suppress cocaine seeking occurred *during cocaine-induced increases in DA neurotransmission* (and possibly during stressor-induced increases in other neurotransmitter systems). To assess the role of the MPFC in this DS-triggered inhibitory

control over cocaine seeking, bilateral infusions of the GABA-A receptor agonist muscimol were delivered into either the dorsal or ventral MPFC prior to a test of cocaine-induced reinstatement, with the DS- either on or off. The results demonstrated that inactivation of dorsal MPFC abolished the inhibitory effects of DS- on cocaine seeking, whereas inactivation of ventral MPFC had no effect on DS-cued inhibitory control over lever pressing for cocaine. Thus, these results are in line with the study by Chen and colleagues (2013), which found that dorsal MPFC activity contributed to such suppression, and are less consistent with traditional cocaine-reinstatement studies (e.g., (Di Pietro et al., 2006; Fuchs et al., 2005; McFarland and Kalivas, 2001; McLaughlin and See, 2003)), in which dorsal MPFC activity promoted cocaine seeking following extinction training.

These data suggest a tentative interpretation of the role of the dorsal MPFC in regulating cocaine seeking following some form of inhibitory training (whether extinction, fear conditioning, or a hybrid of the two). The dorsal MPFC has been postulated to play a critical role in integrating salience and control processes to guide decision making in a dynamically changing environment (for a recent review, see (Shackman et al., 2011)). In the present context, the dorsal MPFC is engaged when there is a conflict between two competing response tendencies associated with a given stimulus. We postulate that, in case of such conflict, activity in the dorsal MPFC will promote the execution of the strongest—whether best previously learned or most currently motivated—behavioral response at the expense of a less well learned or less motivated response. Since cocaine-induced DA increases are known to enhance learning, whatever behavioral response is learned while in the presence of cocaine is likely to be the strongest of the competing responses. In most experimental paradigms, it is the *cocaine-seeking response* that is learned in this fashion. However, in paradigms that combine cocaine self-administration with fear conditioning—and including the hybrid aversive-inhibitory-cue paradigm employed by Mihindou et al. (2013)—it is the *suppression of cocaine-seeking responses* that is learned while under cocaine's influence (and possibly under synergistic enhancing effects due to stressor-related activation of other modulatory neurotransmitter systems, further potentiating the learning process). Therefore, stimulation of the dorsal MPFC can be expected to *induce* reinstatement to cocaine seeking following extinction training in reinstatement paradigms—conversely, stimulation of the dorsal MPFC is likely to *inhibit* cocaine seeking in fear-conditioning paradigms.

Comparison between preclinical and human neuroimaging studies of cocaine use

Of course, the ultimate goal of animal models of drug use is to elucidate the neurobiological mechanisms of human drug addiction, enabling translation of this knowledge to the design and selection of novel, more effective treatments and prevention strategies in humans. It is therefore critical to examine—and reexamine—how growing understanding of the brain circuits and processes involved in drug addiction gained from preclinical studies relates to the accumulating evidence from human-subject research, with the expectation that cross-species concordance may signal fruitful targets for clinical interventions.

Admittedly, a comparison of human and rodent studies in this context is complicated by at least two considerations. While the imperfect and incompletely understood anatomical

homologies between human and rodent MPFC circuitries have led some to question whether rodents even have a prefrontal cortex, and while the proportion of granular to agranular cortex varies greatly across species (e.g., the rat prefrontal cortex is exclusively agranular), nevertheless, there are sufficient similarities in prefrontal connections, in the relative positional relationships between these regions, in their connections with subcortical nuclei (notably mediodorsal thalamus, striatum and brainstem), and in their function across the species, as assessed with lesion and electrophysiological studies, that most investigators have now accepted that the MPFC is relatively comparable across species (for reviews, see (Ongür and Price, 2000; Perry et al., 2011; Seamans et al., 2008; Uylings et al., 2003)).

A second critique is the considerable methodological differences that necessarily exist between typical human and rodent study designs. However, while neuroimaging techniques, notably functional magnetic resonance imaging (fMRI), have their own interpretive neurobiological limitations (for reviews, see (Bartels et al., 2008; Logothetis, 2002, 2008)), they nevertheless reflect changes in neuronal activity (albeit via a still poorly understood hemodynamic filter). As such, the human neuroimaging studies discussed collectively support the dynamic roles of MPFC subregions in cocaine addiction observed in preclinical models and highlight implications of these findings for translation to therapeutics.

Dual role of human dorsal MPFC in cue-reactivity and control processes

In human cocaine users, exposure to cocaine-associated cues produces intense psychological craving and physiological arousal that mirror those produced by cocaine itself (Childress et al., 1988). Cue-induced craving is also a predictor of relapse to cocaine use following treatment (Weiss et al., 2003). Reactivity to drug-related cues in drug users has been investigated with both fMRI and positron emission tomography (PET) (for reviews, see (Goldstein and Volkow, 2002, 2011; Jasinska et al., 2013; Sinha and Li, 2007; Volkow et al., 2003; Yalachkov et al., 2012)). Cocaine-cue reactivity studies consistently demonstrate that the dorsal MPFC, encompassing the dorsal ACC, is one of the key brain regions that increase in activity in response to specific cocaine-related cues (e.g., (Garavan et al., 2000; Kilts et al., 2004; Kilts et al., 2001; Wexler et al., 2001)). A recent meta-analysis (Kühn and Gallinat, 2011) confirmed cocaine cue activation not only in the dorsal ACC, but also other regions including ventral MPFC/orbitofrontal cortex, insula, dorsolateral PFC, parietal cortex, amygdala, and ventral and dorsal striatum. The dorsal ACC is also activated by acute intravenous cocaine in cocaine users (Breiter et al., 1997). In addition, cocaine-cue reactivity in the dorsal MPFC is associated with treatment outcome and risk of relapse. A greater dorsal ACC activation related to attentional bias to cocaine-related cues at the start of drug detoxification was predictive of higher cocaine use at 3-month follow-up (Marhe et al., 2013).

These neuroimaging studies suggest that dorsal MPFC response to cocaine cues may serve to *promote* cocaine seeking in cocaine users. These findings are in agreement with the pattern of results from preclinical models of cocaine reinstatement. Namely, when dorsal MPFC activity is dominated by cue-reactivity processes (which reflect the learned associations between drug cues, and drug seeking and drug taking), inactivation or impaired

response of dorsal MPFC *reduces* cocaine seeking and risk of relapse, whereas activation or enhanced response of dorsal MPFC *increases* cocaine seeking and risk of relapse.

In addition to increased cue reactivity, chronic use of cocaine and cocaine dependence are also associated with cognitive deficits, including impaired cognitive-control performance (for reviews, see (Aron and Paulus, 2007; Crunelle et al., 2012; Garavan and Hester, 2007)). Cognitive control processes are typically engaged when a prepotent, stimulus-driven or habitual response has to be overridden in the service of an alternative option. Compared to non-using controls, cocaine-dependent individuals perform worse on tasks measuring response inhibition and conflict resolution (e.g., (Kaufman et al., 2003)). As with drug-cue reactivity, there is also growing evidence that greater deficits in cognitive control are associated with higher risk of relapse to cocaine following treatment. The most commonly used cognitive-control tasks include the Go/NoGo, Stop-Signal, and Stroop tasks.

In fMRI studies of response inhibition, active chronic cocaine users display *reduced* activation in the dorsal ACC, extending into the dorsal MPFC, during successful inhibition as well as during commission errors, relative to non-using controls (Hester and Garavan, 2004; Kaufman et al., 2003). In both studies, non-users performed significantly better than cocaine users. Similarly, an fMRI study using a drug-related version of the Stroop task (indicating the print color of drug-related or neutral words) found that current cocaine users had a *reduced* response in the caudal-dorsal ACC when performing the task on both drug-related and neutral trials, compared to non-using controls (Goldstein et al., 2009). Furthermore, the magnitude of task-related activation in the dorsal ACC was negatively correlated with amount of recent cocaine use, such that users reporting more frequent cocaine use in the past 30 days also displayed a lower dorsal ACC response when performing the task (Goldstein et al., 2009).

In contrast, those cocaine users in treatment studies who succeeded in staying abstinent for a prolonged period of time (40–102 weeks) showed an *enhanced* dorsal ACC/dorsal MPFC response during commission errors compared to non-using controls, although in the absence of significant group differences in task performance (Connolly et al., 2012). As might be expected, recently abstinent cocaine users (minimum of 3 days) showed an *enhanced* activation in the dorsal ACC/dorsal MPFC during a multi-sensory (visual and auditory) Stroop task compared to non-using controls, again with no significant differences in task performance between the groups (Mayer et al., 2013). A decreased dorsal ACC response during cognitive-control tasks in cocaine users has also been shown to predict treatment outcome and relapse. In a large prospective study of cocaine-dependent individuals seeking treatment, lower dorsal ACC response to error trials in the Stop-Signal task was predictive of an earlier time to relapse (Luo et al., 2013).

Thus, human neuroimaging studies suggest that dorsal ACC/ dorsal MPFC processes engaged during cognitive-control tasks may also be engaged when *suppressing* cocaine seeking. We postulate that these findings mirror the pattern of results obtained in preclinical studies combining cocaine self-administration and fear conditioning. In this case, when dorsal MPFC activity is dominated by inhibitory-control processes (which reflect, for instance, a learned association between drug cues and aversive footshock), inactivation or

impaired response of dorsal MPFC *aggravates* cocaine seeking and risk of relapse, whereas activation or enhanced response of dorsal MPFC *suppresses* cocaine seeking and risk of relapse.

It should be emphasized that while it has been traditionally assumed that addiction-related dysregulation of psychological processes (e.g., reward, emotional, cognitive operations) is attributable to activity *within* circumscribed brain regions, an emergent view regards such dysregulation as also a function of aberrant interactions *between* distributed regions (Koob and Volkow, 2010; Sutherland et al., 2012). One of the most powerful tools to examine such large-scale brain networks is resting state functional connectivity, which is providing a more complete and coherent framework to appreciate the neurobiological underpinnings of multifaceted neuropsychiatric disorders like drug addiction. And while a discussion of brain networks goes beyond the mandate of this review, it is noteworthy that many of the regions discussed are key components of brain networks implicated in addiction. Specifically, the salience network (SN), including dorsal ACC and insula, is thought to causally influence the relative activity of two opposing networks subserving internal (default-mode network: DMN, anchored by the medial PFC, along with the posterior cingulate and parahippocampal gyrus) and external (executive control network: ECN, composed of lateral parietal and prefrontal cortex) information processing (Fox et al., 2005; Hamilton et al., 2011; Menon, 2011b; Seeley et al., 2007; Sridharan et al., 2008). An extensive review of brain networks and drug addiction has recently appeared (Sutherland et al., 2012).

Implications for treatment and prevention strategies for human drug addiction

Currently available interventions for cocaine addiction have shown only limited efficacy. The findings reviewed above, and the hypothesized dual function of the dorsal MPFC circuitry in cocaine seeking, may have implications for development of more effective treatment and prevention strategies for cocaine addiction, and may generalize to the treatment and prevention of other substance use disorders.

The view that one brain region serves to promote a given behavior, and another region serves to suppress this behavior, always and under all conditions, is very likely overly simplistic. Instead, the evidence reviewed above suggests that a given region (and its associated circuitry) may differentially participate in promoting a given behavior in some conditions, and in suppressing that behavior in other conditions. In this case, dorsal MPFC activation in reinstatement tests in animals and cue-reactivity protocols in humans reflect conditioned cue-response associations and serve to promote cue-induced drug seeking and relapse; whereas activation of the same region after drug cues have acquired aversive salience may participate in conditioned-fear processing and serve to suppress such cue-elicited drug seeking and relapse.

If this hypothesis is supported by experimental evidence, then it may not be sufficient for an intervention to target a given brain region—but instead, an effective intervention would need to target *a specific computational process within that brain region and related circuitry*.

How can we target—and either enhance or suppress—a specific computational process to combat drug addiction? Building on previous theoretical and experimental work (for reviews, see (Barr et al., 2011; Feil and Zangen, 2010; Gass and Chandler, 2013; Kalivas and Volkow, 2011; Mariani and Levin, 2012; Taylor et al., 2009), we postulate that such interventions would require an integrative approach combining a behavioral intervention (e.g., cognitive-behavioral training) with brain stimulation and/or a pharmacological manipulation, all of which have individually shown both promise and limitations in treating various neuropsychiatric disorders, including drug addiction.

The goal of such process-targeting interventions for drug addiction would be twofold: on the one hand, to weaken or extinguish the computational processes underlying cue- and stressor-elicited drug seeking; and on the other hand, to strengthen or restore the processes underlying a suppression of such conditioned drug-seeking behaviors. Cue presentations and/or cognitive-control tasks could be used to engage the processes of interest; and a simultaneous application of brain-stimulation techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and/or pharmacological agents could then be employed to weaken or strengthen the given process and behavioral outcome. For instance, a cue-reactivity process could be engaged with the presentation of multisensory and personalized drug-related cues, and then weakened with a simultaneous application of inhibitory TMS. Similarly, a cognitive-control process could be activated with a craving-regulation task or with delivery of drug cues accompanied by aversive stimulation, and this cognitive-control process could then potentially be strengthened with a simultaneous administration of a psychostimulant such as methylphenidate. In both cases, the intervention would involve activating the process of interest, and then modulating or transforming this process in the desired manner. Furthermore, all components of the intervention might be optimized for different stages and levels of severity of the disease, and possibly even personalized to individual patients, based on knowledge about the molecular, cellular, and network mechanisms of drug addiction.

Outstanding questions and potential future directions

Additional research is required to address the many remaining outstanding questions, including: What are the mechanisms underlying the apparent dual function of the dorsal MPFC in cocaine addiction? Are there two distinct processes involved, one process underlying cue reactivity and promoting drug seeking and drug taking, and another process underlying inhibitory control over such cue-induced drug-seeking and drug-taking behaviors? Or is it a unitary process that can lead to different behavioral outcomes depending on specific external and internal factors, including prior learning, current motivational state, and compensatory network or circuit activity? A dual-process account allows for a competition between the two processes, which arguably can and do co-occur (e.g., a cocaine user experiencing cue-induced craving and desire to use but refraining from acting on this desire). Answers to these questions will also depend on the definition of a “process” and the level of analysis (e.g., network, region, synapse) employed.

Another critical question for future research pertains to the contribution of the ventral MPFC and its relationship with the dorsal MPFC to cocaine addiction. Although we focused

primarily on the dorsal MPFC, rich and compelling evidence also supports a key role of the ventral MPFC in cocaine seeking (e.g., (Peters et al., 2008a; Peters et al., 2008b), although see (Fuchs et al., 2005; McLaughlin and See, 2003)). In particular, the ventral MPFC, partially overlapping with the orbitofrontal cortex (OFC), is believed to play a key role in integrating sensory inputs, reward values, and homeostatic signals about the current state and needs of the organism in order to guide motivated behavior, and dysfunction of OFC/ventral MPFC has been implicated in maladaptive decision-making in cocaine addiction (for reviews, see (Lucantonio et al., 2012; Schoenbaum and Shaham, 2008)).

Similarly, we focused on one brain region (the dorsal MPFC) but a network perspective is likely to be more informative. Indeed, recent theories of the functions of and dysregulations within and between large-scale brain networks have been posited to reflect many neuropsychiatric disorders (Menon, 2011a), including addiction (Sutherland et al., 2012). Further, the dorsal MPFC and dACC together with the anterior insula are thought to be key components of a so-called Salience Network, thought to be involved in network switching based on current physiological needs, while the ventral MPFC is a key component of the Default Mode Network, thought to be involved in introspection, ruminations and mental time travel. In this context, what are the respective roles of the extended dorsal and ventral MPFC circuitries, as well as their dynamic interactions, in both drug seeking and control over drug seeking? What is the contribution of monoaminergic neuromodulators such as DA, serotonin, and noradrenaline, which both modulate, and are modulated by, the MPFC?

And finally, do the drug-use-promoting and drug-use-inhibiting mechanisms within the MPFC generalize to other drugs of abuse and/or other compulsivity disorders (e.g., gambling and eating disorders)? Or is it more likely that different classes of drugs, with different primary molecular targets, involve different, perhaps even reversed, mechanisms, as has been suggested for psychostimulants such as cocaine as compared with opiates such as heroin (Badiani et al., 2011; Peters et al., 2013)? Experiments designed to address these and other questions will not only add to our understanding of the underlying neurobiology but may also suggest novel targets and approaches in the treatment and prevention of drug addiction.

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