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Orbitofrontal Cortex in Alcohol Dependence: A Disrupted Cognitive Map?

Chloe N. Shields, M.A.[1], **Christina M. Gremel, Ph.D.**[1,2]

[1]Department of Psychology, University of California San Diego, La Jolla, CA 92093, USA

[2]The Neurosciences Graduate Program, University of California San Diego, La Jolla, CA 92093, USA

Abstract

Alcoholism is a persistent worldwide problem associated with long-lasting impairments to decision-making processes. Some aspects of dysfunction are thought to reflect alcohol-induced changes to relevant brain areas such as the orbitofrontal cortex (OFC). In this review, we will examine how chronic alcohol exposure alters OFC function to potentially contribute to maladaptive decision-making, and explore experimental behavioral approaches that may be better suited to test whether alcohol dependence disrupts OFC's function. We argue that although past works suggest impairments in aspects of OFC function, more information may be gained by specifically targeting tasks to the broader function of OFC as put forth by the recent hypothesis of OFC as a "cognitive map" of task space. Overall, we suggest that such a focus could provide a better understanding of how OFC function changes in alcohol dependence, and could inform better assessment tools and treatment options for clinicians working with this population.

Keywords

Orbitofrontal cortex; alcohol dependence; decision-making; cognitive map; goal-directed

The Orbitofrontal Cortex

Deficits in decision-making are seen in alcohol dependence and use disorders, and likely contribute to continuing alcohol use and relapse. However, the basic behavioral and neural mechanisms underlying this dysfunctional decision-making are not altogether clear. A growing body of evidence suggests the observed dysfunction may in part reflect alcohol-induced changes to the orbitofrontal cortex (OFC), a region integral to decision-making. Here we review the current state of OFC's role in supporting decision-making and provide an overview of the existing evidence for disrupted OFC function in alcohol dependence. Based on the recent cognitive map hypothesis of OFC function, we propose that alcohol dependence may affect OFC's contribution to inference-based decision making (Figure 1). As prolonged exposure to alcohol alters OFC function, conceptualizing and examining OFC

Correspondence: Christina M. Gremel, University of California San Diego, 9500 Gilman Drive, Mail Code 0109, La Jolla, CA 92093-0109, Phone: 858-594-8933, Fax: 858-534-7190, cgremel@ucsd.edu.

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according to the cognitive map hypothesis may be more informative and increase our understanding of how alcohol dependence disrupts OFC-dependent decision-making. Overall, we argue that an increased understanding of how alcohol dependence disrupts OFC function in the context of the most up-to-date theories is crucial to better inform potential therapeutic approaches in the clinical treatment of alcohol use disorder.

OFC Function

In general, the cortical and subcortical connections of OFC suggest the area is well-positioned to contribute to ongoing decision-making by integrating sensory information with learning and motivational processes (for an in-depth review of OFC anatomy, see Kringelbach and Rolls, 2004). Recent works showing similar patterns of afferent and efferent connectivity across rodents and primates support this general function of OFC and suggest reasonable homology between species (Heilbronner et al., 2016; Hunnicutt et al., 2016). However, OFC's contribution to decision-making has long been debated, leading to numerous theories over time (for review, see Stalnaker et al., 2015). One of the earlier dominant theories of OFC function was response inhibition, often operationalized in reversal learning tasks where subjects should alter behavior following the reversal of a previously-learned association between a reward and a cue or response. Indeed, OFC lesions often impair performance on reversal learning tasks (e.g., Dias et al., 1996a; Jones and Mishkin, 1972; Rolls et al., 1994; Teitelbaum, 1964), with the interpretation that OFC-lesioned subjects were unable to inhibit the now-incorrect response (Dias et al., 1996a; Jones and Mishkin, 1972). Another classic task impaired by OFC damage is reinforcer devaluation, where an outcome (e.g., food) is devalued with selective satiation or paired illness. In Pavlovian and instrumental tasks, intact animals decrease responding for a devalued outcome, whereas animals with OFC disruption often fail to diminish behavior to the same degree or at all (Bradfield et al., 2015; Gallagher et al., 1999; Gourley et al., 2016; Gremel and Costa, 2013; Izquierdo et al., 2004; Pickens et al., 2005; Rhodes and Murray, 2013; Rudebeck et al., 2013), but not always (see Ostlund and Balleine, 2007; Parkes et al., 2018 for two-choice instrumental tasks where outcome devaluation was not affected). While these deficits alone do not provide a complete picture of OFC contributions, they do provide a framework with which to build broader theories of OFC function.

One recent hypothesis conceptualizes OFC function as a "cognitive map" of task space. According to this proposal, OFC abstractly represents the information relevant for a given decision as the current task state—essentially, the current "location" in a task (Rich and Wallis, 2016; Schuck et al., 2016; Wilson et al., 2014; Zhou et al., 2019). This hypothesis accounts for OFC integrating rich sensory and value information to build a representation of the associative structure of a task, and could explain OFC's contribution to decision-making as a comparison of different decision-making values at each task state (Schuck et al., 2016). The OFC cognitive map hypothesis therefore aligns with broader theories that prefrontal cortex flexibly represents current relevant information (Duncan 2001). Importantly, OFC's contribution to such flexible representations is thought to be most critical for inferred, partially unobservable task properties (Wilson et al., 2014). For example, in reinforcer devaluation procedures, OFC may be important for informing behavior related to a devalued reward when that reward cannot be sampled, meaning that its reduced value is perceptually

unavailable and must be inferred from memory. This process is distinguishable from working memory, thought to involve other prefrontal areas such as the medial prefrontal cortex (Liu et al., 2014), as unobservable information may be recalled only when relevant for task performance and is not necessarily actively retained in memory. Other examples of hidden task properties include associative task structure (e.g., in reversal learning tasks, where the task structure may change without warning), or reward value informed by motivational state (e.g., in incentive learning tasks, where hunger state can indirectly alter the value of reward outcomes). In contrast, observable task properties include perceptually available information such as cues in the environment, reward value attained through direct consumption, and other information gained through sensory experience. Thus, though OFC is thought to represent both observable and unobservable information, its crucial contribution to decision-making involves the latter (Wilson et al., 2014).

The cognitive map hypothesis accounts for behaviors thought to involve OFC. For example, in a reversal learning task, an animal with intact OFC function might construct a map of task space that integrates the relationships between actions and their outcomes, flexibly updating these relationships when contingencies are reversed. In this framework, for example, poorer reversal learning in animals with OFC damage suggests impaired updating of task structure after contingency reversal, where the new contingency is not apparent from observable task features and must be inferred (Bradfield et al., 2015). This hypothesis also accounts for other recent theories of OFC function, such as the proposal that OFC provides flexible encoding of cue-elicited outcome expectancy (e.g., Schoenbaum and Roesch, 2005), and even represents valueless sensory associations (Sadacca et al., 2018). For instance, neurophysiological work suggests that OFC can represent outcome sensory properties that are unrelated to value (McDannald et al., 2014), as well as more complex schemas integrating value with the context and position of objects (Farovik et al., 2015). These findings emphasize that OFC represents task features beyond just outcome value, consistent with a map of overall task structure. Thus, though work is ongoing, the cognitive map hypothesis appears to be a promising framework to investigate OFC and its dysfunction in diseases such as addiction. Though some abnormalities may pre-exist pathology, accruing evidence suggests addictive drugs produce deficits in behavior by directly altering OFC function (e.g., DePoy et al., 2014; Renteria et al., 2018). We will next review evidence for changes to OFC in alcohol dependence.

Orbitofrontal Cortex in Human Alcohol Dependence

OFC Structural and Functional Changes

Chronic alcohol use in humans has repeatedly been associated with structural changes to OFC. Studies of patients with alcohol use disorder report lower volume in OFC (e.g., Demirakca et al., 2011; Durazzo et al., 2011; Wang et al., 2016), with differences between patients and controls continuing even months into sustained abstinence (Laakso et al., 2002). Differences in OFC volume may also indicate disorder severity. Compared to active heavy drinkers, abstinent recovering patients had greater white and grey matter volume in OFC (O'Neill et al., 2001), and a more recent study found greater volume in the left lateral OFC of abstinent recovering patients compared to even light drinkers (Cardenas et al., 2011).

Additional evidence suggests lower OFC volume correlates with relapse risk and relapse drinking behavior (Cardenas et al., 2011; Durazzo et al., 2011). Furthermore, OFC volume can increase over abstinence and correlates positively with abstinence duration (Demirakca et al., 2011; O'Neill et al., 2001).

Structural changes to OFC extend beyond reductions in volume. A diffusion tensor MRI study revealed decreased fractional anisotropy in the right OFC of abstinent alcoholics, suggesting white matter damage (Harris et al., 2008). In postmortem OFC, alcoholics had about 25% lower neural and glial density than controls, which also correlated negatively with duration of alcohol use disorder (Miguel-Hidalgo et al., 2006). These results are consistent with observed increases in neuroinflammation and neurodegeneration in OFC of postmortem human alcoholic brains and likely reflect the long-term neurotoxic effects of chronic alcohol use (Crews et al., 2013; Qin and Crews, 2012; Vetreno et al., 2013). Together, these studies support that chronic alcohol use is associated with extensive structural changes to OFC.

Given these structural changes, it is not surprising that alterations to OFC function have also been reported with chronic alcohol use. These functional changes observed at rest (i.e., independent of any behavioral task) generally suggest persistent OFC hypoactivity. Two studies reported reduced glucose metabolism in the OFC of abstinent alcoholics compared to controls that lasted weeks to months after detoxification (Volkow et al., 1994; Volkow et al., 1997), and the same group also found lower regional cerebral blood flow in the left OFC of 10-day abstinent alcoholics compared to healthy controls (Catafau et al., 1999). Combined with data suggesting chronic alcohol may be associated with OFC changes in inhibitory neurotransmission (Jin et al., 2012; Volkow et al., 1993; Volkow et al., 1997; Volkow and Fowler, 2000), increased opioid release (Mitchell et al., 2012), and other changes in neuromodulator relationships (e.g., Hommer et al., 1997; Volkow et al., 2007), these results indicate baseline alterations to OFC function and point to a role for OFC in behavioral changes associated with chronic alcohol use.

OFC Dysfunction in Decision-Making Behavior

Given the changes to baseline OFC structure and function, it seems likely that chronic high consumption of alcohol could change how OFC is recruited during behavior. Individuals with alcohol use disorder do often perform worse in behaviors thought to involve the OFC. For instance, impaired reversal learning performance of alcohol dependent patients has been seen in go/nogo tasks (Fillmore and Rush, 2006; Vanes et al., 2014) as well as reflexive behaviors (Fortier et al., 2008; Fortier et al., 2009). Other tasks requiring inhibition of a response, classically thought to involve OFC, show similar deficits in alcohol dependent patients (for meta-analyses, see Smith et al., 2014; Stavro et al., 2013). In a go/nogo task, alcoholics made significantly more errors than controls in both go and nogo conditions (Kamarajan et al., 2005). One interesting study examined the effect of multiple alcohol detoxifications in an incentive conflict task, where two stimuli individually produced reward but together were unrewarded or punished (Duka et al., 2011). The task recruited OFC in healthy controls, but the authors were unable to perform any correlations in the patient group because performance on the task was so poor, particularly in alcoholics with multiple

detoxifications (Duka et al., 2011). These results suggest that normal OFC function, important for integrating the inferred relationship between two normally-rewarded cues into task structure, was greatly impaired in alcoholics.

As well as showing deficits in behaviors classically considered OFC-dependent, people with alcohol use disorder exhibit differences in OFC activity during reward-related decision-making. In a delay discounting task, abstinent alcoholics chose disadvantageous immediate rewards more frequently and exhibited decreased OFC activity during decision-making compared to controls (Boettiger et al., 2007). In addition, OFC activity correlated positively with tendency to choose the beneficial delayed reward across groups, suggesting that OFC hypoactivation in alcoholic subjects could contribute to poorer decision-making (Boettiger et al., 2007). In a rewarded card-guessing task with fixed outcomes, the lateral OFC was less active in abstinent alcoholics compared to controls in response to monetary rewards (Forbes et al., 2014). These results support the notion that OFC dysfunction may contribute to maladaptive decision-making following chronic alcohol use, particularly when reward value is involved.

It is also important to note that behavioral deficits in alcoholic subjects often overlap with those in patients with OFC damage. Severe deficits in reversal learning are widely demonstrated in OFC lesion patients, similar to people with alcohol use disorder (Camille et al., 2011; Fellows and Farah, 2003; Fellows, 2011; Hornak et al., 2004; Rahman et al., 1999; Rolls et al., 1994; Tsuchida et al., 2010). Another area of clear overlap is in the Iowa Gambling Task (IGT), where participants must learn through trial and error which deck of cards provides the best reward/penalty ratio (Bechara et al., 1994). Patients with damage to ventromedial prefrontal cortex, a broader area that overlaps with OFC, show severe impairment in the IGT compared to controls (Bechara et al., 1994; Bechara et al., 1997; Bechara et al., 1999). Similarly, alcoholics also perform poorly on the IGT relative to controls (Bechara et al., 2001; Brevers et al., 2014; Cantrell et al., 2008; Dom et al., 2006; Fein et al., 2004; Le Berre et al., 2014; Miranda et al., 2009; Noël et al., 2007). In light of these data, it appears that OFC dysfunction may underlie the impaired ability of alcoholics to retrieve and infer previous information—such as experience with value—to influence future decision-making behavior.

OFC Dysfunction in Alcohol Cues

Decision-making is often influenced by predictive environmental cues, and this process is commonly disrupted in alcohol dependence, especially for stimuli with a conditioned association with alcohol. In contrast to decreased OFC activation in other decision-making tasks, cue reactivity studies of alcoholics commonly find OFC hyperactivation to pictures of alcoholic versus non-alcoholic beverages (Ernst et al., 2012; Hermann et al., 2006; Myrick et al., 2008; Reinhard et al., 2015; Tapert et al., 2003; Wrase et al., 2002). One study intriguingly found patients with alcohol use disorder were more likely to approach alcohol cues and showed greater OFC activation when approaching alcohol cues compared to controls (Ernst et al., 2012). Another found similarly increased OFC activation to alcohol versus juice taste cues, and that this response correlated positively with clinical measures of alcohol dependence (Claus et al., 2011).

OFC cue reactivity may have clinical relevance for craving and relapse risk. In non-treatment seeking alcoholics, exposure to alcohol cues elicited increased OFC activity and self-reported craving compared to social drinkers (Myrick et al., 2004; Myrick et al., 2008). In abstinent alcoholics undergoing treatment, alcohol cue-induced OFC activity related to later risk of relapse (Reinhard et al., 2015). OFC alcohol cue reactivity may even predict the transition to heavy drinking and alcohol problems (Dager et al., 2014), suggesting that some OFC differences could either predate alcohol use or emerge in early stages of alcohol use. Supporting possible clinical relevance of OFC cue reactivity, varenicline, a nicotinic acetylcholine receptor agonist, reduced both cue-induced OFC activity and alcohol craving in non-treatment-seeking alcoholics (Schacht et al., 2014). That said, other drugs have been shown to reduce cue-induced craving without necessarily affecting OFC (Myrick et al., 2008), suggesting OFC's role needs to be considered in the broader circuit controlling cue-related behaviors.

It is important to note that OFC hyperactivation is not a universal finding of alcohol cue reactivity studies. One study puzzlingly shows the opposite, finding reduced OFC activation in response to alcohol cues (Seo et al., 2013), though some have cautioned these findings may reflect some aspect of the experimental stress condition used in the study or the authors' method of delineating OFC (Moorman, 2018). Other studies do not report any cue-induced activity in OFC (George et al., 2001; Ihssen et al., 2010; Lingford-Hughes et al., 2006; Schneider et al., 2001; Tapert et al., 2004). The reason for this discrepancy is uncertain, but previous reviews (e.g., Dom et al., 2005) have offered some suggestions. Briefly, there may be sex differences in cue-induced OFC activity, treatment status and abstinence may reduce cue reactivity in general, activation may differ for cues of different modalities, and older fMRI studies may be particularly susceptible to technical limitations in measuring OFC due to artifacts related to the air-tissue interface of the sinuses (for greater discussion, see Dom et al., 2005). Though there remains convincing evidence for OFC involvement in aspects of alcohol cue behavior, these results emphasize that the exact parameters are unclear. In addition, the behavioral and neural mechanisms underlying OFC dysfunction in chronic alcohol use are not entirely understood, and whether dysfunction was pre-existing or produced by alcohol exposure is often not established in human research. To begin answering these questions, we next move to animal models.

Orbitofrontal Cortex in Nonhuman Animal Chronic Alcohol Exposure

Findings from Nonhuman Primates

Nonhuman primate models of chronic alcohol use can offer excellent translational relevance due to established homologies between human and nonhuman primate OFC (Mackey and Petrides, 2010; Petrides and Pandya, 1994). Nonhuman primates will drink alcohol to high levels voluntarily, with a subpopulation of "heavy drinkers" displaying high intake, escalated consumption, and behavioral inflexibility (Carlson et al., 2011; Grant et al., 2008; Vivian et al., 2001). Monkeys also display changes to brain structure under chronic alcohol that are similar to humans. One study found similar cortical volume loss in high-drinking monkeys that was proportional to intake; however, there was no statistical relationship between drinking and frontal cortex volume (Kroenke et al., 2014). Other studies have found

evidence of functional changes to OFC in chronic high-drinking monkeys, including a reduction in the excitability of OFC neurons (Nimitvilai et al., 2017b) that parallels lower baseline OFC neural activity in human alcoholics (Catafau et al., 1999; Volkow et al., 1994; Volkow et al., 1997). Chronic alcohol use in monkeys was also associated with decreased expression of $GABA_A$ receptor subunit mRNA in the OFC (Hemby et al., 2006), aligning with similar results in humans (Jin et al., 2012) and decreased GABAergic function more generally in the OFC of human chronic alcohol users (Volkow et al., 1993; Volkow et al., 1997). Other studies support OFC glutamate receptor dysregulation in monkeys with chronic alcohol intake (Acosta et al., 2010; Acosta et al., 2012), providing further evidence for disruption to baseline OFC function and potentially mirroring altered prefrontal cortex glutamatergic neurotransmission in human alcoholism (Davis and Wu, 2001; Krystal et al., 2003; Tsai, 1998). Monkeys with OFC lesions also show similar behavioral deficits as humans with OFC dysfunction. These deficits include impaired performance in reversal learning tasks (Dias et al., 1996a; Dias et al., 1996b; Izquierdo et al., 2004) and in instrumental reinforcer devaluation, with impairment lasting even 19 months after surgery (e.g., Izquierdo et al., 2004; Rhodes and Murray, 2013). In summary, though work on nonhuman primate OFC in chronic alcohol use is relatively limited, the findings overall correspond with results from human research.

OFC Structural and Functional Changes in Rodent Alcohol Models

Rodent models offer excellent manipulability of genetic and neural factors. However, as reliable drinking behavior to the level of physical dependence is often difficult to obtain in rodents, involuntary models of alcohol exposure are commonly used for examining the effects of alcohol dependence. Chronic intermittent ethanol (CIE) vapor exposure and intragastric (IG) administration have been used to reliably produce chronically elevated blood alcohol concentrations (BACs), physical dependence, and withdrawal symptomology (Becker, 2000). Indeed, work using these models has demonstrated changes to OFC that converge with human research in a number of areas.

Structural changes to OFC have been identified using both CIE and IG models. Seven days after CIE, one study found reduced spine density in the lateral OFC of CIE mice compared to controls exposed only to air (McGuier et al., 2015), consistent with changes to dendritic morphology in humans such as reduced spine density and arborization in the frontal cortex of alcoholic postmortem brain tissue (Ferrer et al., 1986; Harper and Corbett, 1990). However, two previous studies examining lateral OFC spine density three days after CIE found no effect of alcohol vapor exposure (DePoy et al., 2013; Holmes et al., 2012), suggesting that the underlying mechanisms are likely complex and highly dependent on time since withdrawal, among other factors. Rodents treated with IG alcohol show evidence of neuroinflammation and degeneration in the OFC (Corso et al., 1998; Crews et al., 2013; Vetreno et al., 2013), similar to changes in OFC of human alcoholic postmortem brain tissue (Crews et al., 2013; Qin and Crews, 2012; Vetreno et al., 2013).

Rodent models have also revealed functional changes to OFC. A prominent finding in this area is altered OFC neuron excitability, though the direction of change is inconsistent. Previous electrophysiological work from our lab identified decreased excitability of OFC

neurons in CIE-exposed mice (Renteria et al., 2018). These results are consistent with past work showing reduced OFC excitability in high-drinking nonhuman primates (Nimitvilai et al., 2017b) and lower baseline OFC activity in human alcoholics (Catafau et al., 1999; Volkow et al., 1994; Volkow et al., 1997). However, the same group that found reduced OFC excitability in macaques has also consistently reported opposite results in CIE mice, finding increased excitability in both males and females (Nimitvilai et al., 2016; Nimitvilai et al., 2017a; Nimitvilai et al., 2018a; Nimitvilai et al., 2018b). Though these discrepancies are not yet fully understood, the underlying effect of altered OFC excitability remains. Additional work points to other adaptations within OFC that may occur with chronic alcohol. A study found alterations to glutamatergic transmission in the medial OFC of CIE mice, including upregulation of NMDA receptor subunit expression and increased NMDA receptor-mediated currents (Radke et al., 2017), likely reflecting long-term neuroadaptations. In addition, mice exposed to IG alcohol show reduced D4 dopamine receptors in OFC, indicating changes to dopamine function reminiscent of altered dopamine response in alcoholic humans (Volkow et al., 2007).

Communication between OFC and other brain areas is also altered in rodent chronic alcohol models. Our lab has previously reported that mice exposed to CIE had decreased neurotransmission between OFC and the dorsal medial striatum, another area necessary for goal-directed control (Renteria et al., 2018). Similar results were found in a study using fMRI to examine resting state connectivity in the brains of adult rats exposed to intermittent IG alcohol during adolescence. Broad decreased functional connectivity was found between OFC and a number of other brain areas, including the dorsal striatum, nucleus accumbens, and infralimbic prefrontal cortex (Broadwater et al., 2018). OFC connectivity is also disrupted in alcohol dependent humans, where past work has shown lower resting state functional connectivity between OFC and hippocampal gyrus (Wang et al., 2016), and altered dopamine activity that is suggestive of reduced prefrontal control over dopaminergic mesolimbic pathways (Volkow et al., 2007).

Additional work has emphasized altered monoamine circuit contribution following chronic alcohol. Human alcoholics showed reduced OFC glucose utilization following administration of a mixed serotonin agonist/antagonist (Hommer et al., 1997). In CIE mice, monoamine application to OFC slices did not produce the normal inhibition of lateral OFC firing (Nimitvilai et al., 2017a; Nimitvilai et al., 2018a). In summary, chronic alcohol affects OFC function across a variety of measures, suggesting potential disrupted or compensatory mechanisms that might underlie behavioral deficits associated with alcohol. Further, these studies frequently overlap with OFC functional changes in human alcoholics, supporting involuntary methods of alcohol administration such as IG and CIE as valid models of chronic alcohol exposure in rodents.

OFC Dysfunction in Rodent Behavioral Models

Structural and functional changes to brain areas such as the OFC are associated with altered behavior in rodent alcohol models. These changes frequently overlap with those seen in humans with both alcohol dependence and lesions to OFC. For instance, poorer performance in reversal learning tasks has been demonstrated across various animal models of alcohol

exposure. Using the CIE model, one study found that reversal learning was impaired in mice up to ten days after CIE (Badanich et al., 2011), although a separate group found CIE mice made fewer errors in later sessions of reversal learning (DePoy et al., 2013). A number of IG studies have demonstrated selective deficits in reversal learning, particularly using a binge model of exposure in adolescent rodents (Coleman et al., 2011; Coleman et al., 2014; Fernandez et al., 2017; Obernier et al., 2002). Furthermore, longer periods of BAC elevation are associated with poorer reversal learning (Badanich et al., 2016; McMurray et al., 2014). Thus, it appears that chronic high levels of intoxication and physical dependence may be critical for producing alcohol-related behavioral deficits in animal models that overlap with poor reversal learning performance in humans with OFC lesions or alcohol use disorder.

Other tasks indicate similarly impaired performance. Rats exposed to CIE exhibit poorer behavioral flexibility in operant (Gass et al., 2014; Trantham-Davidson et al., 2014) and attentional set-shifting tasks (Hu et al., 2015; Kroener et al., 2012; Rodberg et al., 2017). In reward-related decision-making, rodents exposed to chronic alcohol typically display greater preference for risky behavior, an effect particularly well demonstrated in adolescents (Boutros et al., 2015; Clark et al., 2012; McMurray et al., 2014; Nasrallah et al., 2009; Nasrallah et al., 2011; Schindler et al., 2014). Interestingly, one study found that increased risk preference was associated with blunted response in OFC specifically for reward outcomes, suggesting disruption to reward-related OFC activity (McMurray et al., 2016).

Importantly, one OFC-dependent task affected by alcohol is instrumental outcome devaluation. In a chronic drinking model, rats trained to lever press for alcohol were insensitive to alcohol devaluation after 8 weeks of training (Corbit et al., 2012; Corbit et al., 2014). Impaired outcome devaluation was also found in alcohol-dependent CIE mice trained to self-administer alcohol (Lopez et al., 2014; Renteria et al., 2020). Furthermore, prior CIE exposure left even food reward seeking in mice insensitive to outcome devaluation (Renteria et al., 2018). These findings echo impairments in devaluation produced by OFC chemical lesions, chemogenetic inhibition of OFC projection neurons, and knockdown of brain-derived neurotrophic factor in OFC (Bradfield et al., 2015; Gourley et al., 2016; Gremel and Costa, 2013), suggesting that alcohol dependence itself may affect OFC-based devaluation through alterations to OFC function.

Indeed, recent work has begun to uncover OFC neural mechanisms underlying behavioral deficits associated with alcohol dependence. Renteria et al. (2018) found that decreased sensitivity to outcome devaluation in CIE mice was associated with decreased OFC excitability as well as decreased synaptic transmission from OFC to the direct pathway in dorsal medial striatum, a circuit implicated in goal-directed behavior. CIE-induced behavioral deficits were rescued with OFC chemogenetic activation (Renteria et al., 2018), aligning with past work showing goal-directed behavior is strengthened with OFC activation and disrupted by OFC inhibition (Gremel and Costa, 2013). Another group found that lateral OFC lesions and OFC chemogenetic inhibition increased alcohol consumption in CIE mice, an effect that continued even after the addition of bitter quinine to devalue alcohol (den Hartog et al., 2016). Together, these studies support the hypothesis that OFC disruption contributes to the loss of goal-directed control in chronic alcohol exposure.

OFC Dysfunction in Rodent Alcohol Cue Behavior

Although human research often reports cue-induced OFC activation in chronic alcohol users, the mechanisms behind this cue reactivity are not well understood. Just a handful of rodent studies have investigated OFC involvement in alcohol cues, generally echoing findings of OFC overactivation in human alcoholics. For example, exposure to contextual, light, and olfactory cues associated with alcohol in reinstatement paradigms increases Fos expression in OFC (Bianchi et al., 2018; Jupp et al., 2011). Further, inactivation of OFC disrupted the reinstatement of alcohol seeking after exposure to alcohol cues (Bianchi et al., 2018). These studies parallel human work by suggesting OFC hyperactivity to alcohol cues that perhaps induce craving and alcohol seeking, overall supporting increased OFC-mediated cue control over alcohol behavior. However, more work is needed to tease apart how cue-related information engages the OFC to produce hyperactivity, and to better understand the role OFC plays in cue control over alcohol-related behaviors.

Alcohol Dependence and the Orbitofrontal Cortex Cognitive Map

OFC as a Cognitive Map of Task Space

The picture emerging from the literature so far is one of extensive changes to OFC structure, function, and dependent behaviors in chronic alcohol exposure across species. However, it is not yet clear how alcohol dependence alters OFC function and behaviors within the framework of the recent “cognitive map” hypothesis of OFC function. Future work in both humans and non-human research subjects could provide better understanding by explicitly examining the partially unobservable states thought to be OFC’s crucial contribution to representations of task structure. To accomplish this, an appropriate task would incorporate properties that cannot be perceived through direct sensory experience. For instance, in rodent reversal learning procedures, observable task properties may include cue lights, instrumental levers, and other directly perceivable contextual information in the training environment. In contrast, an unpredictable and unsignaled change in task associative structure is an unobservable task property (not experienced sensorially), and the ability to alter behavior after such a change is crucial for performance in reversal learning. Disrupted ability to infer the change in associative structure, for example produced by alcohol-induced changes to OFC function, could lead to deficits in task performance (Figure 2).

In an example of an OFC task designed for human participants, Schuck et al. (2016) examined OFC function by utilizing both observable and unobservable task features. The task involved judging the age (young or old) of just one object within an image of two superimposed objects, and participants had to recall information from previous trials to know which object to judge. Thus, the observable task properties were the ages and identities of the images in the current trial, but task performance relied on unobservable task properties such as the knowledge of which object and age were judged in the previous trial. The authors found that unobservable task states could be decoded from OFC neuroimaging data, and that decoding accuracy was related to task performance (Schuck et al., 2016). This task could certainly be used to examine how alcohol dependence alters OFC function in humans. However, it is important to highlight that within experimental psychology there already exist well-validated, experimentally-defined tasks used in both humans and

nonhumans that incorporate hidden states and therefore have the potential to reveal deficits in OFC function within the context of the cognitive map hypothesis. We suggest three such tasks next.

Tasks to Examine Alcohol Dependence Effects on OFC

Performance following outcome devaluation, already demonstrated to be OFC-dependent, can be used to examine inferred value control over both Pavlovian and instrumentally controlled behavior. That is, devaluing an outcome can reduce the amount of conditioned responding supported by a cue (Colwill and Motzkin, 1994; Holland, 1990), as well as reducing the amount of actions made toward procuring the outcome (Adams and Dickinson, 1981; Colwill and Rescorla, 1985). Additionally, though outcome devaluation is commonly examined in rodents, the task is also suited to primate research and has been demonstrated to involve OFC in both macaques (West et al., 2011) and humans (Gottfried et al., 2003; Valentin et al., 2007).

Outcome devaluation of the cue- or action-paired outcome is often performed in one of two ways: with sensory-specific satiation, or with repeated aversive pairings of the outcome with illness (see Box 1A). Following devaluation procedures, either conditioned responding or instrumental responding is assessed in subsequent extinction tests. Subjects with intact outcome devaluation demonstrate lower conditioned responding or reduce the frequency of actions made to get the outcome, respectively. In both tasks, subjects cannot directly experience the now-devalued outcome during testing; instead, they must infer this perceptually unavailable change in outcome value from memory to appropriately alter their behavior. In the framework of the cognitive map hypothesis, a rodent performing an outcome devaluation task might for example construct a map of task space that integrates lever pressing for food (an action-outcome contingency) with the reduced value of the food after devaluation (an inferred outcome property), resulting in decreased lever pressing. Multiple labs have reported an insensitivity to outcome devaluation of rodent instrumental responding following chronic alcohol consumption (Corbit et al., 2012) or following induction of alcohol dependence (Lopez et al., 2014; Renteria et al., 2018). In addition, alcohol-related contextual cues can produce an immediate and selective loss of goal-directed control in rats (Ostlund et al., 2010). However, in contrast, outcome devaluation of Pavlovian alcohol-related conditioned responses has been more elusive.

Another behavioral task that may better capture OFC function is Pavlovian-to-instrumental transfer (PIT; see Box 1B). Broadly, PIT is the process by which previously conditioned Pavlovian cues influence instrumental behavior. Described as an interaction between Pavlovian and instrumental associative learning processes (Holmes et al., 2010), PIT has been demonstrated across species, including in humans (e.g., Garbusow et al., 2016; Lehner et al., 2017; Talmi et al., 2008). A basic PIT procedure involves a period of training a Pavlovian association (e.g., auditory tone predicts outcome delivery), a separate period of training an instrumental contingency (e.g., lever press now produces the same outcome), and a test session in which the instrumental action is available and the Pavlovian cues are presented intermittently but no rewards are delivered. If transfer occurs, the frequency of instrumental behaviors changes during cue presentation (e.g., lever presses are energized

during the Pavlovian cue), even though the Pavlovian cue and instrumental action were never previously associated. This means that PIT explicitly includes partially unobservable states, important for investigating OFC function, in two ways. First, the reward outcome is not delivered at any point during the test, meaning its value and sensory characteristics are perceptually unavailable; second, connections between the Pavlovian cue, instrumental behavior, and any overlap in their outcome representations must be inferred, as the PIT test represents the first and only time Pavlovian cues are presented during instrumental behavior. Indeed, previous work indicates post-training OFC lesions (Ostlund and Balleine, 2007) and chemogenetic inactivation of isolated basolateral amygdala terminals located in OFC (Lichtenberg et al., 2017) can disrupt transfer in the PIT test, when partially unobservable states become critical.

It is unclear how alcohol might disrupt OFC function as measured with PIT. Clues come from research in humans. One study found stronger PIT in abstinent human alcoholics compared to controls (Garbusow et al., 2016), with alcoholics showing potentiated instrumental behavior when predictive cues were present. Importantly, this was observed for non-drug Pavlovian cues, suggesting that chronic alcohol may induce long-lasting functional changes to neural circuits that support PIT processing. However, the authors limited their fMRI analyses in this study to the nucleus accumbens, so the contribution of other brain areas such as OFC is unknown (Garbusow et al., 2016). Future work could specifically investigate the impact of chronic alcohol exposure on OFC function using PIT, focusing in particular on any differences in OFC function during the PIT test, when partially unobservable states become an integral part of the task structure.

Another task demonstrated to engage OFC function is incentive learning (see Box 1C), which underlies the ability to use motivational states to assign value to our actions (Balleine and Dickinson, 1991; Balleine, 1992; Balleine et al., 1995; Balleine et al., 2005; Corbit and Balleine, 2003; Wassum et al., 2009). In rodents, an incentive learning task usually involves completing a lever press requirement on one lever, which then releases a second lever that, when pressed, triggers food delivery. Following a shift in motivational state (e.g., from hungry to full), intact animals only reduce lever pressing on the first lever in the sequence, and do so only if allowed prior experience of the outcome in the new motivational state. This task involves an excellent example of partially unobservable states, as the updated incentive value of the outcome must be inferred from memory during testing, when no rewards are delivered. In other words, animals unable to encode or retrieve the updated outcome value will not change their behavior even after a shift in motivational state. An additional benefit of this task is that the change in motivational state can be bi-directional, with incentive learning demonstrable following both increases as well as decreases in motivational state.

Recent work suggests OFC is critical for incentive learning processes, both at the point of encoding the updated value (Baltz et al., 2018; Malvaez et al., 2019) and when retrieving the updated value from memory to control responding (Malvaez et al., 2019). However, it is currently unknown whether alcohol-induced deficits in incentive learning are largely driven by changes to OFC function. Future work could investigate alcohol's effect on OFC function using the incentive learning task, focusing in particular on the inferred change in incentive value that drives behavior after a shift in motivational state.

Together, the tasks discussed above and illustrated in Box 1 could provide a better understanding of how alcohol affects OFC function. The use of experimentally defined behaviors that critically depend on OFC function offers an excellent way to examine the neural mechanisms underlying behavioral deficits in task structures that include unobservable states.

Summary

A wealth of past work indicates that aspects of OFC structure, function, and dependent behaviors are disrupted in alcohol dependence. However, it remains unclear how alcohol affects OFC function as understood in the most recent theories of OFC's role in decision-making. We suggest future research could better investigate the impact of long-term alcohol on OFC by using tools that incorporate partially unobservable task states, which are better suited to capture OFC's complex representation of task structure. Finally, advancing work in this area has important clinical implications, as insights into alcohol-induced changes to OFC could help identify methods for assessing and potentially even treating OFC-dependent decision-making deficits in patients with alcohol use disorder.

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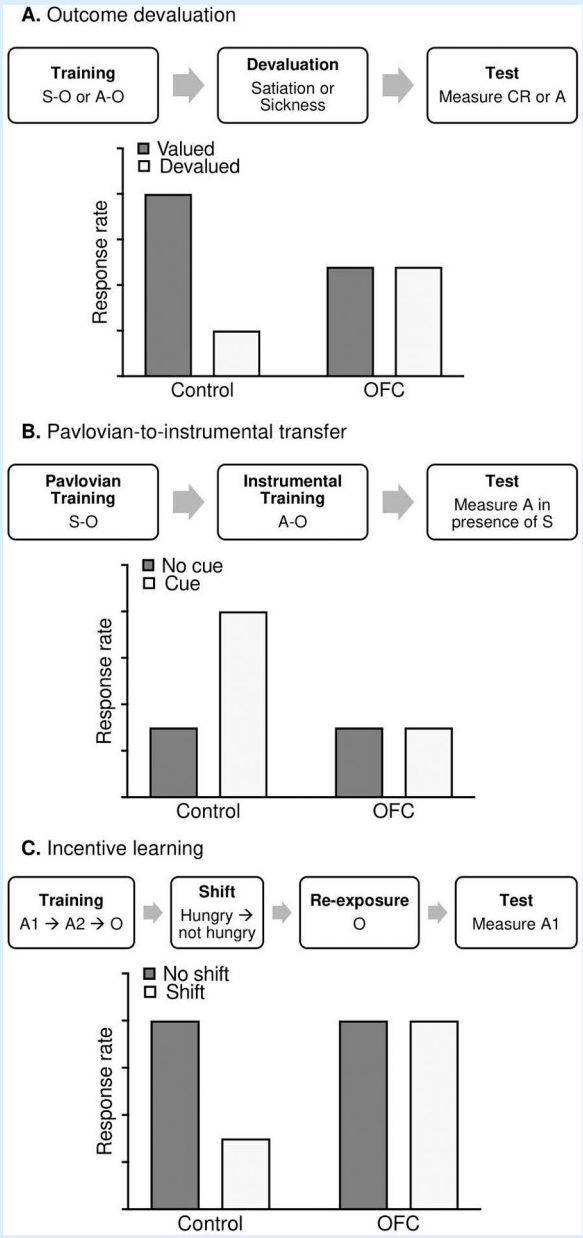
Box 1.

OFC-dependent tasks

The basic outcome devaluation procedure is illustrated in **A.** The procedure involves an initial stimulus-outcome (S–O) or action-outcome (A–C)) training period, followed by devaluation of the outcome with either selective satiation (e.g., Gremel & Costa, 2013) or paired sickness (e.g., Gallagher et al., 1999). Final testing involves comparing responses (the trained action, A, or the conditioned response, CFR) for a valued outcome versus a devalued outcome. Previous work has demonstrated that animals with OFC disruption fail to reduce responding for the devalued outcome, showing similar levels of responding as for a non-devalued outcome (see A for simulated data; Gremel and Costa, 2013; Gourley et al., 2016; Gallagher et al., 1999). **B.** Pavlovian-to-instrumental transfer (PIT) introduces Pavlovian (S–O) and instrumental (A–O) associations in separate training periods. In the subsequent test session, the instrumental action is measured in the presence of the conditioned stimulus. with PIT demonstrated via an increase in A during S (compared to A during no S). Previous work has shown that post-training OFC lesions (Ostlund and Balleine. 2007) and inactivation of basolateral amygdala terminals in OFC (Lichtenberg et al., 2017) can reduce or eliminate transfer in the PIT test (see B for simulated data). **C.** The incentive learning procedure trains an instrumental chain in which completion of the first action requirement (A1) produces a second action (A2) that when made earns the reward outcome. After training this instrumental sequence, a shift in motivational state is achieved by changing food restriction state (e.g., from hungry to not hungry). Importantly, subjects only update the value of the outcome if subsequently re-exposed to the outcome in the new motivational state. The incentive learning test then compares responses for shifted animals vs non-shifted animals. Previous work suggests that OFC is critical for altering behavior following the shift in motivational state (Baltz et al., 2018; Malvaez et al.. 2019; see C for simulated data). Though the tasks discussed above incorporate hidden states and have been shown to involve OFC, it is unclear how alcohol-induced changes to OFC might affect their performance.



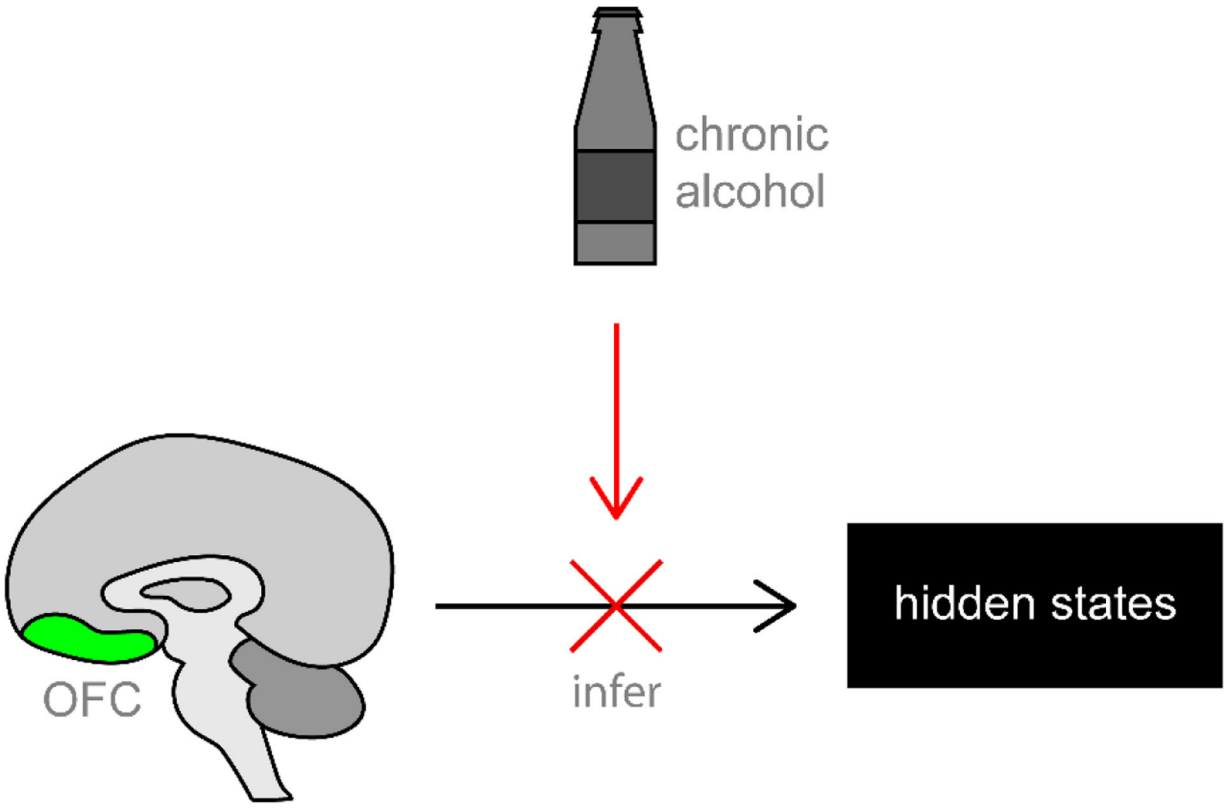


Figure 1.

A recent hypothesis conceptualizes the orbitofrontal cortex (OFC) as providing a "cognitive map" of task space. In line with this hypothesis, alcohol dependence may alter decision-making by disrupting OFC function critical for inferring hidden task states. We argue that research using tasks targeted to this broader function will provide better understanding of how OFC changes in alcohol dependence, and could better inform future clinical practice for alcohol dependent populations.

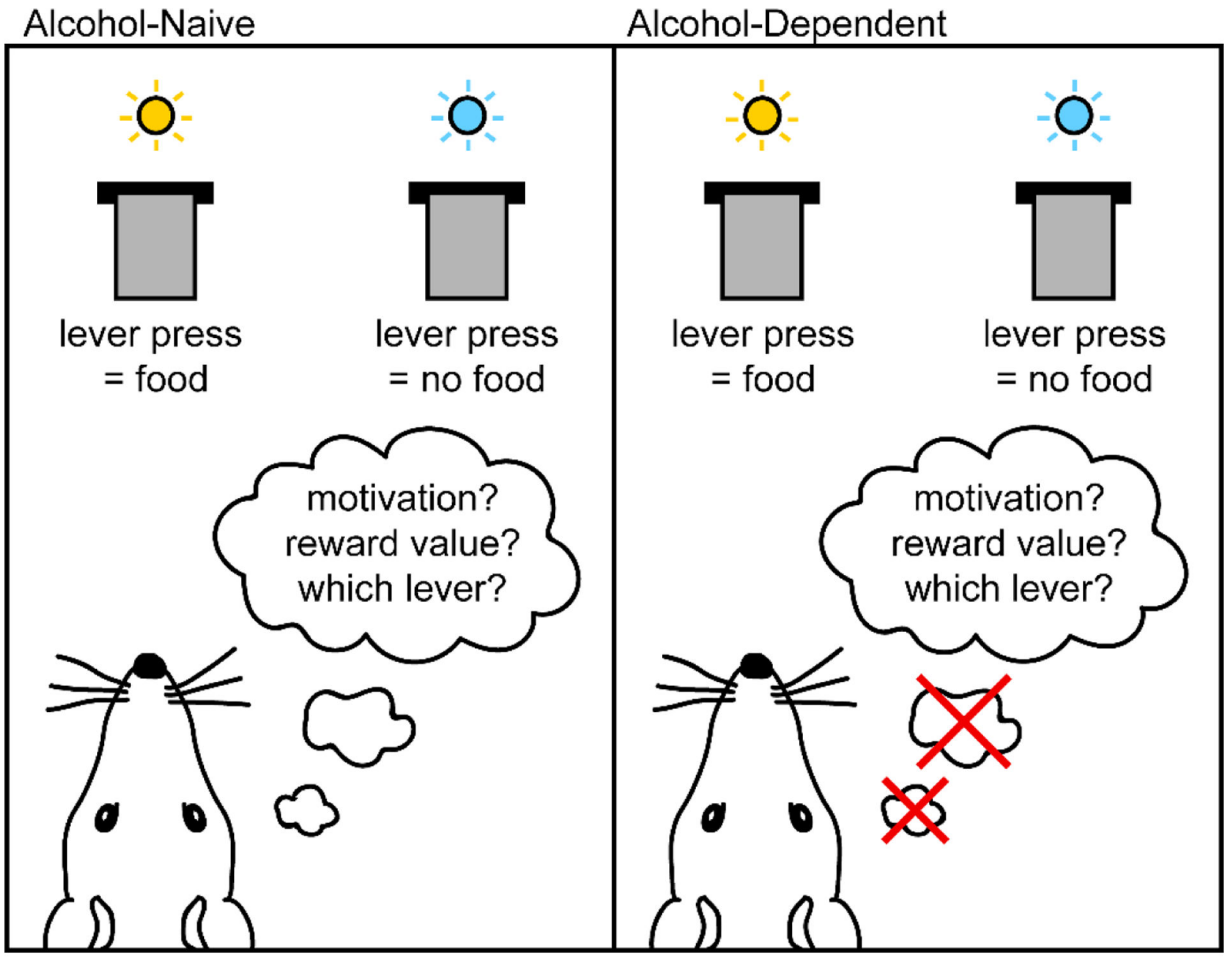


Figure 2.

Example of task properties in reversal learning. In this scenario, reward delivery had previously occurred when the right lever was pressed, but has just switched unpredictably such that reward delivery now only occurs when the left lever is pressed. Properties in the task are distinguishable as observable (available through sensory experience) and unobservable (not available through sensory experience). Here, observable properties include both levers and cue lights, and other sensory information in the environment such as visual, auditory, or olfactory contextual cues. Unobservable properties include motivation to perform the task, expected reward value, and representation of task associative structure. Performance on reversal learning tasks relies on such unobservable properties, in particular the ability to infer the change in task structure following reversal of a previously-learned association. We propose that alcohol dependence may disrupt performance in tasks like reversal learning by altering the function of the orbitofrontal cortex, which is thought to be crucial in representing unobservable task properties.