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Emerging role for the medial prefrontal cortex in alcohol-seeking behaviors

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HIGHLIGHTS

- Studies investigating the role of the mPFC in alcohol-seeking are discussed.
- Short- vs long-term alcohol use has differential effects on the mPFC.
- Role of mPFC in non-dependent vs dependent preclinical alcohol models are compared.
- Rationale for future studies into the role of the mPFC in dependence are proposed.

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ABSTRACT

The medial prefrontal cortex (mPFC) plays an important role in high-order executive processes and sends highly organized projections to sub-cortical regions controlling mood, motivation and impulsivity. Recent preclinical and clinical studies have demonstrated alcohol-induced effects on the activity and composition of the PFC which are implicated in associative learning processes and may disrupt executive control over impulsivity, leading to an inability to self-limit alcohol intake. Animal studies have begun to dissect the role of the mPFC circuitry in alcohol-seeking behavior and withdrawal, and have identified a key role for projections to sub-cortical sites including the extended amygdala and the nucleus accumbens (NAc). Importantly, these studies have highlighted that alcohol can have contrasting effects on the mPFC compared to other addictive substances and also produce differential effects on the structure and activity of the mPFC following short-term versus long-term consumption. Because of these differences, how the mPFC influences the initial aspects of alcohol-seeking behavior and how we can better understand the long-term effects of alcohol use on the activity and connectivity of the mPFC need to be considered. Given the lack of preclinical data from long-term drinking models, an increased focus should be directed towards identifying how long-term alcohol use changes the mPFC, in order to provide new insights into the mechanisms underlying the transition to dependence.

The development of alcohol use disorders (AUDs) is a progressive cycle that often involves extended periods of heavy alcohol use (Koob, 2013). Long-term alcohol consumption facilitates adaptations in several neurochemical signalling pathways which are thought to underlie the behavioral features of dependence, including the emergence of negative withdrawal states and compulsive drinking (Koob, 2013; Koob & Volkow, 2010). AUD patients often present with long histories of alcohol use and exhibit heightened responses to alcohol associated cues (Grusser et al., 2004; Myrick et al., 2004), which has been linked to prefrontal cortex (PFC) activation (Goldstein & Volkow, 2011). Results from human brain imaging studies have also demonstrated changes in PFC composition and functionality in those addicted to alcohol, including reduction in PFC gray matter (Chanraud et al., 2007; Fein et al., 2002), decreased dopamine responses (Volkow et al., 2007) and reduced dopamine transmission in the medial PFC (mPFC) (Narendran et al., 2014). These changes can result in deficits in working memory, decision making and executive control (Goldstein & Volkow, 2011). The contribution of the mPFC to the development of AUDs is thought to result from cognitive dysfunction and impairment of executive functions which together, facilitate compulsive drinking, despite negative consequences (Goldstein & Volkow, 2011; Koob, 2013).

Animal studies have recently been used to investigate and uncover the contribution of the mPFC to alcohol-seeking behaviors. By utilizing operant-conditioning paradigms that initiate alcohol-seeking behavior, rodents can be trained to lever press or nose poke to receive an alcohol reward, following the presentation of a cue, that generally consists of a light or tone being activated to signal reward availability (Lynch, Nicholson, Dance, Morgan, & Foley, 2010). Following a conditioning period, where stable levels of alcohol self-administration are maintained, extinction training where conditioned responding no longer

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results in alcohol delivery and cue-induced reinstatement in which cues previously associated with alcohol reward are presented, can then be used to study alcohol-seeking behaviors. Using these methods, studies have shown that mPFC projections to the nucleus accumbens (NAc) are involved in the formation of paired alcohol-cue associations (Dayas, Liu, Simms, & Weiss, 2007; Keistler et al., 2017) and that ablation of mPFC neurons projecting to the NAc significantly reduces cue-induced reinstatement for alcohol (Keistler et al., 2017). Similarly, in humans, presentation of alcohol-associated cues has been shown to activate the PFC (Grusser et al., 2004; Myrick et al., 2004). Interestingly, this neural circuitry has also been widely implicated in cue-induced reinstatement of cocaine (Kalivas, 2004). This well-established glutamatergic pathway contributes to cocaine-seeking behavior and is activated during reinstatement of a cocaine-paired stimulus, which facilitates PFC mediated glutamate release in the NAc core (McFarland, Lapish, & Kalivas, 2003). Although the precise cellular and synaptic mechanisms involved in paired alcohol-cue associations have not yet been determined, it is conceivable that glutamatergic signalling between the mPFC and NAc is an important factor contributing to cue-induced reinstatement of alcohol-seeking behavior and may contribute to the high incidence of relapse amongst AUD patients.

Studies have also revealed the contribution of the mPFC to the extinction of alcohol-seeking behavior. It has been proposed that extinction behavior manifests as a form of inhibitory learning during the absence of drug-reward, which supersedes previously paired drug-associations and reduces drug-seeking behavior over time (Gass & Chandler, 2013). Previous investigations have shown that connections between the hypothalamus, amygdala and the NAc shell are a critical component of the neural circuitry involved in the extinction of alcohol-seeking behavior (Millan, Furlong, & McNally, 2010; Millan & McNally, 2011). In more recent studies that build upon results obtained for fear-extinction and extinction to cocaine-seeking, various subregions of the PFC have been identified as important contributors to extinction learning for alcohol. In particular, the infralimbic subregion of the mPFC, which innervates the medial shell portion of the NAc as well as the amygdala, hypothalamus and midbrain dopamine regions, has been shown to be activated during extinction of alcohol-seeking behavior and enhance extinction learning via mGlu5 receptors (Cannady et al., 2017; Gass et al., 2014). Although inactivation of the infralimbic mPFC was previously shown to inhibit extinction learning and reinstate cocaine-seeking and fear, this does not appear to be the case for alcohol-extinction or reinstatement (Keistler et al., 2017; Meinhardt et al., 2013; Willcocks & McNally, 2013). Moreover, it was recently reported that inactivation of the prelimbic subregion of the mPFC had no effect on alcohol self-administration or cue-induced reinstatement (Pfarr et al., 2015). This work is in contrast to reports that have noted opposing roles with respect to the prelimbic and infralimbic subdivisions of the mPFC in fear and stress paradigms, with previous studies showing that activation of the prelimbic mPFC can enhance fear and acute stress responses, while infralimbic mPFC activity is critical for fear-extinction and the attenuation of acute stressor effects (Radley, Arias, & Sawchenko, 2006; Sotres-Bayon & Quirk, 2010). The dichotomous relationship of the prelimbic and infralimbic mPFC in drug-extinction has also been reported for other addictive substances including heroin and cocaine (Peters, Kalivas, & Quirk, 2009).

The basolateral amygdala (BLA) is another important brain region involved in associative learning paradigms including fear-conditioning and extinction (Pape & Pare, 2010). Additionally, the BLA plays a pivotal role in assigning incentive value to rewarding stimuli (Wassum & Izquierdo, 2015) and to the development of associations that pair drug-taking to environmental contexts (Crombag, Bossert, Koya, & Shaham, 2008). The BLA receives sensory input in the form of glutamatergic afferents from the cortex and hypothalamus (McDonald, 1998; Sah, Faber, Lopez De Armentia, & Power, 2003). Studies have revealed that glutamate signalling in the BLA, contributes to cue- and context-induced reinstatement of alcohol-seeking behavior (Gass, Sinclair, Cleva, Widholm, & Olive, 2011; Sciascia, Reese, Janak, & Chaudhri, 2015; Sinclair, Cleva, Hood, Olive, & Gass, 2012). Despite the lack of studies specifically investigating the role of connections between the mPFC and the BLA in alcohol-seeking behavior, a recent report concluded that this pathway does not contribute to alcohol-extinction or reinstatement (Keistler et al., 2017). This result is somewhat surprising given that previous reports suggest significant overlap between brain circuitry involved in extinction of learned fear and drug-extinction (Gass & Chandler, 2013; Peters et al., 2009). Nonetheless, these insights have identified specific contributions of mPFC with respect to alcohol-seeking behavior and have uncovered differential responses compared to other addictive substances.

One possible explanation for the differences in alcohol-induced effects on the mPFC compared to other addictive substances is that the length of consumption plays a critical role in driving the adaptive changes to alcohol (Feduccia, Simms, Mill, Yi, & Bartlett, 2014; Patkar et al., 2017; Steensland, Simms, Holgate, Richards, & Bartlett, 2007), Recently, it has been shown that acute or short-term alcohol exposure has differential effects on the structure and function of mPFC neurons compared to long-term consumption. For example, application of ethanol in the millimolar range (22 mM–100 mM) has been shown to reduce mPFC pyramidal neuronal activity and reduce NMDA-mediated post-synaptic currents (Tu et al., 2007; Weitlauf & Woodward, 2008), while chronic intermittent ethanol (CIE) exposure and long-term, binge-like alcohol consumption enhances excitatory post-synaptic currents in mPFC neurons (Klenowski et al., 2016; Kroener et al., 2012). Furthermore, prolonged alcohol consumption produces a significantly greater level of dendritic restructuring in mPFC pyramidal neurons compared to short-term intake (Holmes et al., 2012; Kim, Zamora-Martinez, Edwards, & Mandyam, 2015; Klenowski et al., 2016; Kroener et al., 2012). This suggests that significant differences are likely to arise in the contribution of the mPFC circuit to alcohol-seeking behavior following acute or short-term alcohol exposure compared to long-term consumption and in models of alcohol dependence. These factors should be considered in future studies aimed at uncovering the role of the mPFC in alcohol-seeking behavior following prolonged alcohol use and determining changes in the functional connectivity of the mPFC that are involved in the transition to dependence.

Glutamatergic dysfunction and hyperactivity of limbic inputs to the mPFC have been proposed as mechanisms that underlie the behavioral effects of compulsive drug-seeking (Bechara, 2005; Pfarr et al., 2015). Although a previous study found that no effect extinction or reinstatement of alcohol seeking occurred following ablation of mPFC projections to the BLA, a long-term study by George et al. (2012) has implicated dysfunction between the mPFC and the central amygdala (CeA), following an extended period of binge-like ethanol consumption. Although neuronal projections between the mPFC and the CeA were not specifically manipulated, results showed significant differences in the correlation between cfos expression (a marker of neuronal activation) in the mPFC and CeA, and deficits in working memory during withdrawal (George et al., 2012). While previous studies have demonstrated significant differences in PFC structure and function in alcohol dependence, including enhanced responses to alcohol associated cues (Grusser et al., 2004; Myrick et al., 2004), it remains unclear to what extent the effects of extended periods of heavy alcohol use may have on the reciprocal connections between the mPFC and other limbic brain areas, due to the lack of data from long-term animal drinking models and studies that have pharmacologically or genetically manipulated this brain circuitry.

The mPFC receives a high level of dopaminergic input from the ventral tegmental area (Bjorklund, Divac, & Lindvall, 1978; Emson & Koob, 1978). Human brain imaging has revealed decreased dopamine responses (Volkow et al., 2007) and reduced dopamine transmission in the mPFC of AUD patients (Narendran et al., 2014). Conflicting reports have shown both excitatory and inhibitory effects of dopamine on mPFC pyramidal cell activity (Gulledge & Jaffe, 1998;