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The role of the orbitofrontal cortex in alcohol use, abuse, and dependence

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Abstract

One of the major functions of the orbitofrontal cortex (OFC) is to promote flexible motivated behavior. It is no surprise, therefore, that recent work has demonstrated a prominent impact of chronic drug use on the OFC and a potential role for OFC disruption in drug abuse and addiction. Among drugs of abuse, the use of alcohol is particularly salient with respect to OFC function. Although a number of studies in humans have implicated OFC dysregulation in alcohol use disorders, animal models investigating the association between OFC and alcohol use are only beginning to be developed, and there is still a great deal to be revealed. The goal of this review is to consider what is currently known regarding the role of the OFC in alcohol use and dependence. I will first provide a brief, general overview of current views of OFC function and its contributions to drug seeking and addiction. I will then discuss research to date related to the OFC and alcohol use, both in human clinical populations and in non-human models. Finally I will consider issues and strategies to guide future study that may identify this brain region as a key player in the transition from moderated to problematic alcohol use and dependence.

Keywords

Orbital; prefrontal; ethanol; addiction; alcoholism; alcohol use disorders; decision-making; reversal learning; behavioral flexibility; cognitive dysfunction

1. Introduction

Alcohol use disorders (AUDs) are highly problematic from both medical and societal standpoints. In 2015, over 15 million adults in the United States exhibited AUDs (Center for Behavioral Health Statistics and Quality, 2016). Globally, approximately 2 billion people worldwide consume alcoholic beverages, 76.3 million people have been diagnosed with an alcohol use disorder, and alcohol use results in 3.2% of deaths worldwide (World Health Organization, 2014). It has been estimated that alcohol misuse is the main leading cause of death among people between the ages of 15–49 (Lim et al., 2012). These, and numerous

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other statistics associating problematic alcohol use with negative outcomes, indicate that we are in need of new treatments and prevention strategies. Critical to developing these new strategies is a comprehensive knowledge of the brain systems that control motivation for alcohol and how they are disrupted in AUDs.

As our understanding of the neural circuitry underlying motivated behavior and its disruption in AUDs advances, more and more brain areas have been implicated, and the specific roles played by these diverse brain regions are increasingly revealed as complex and multifaceted. This point is made particularly salient when considering the roles of neural systems underlying drug and alcohol use and addictions. The canonical addiction-related network, encompassing the nucleus accumbens, amygdala, ventral tegmental area, and prefrontal cortex, has expanded over time and through intense investigation (Koob, 2014; Koob and Volkow, 2010; Volkow et al., 2011). Based on a growing number of studies, this distributed network now includes numerous nuclei of the extended amygdala, thalamus, hypothalamus, and brainstem, and includes signaling through multiple neurotransmitter and modulatory systems: glutamate, GABA, dopamine, norepinephrine, serotonin, acetylcholine, and multiple neuropeptide systems. Even this list is likely incomplete as new brain systems associated with reward-seeking continue to be revealed (Wagner et al., 2017).

In recent years the orbitofrontal cortex (OFC) has been identified as a region that is disrupted in addiction to drugs of abuse (Dom et al., 2005; Everitt et al., 2007; Fettes et al., 2017; London et al., 2000; Porrino and Lyons, 2000; Schoenbaum and Shaham, 2008; Volkow and Fowler, 2000). However, only recently has attention been directed to the role of the OFC in alcohol use and dependence, particularly in the context of animal models, through which we are able to precisely identify cellular mechanisms of its contributions. Given the primary role that the OFC plays in controlling of flexible, goal directed behavior, as well as its association with reward identification and acquisition, it is likely that the OFC will emerge as a key player in regulating excessive alcohol seeking seen in AUDs. Indeed, recent reports have begun to implicate the OFC in alcohol motivation and dependence. In this review, I will discuss the progress that has been made in understanding what role the OFC plays in alcohol motivation and how disruptions of OFC function may contribute to alcohol use disorders. I begin with a brief overview of OFC anatomy and function, followed by a discussion of the contributions of the OFC to drug seeking and addiction. I will then present a description of studies, both in human patients and animal models, which have begun to implicate this region in alcohol use and abuse, and will conclude with a summary and consideration of future directions. The overarching theme of this review is that the OFC is very likely a key player in regulated alcohol seeking and that disruptions in OFC signaling play an important, if not essential, role in excessive alcohol use and dependence. However, much work remains to be done in order to understand the details of the involvement of the OFC in alcohol use and dependence.

2. OFC Overview

The structure and function of OFC and its role in behavioral control have been extensively studied, and are the subjects of ongoing investigation by many research groups. Consequently, models and descriptions of OFC have evolved to encompass a wide range of

complex functions. Since the focus of this review is primarily on the OFC in the context of alcohol use and dependence, I will not present a comprehensive discussion of the OFC more generally. I refer interested readers to some of the many excellent reviews on OFC structure and function (Balleine et al., 2011; Dalley et al., 2004; Izquierdo, 2017; Kringelbach, 2005; Kringelbach and Rolls, 2004; Mainen and Kepecs, 2009; McDannald et al., 2014b; Noonan et al., 2012; O'Doherty, 2007; Ongur and Price, 2000; Padoa-Schioppa, 2011; Price, 2007; Rolls and Deco, 2016; Rolls and Grabenhorst, 2008; Rudebeck and Murray, 2014; Schoenbaum et al., 2009; Schoenbaum et al., 2011; Stalnaker et al., 2015; Wallis, 2011; Walton et al., 2011). However, before focusing specifically on the OFC and alcohol, it is worth considering some of the modern conceptualizations of what the OFC is and what role it plays in motivated, goal-directed behavior outside the context of drugs or alcohol.

2.1. OFC Overview – Anatomy

In both primates and rodents, the OFC makes up a substantial proportion of the ventral extent of the prefrontal cortex, encompassing medial and lateral regions (Hoover and Vertes, 2011; Izquierdo, 2017; Ongur and Price, 2000; Petrides and Pandya, 1994; Price, 2007; Reep et al., 1996; Uylings and van Eden, 1990; Wallis, 2011). At the coarsest anatomical level, there are subregions within both primate and rodent OFC, exhibiting differential connectivity and function. Brodmann described cytoarchitectonic regions in human OFC: areas 11, and 47 and, to a lesser extent, area 10, which is more typically considered frontal pole (Brodmann, 1909; Henssen et al., 2016; Kringelbach, 2005), and (Walker, 1940) expanded the description of OFC to five areas (areas 10–14), extending to the frontal pole (Kringelbach, 2005; Kringelbach and Rolls, 2004).

These regions were further subdivided by (Petrides and Pandya, 1994) and by Price and colleagues, who have clustered the approximately 20 subregions of primate OFC and portions of ventromedial prefrontal cortex (vmPFC) into two main networks, an orbital and a medial network, largely based on distinct histochemical and connectivity profiles (Carmichael and Price, 1994, 1995a, b, 1996; Ongur and Price, 2000; Price, 2007; Price et al., 1996). Humans and monkeys have an overall strong degree of homology, with areas 11 and 13 considered central OFC, particularly in studies related to value-based decision making, and areas 10 and 14, and to some degree area 12, considered extensions of vmPFC (Wallis, 2011). Recent work in humans and non-human primates using functional and diffusion-weighted MRI and resting-state connectivity have identified six to eight subregions of OFC and vmPFC, depending on how borders are drawn (Kahnt et al., 2012; Neubert et al., 2015), and these clusters appear to sort broadly into previously-described orbital/medial networks (Zald et al., 2014). These two networks also appear to serve separate, though potentially overlapping, functions. The orbital network is anatomically interconnected with sensory (particularly olfactory and gustatory) systems and the medial network is embedded in systems associated with visceral and visceromotor functions (Ongur and Price, 2000), and there are further functional differences based on anatomical subregions discussed briefly in section 2.2, below. In general, OFC is broadly connected with a number of regions classically associated with flexible motivated behaviors as well as drug and alcohol abuse (Figure 1), including other prefrontal cortical areas, amygdala, dorsal and ventral striatum, ventral tegmental area, and lateral hypothalamus, among other regions (Carmichael and

Price, 1995a, b, 1996; Cavada et al., 2000; Floyd et al., 2001; Gabbott et al., 2005; Heilbronner et al., 2016; Hoover and Vertes, 2011; Morecraft et al., 1992; Ongur and Price, 2000; Schoenbaum et al., 2006). However, specific OFC subregions exhibit differential connectivity, arguing for consideration of separate subregional functions when possible.

There are also subdivisions within the rodent OFC, which, based on anatomical connectivity as well as function, allow clustering into two main networks – medial (medial OFC – MO, and ventral OFC – VO) and lateral (lateral OFC – LO, dorsolateral OFC – DLO, and sometimes including portions of the agranular insular cortex (AI) (Floyd et al., 2000, 2001; Heilbronner et al., 2016; Hoover and Vertes, 2011; Reep et al., 1996). In both primates and rodents, OFC in general receives projections from medial nucleus of the mediodorsal thalamus, a feature which is commonly used to identify prefrontal cortical structures broadly (Leonard, 1969, 1972; Preuss, 1995; Reep et al., 1996; Rose and Woolsey, 1948). Homologies between rodent and primate OFC, as defined by subregional connectivity with other subcortical areas such as periaqueductal gray, amygdala, hypothalamus, and striatum, are relatively well-established (Carmichael and Price, 1995a, b, 1996; Floyd et al., 2000, 2001; Heilbronner et al., 2016; Leonard, 1969, 1972; Ongur and Price, 2000; Preuss, 1995; Price, 2007), indicating that functional OFC parallels across species may be relatively robust (Heilbronner et al., 2016; Preuss, 1995). Some have argued that primate-rodent OFC homologies are limited, particularly given the absence of dysgranular and granular cortex which makes up the rostral extent of the OFC in primates (Passingham and Wise, 2012; Wise, 2008). In contrast, however, connectivity studies have indicated a relatively reliable mapping across species, particularly with respect to corticostriatal projections (Heilbronner et al., 2016; Ongur and Price, 2000; Petrides and Pandya, 1994; Price, 2007; Reep et al., 2003; Uylings and van Eden, 1990), which is supported by the apparent grouping of medial and orbital/lateral OFC categories in both rodents and primates.

The use of broad medial/lateral (in rodents) or medial/orbital (in primates) divisions is valuable in refining anatomical foundations of the diverse functions supported by the OFC and has provided a more nuanced understanding of its contributions to behavior. As noted by those studies characterizing further subdivisions based on connectivity and cytoarchitecture, however, even these subdivisions likely oversimplify the complex nature of an area that extends from the pole of the frontal cortex to the rostral position of the striatum, and stretches the extent of the medial/lateral ventral surface. Future work characterizing the similarities and differences across networks and regions will provide a more comprehensive perspective on the contributions of this region to the diverse behaviors supported, as described below, including those related to drug and alcohol use.

2.2. OFC Overview – Function

As noted, a discussion of the many functions of OFC is beyond the scope of this review. The OFC is increasingly revealed as a highly complex structure or collection of structures, and a comprehensive survey of their influence on behavior requires considerable description. As such, I provide only a brief overview of some of the well-accepted and recent framings of OFC function, but refer the reader to some of the many reviews on OFC function (Balleine et al., 2011; Dalley et al., 2004; Kringelbach, 2005; Kringelbach and Rolls, 2004; Mainen

and Kepecs, 2009; McDannald et al., 2014b; Noonan et al., 2012; O'Doherty, 2007; Padoa-Schioppa, 2011; Rolls and Deco, 2016; Rolls and Grabenhorst, 2008; Rudebeck and Murray, 2014; Schoenbaum et al., 2009; Schoenbaum et al., 2011; Stalnaker et al., 2015; Wallis, 2011; Walton et al., 2011), and I apologize in advance for neglect of specific lines of research. The description provided below is designed to dovetail with an understanding of the role of the OFC in alcohol use and use disorders. As I hope is clear from a survey of the major currently appreciated functions of the region, there is a striking concordance between native functions of the OFC and a number of aspects of behavior that either contribute to or are disrupted in motivation for and misuse of alcohol. This is not to say that the OFC should be considered the exclusive nexus of alcohol-associated behaviors, but it does strongly support the continued investigation of its contributions.

The OFC, both in primates (human and non-human) and rodents plays a broad role in flexible decision-making that allows acquisition of positive, and avoidance of negative, reinforcers. Although this overly-general description could be applied to a wide range of brain structures, it is notable that so many subcomponents of this behavioral suite are encoded in the OFC. Among the many functions performed by the OFC, a number of these intersect with those associated with motivation for alcohol use, potentially underlying compulsive alcohol use, and are thought to be disrupted following chronic alcohol use.

The OFC processes sensory stimuli, with a particular emphasis on olfaction, taste, and oral texture and temperature. Part of the OFC has been characterized as a secondary taste and olfactory cortex, at least in primates (Rolls, 2015). Neurons in the OFC respond to odors, tastes, temperatures, and textures, as well as visual and auditory stimuli, particularly those associated with food and drink, and it is proposed that sparse encoding of combinations of stimuli allows the OFC to generate representations of value to guide motivated behavior (Rolls, 2015). Such a close association between OFC and olfactory and gustatory stimuli is highly relevant to the use of alcohol, in which these features play an important role in use, particularly as compared to other drugs of abuse in which the consummatory sensory components are less-pronounced (compare, for example, the types of sensory stimuli associated with a glass of red wine vs. an intravenous injection of heroin).

The encoding of sensory stimuli, both as cues and outcomes, however, occurs at a very high level in the OFC, being more categorical than selective. Although sparse encoding of stimuli allows regulation of sensory specific satiety (Rolls, 2015), OFC representation of stimuli is multifaceted. OFC signals associated with sensory stimuli are modulated by both appetitive (hunger and satiety) and aversive (e.g., noxiousness) motivations, either with respect to primary outcomes themselves or in regard to cues predicting aversive and appetitive outcomes (Critchley and Rolls, 1996; Gallagher et al., 1999; Gottfried et al., 2003; O'Doherty et al., 2001a; O'Doherty et al., 2001b; Pickens et al., 2003; Tremblay and Schultz, 1999; Valentin et al., 2007). OFC activation is also modulated by exteroceptive contextual and cognitive factors such as spatial location and orientation of attention (Abe and Lee, 2011; Bouret and Richmond, 2010; Feierstein et al., 2006; Lim et al., 2011; McGinty et al., 2016; Roesch et al., 2006; Strait et al., 2016), indicating relatively high-level information processing.

The encoding of stimuli is also strongly modulated by and associated with value in the OFC. In fact, some of the most robust signals in OFC are connected with the value, both positive and negative, of cues or outcomes. The broad conceptualization of OFC as encoding value is reflected in numerous findings at the cellular and regional level. Human OFC subregions are activated by the pleasantness (medial OFC) and unpleasantness (lateral OFC) of presented stimuli (e.g. odors or tastes) or outcomes (e.g., winning or losing money) (Berridge and Kringelbach, 2013; Kringelbach, 2005). As noted above, value, and OFC encoding of value, can be relative – modulated by satiety, context, and the presence or absence of other competing outcomes. In addition to encoding the identity of specific reward- or punishment-associated offers or outcomes, OFC neurons signal the subjective preferences and value of specific outcomes compared to other possible outcomes (Padoa-Schioppa, 2011; Saez et al., 2017; Tremblay and Schultz, 1999; Wallis, 2011). OFC signals associated with rewards and cues predicting rewards are also modulated by reward probability, latency, and magnitude (Burton et al., 2014; Roesch et al., 2006; van Duuren et al., 2007; van Duuren et al., 2008; van Duuren et al., 2009) which, in turn, contribute to the overall value of outcomes and facilitate decisions and actions related to them.

The OFC also plays a critical role in the use of this information to make decisions and guide actions. This is present in the encoding of expected outcomes by the OFC and can be seen in primate and rodent studies (Mainen and Kepecs, 2009; Marquardt et al., 2017; Moorman and Aston-Jones, 2014; Murray et al., 2007; Rudebeck and Murray, 2014; Schoenbaum et al., 2009; Sul et al., 2010). Thus, both before and after decisions are made, OFC encodes both the possible expected outcomes and their values and, during or following a choice, an evaluation of the relative value of the chosen outcome. It has been proposed (and debated) that OFC transforms all possible outcomes into a “common currency” that can be used to make value-based decisions (Padoa-Schioppa, 2011; Padoa-Schioppa and Schoenbaum, 2015; Rudebeck and Murray, 2014). A number of recent studies have demonstrated that OFC encodes not only the value of specific stimuli, but the relationship between stimuli and their expected outcomes (including the value) (Howard et al., 2015; Lopatina et al., 2015; McDannald et al., 2014a; Ostlund and Balleine, 2007; Schoenbaum et al., 2011).

The chosen option is not the only outcome represented in OFC activity. In some cases, the overall suite of possible choices is encoded, including non-chosen options (Rich and Wallis, 2016; Steiner and Redish, 2012, 2014), which is valuable in the service of decision-making. In others, OFC activation appears to signal regret for missed opportunities, a useful signal for future decision-making (Camille et al., 2004; Coricelli et al., 2005; Coricelli et al., 2007; Steiner and Redish, 2014). Further codifying the role of OFC in representing each component of decision-making, studies in both rodents and humans have demonstrated neural signals related to decision confidence and uncertainty in OFC and vmPFC (Kepecs et al., 2008; Lak et al., 2014; Lebreton et al., 2015; Rogers et al., 1999b; van Duuren et al., 2009), which underscores the role of this system in representing expected outcomes, as expectation-related signals should be stronger in proportion to an individual’s confidence in the likelihood of a specific outcome.

Thus, OFC appears to play a role at each step of the value/reward decision-making process: evaluating both identity and value of potential outcomes, facilitating choices among these

outcomes potentially by converting outcome into a common framework for decisions, encoding the confidence in which a decision is expected to produce a particular outcome, evaluating the actual outcome once the decision is made, and using this information to determine if the outcome was better or worse (e.g., resulting in regret) to guide future decisions. It should be clear to see how a system so deeply ingrained in the reward/punishment decision process could be so closely associated with motivation for alcohol and other drugs of abuse. Further, one can also envision how a disruption of this system may produce impairment in any number of optimal decision-facilitating processes, ultimately resulting in poor choices (e.g., to continue to use alcohol despite associated negative consequences).

OFC also plays a critical role in regulating flexibility in decision-making and behavior, i.e., the ability to change choices or actions when the outcomes change. This has most commonly been demonstrated through the role of the OFC in controlling reversal learning (Boulougouris et al., 2007; Dalton et al., 2016; Dias et al., 1996; Fellows and Farah, 2003; Ghahremani et al., 2010; Ghods-Sharifi et al., 2008; Graybeal et al., 2011; Groman et al., 2013; Hamilton and Brigman, 2015; Iversen and Mishkin, 1970; Izquierdo et al., 2017; McAlonan and Brown, 2003), although recent studies have questioned the specificity of the role of the OFC vs. fibers passing through the region in this aspect of behavioral flexibility (Rudebeck et al., 2013). Furthermore, recent work has indicated that OFC plays a wide set of roles in flexible behavior, including strategy shifting in a version the Wisconsin Card Sort Task (Buckley et al., 2009; Sleezer et al., 2016; Sleezer et al., 2017) and variants of the classical rodent attentional set-shifting task (Chase et al., 2012). Patients with OFC damage have difficulty in gambling-based decision-making tasks (Bechara et al., 1999), which incorporates not only aspects of outcome prediction, as described above, but requires behavioral flexibility to adapt behavior to avoid accumulating negative outcomes. Other examples of the role of OFC in flexible behavior include the ability to change behaviors when reward devaluation occurs, i.e., flexible goal-directed behavior (Barker et al., 2015; Gallagher et al., 1999; Gottfried et al., 2003; Gourley et al., 2013; Gremel et al., 2016; Gremel and Costa, 2013; Izquierdo and Murray, 2004; Rhodes and Murray, 2013; West et al., 2011). Notably, this mirrors natural changes in OFC coding of value under circumstances of, e.g., satiety, as described above, and provides a clear substrate for disruptions in optimal decision-making associated with chronic alcohol abuse, described below.

As our understanding of the OFC has progressed, conceptualizations of the region have grown more and more complex and have resulted in sophisticated conceptualizations of OFC function. Thus the OFC has been implicated as a key regulator of goal-directed, or model-based action planning and execution (Gremel and Costa, 2013; Jones et al., 2012; McDannald et al., 2011; Miller, K.J. et al., 2017) though see (Ostlund and Balleine, 2007), in part as an amalgamation of the diverse set of functions described above. Model-based behavior, in which decisions and actions are based on explicit representations of expected outcomes, is frequently associated with OFC, and other prefrontal regions, as well as the dorsomedial striatum (Balleine et al., 2007; Daw et al., 2005; Doll et al., 2012; Lucantonio et al., 2014a; McDannald et al., 2012). This is in contract to model-free behaviors, more akin to habitual or automatic behaviors in which cached outcome representations guide action,

which are thought to more directly involve other areas such as dorsolateral striatum (Balleine et al., 2007; Daw et al., 2005). Perhaps at the highest level the OFC has been described as encoding specific cognitive states in a map of task space (Farovik et al., 2015; Lopatina et al., 2017; Saez et al., 2015; Schuck et al., 2016; Wikenheiser and Schoenbaum, 2016; Wilson et al., 2014). An assumption underlying these large-scale theories is that within OFC, subregions or specific circuits perform different components of these high-level functions. Separate regions and even individual neurons in OFC exhibit differential responses during goal-directed behavior, for example, indicating that the overarching function of OFC is subserved by regional and circuit control of specific decision-associated variables (Lopatina et al., 2017).

In support of this perspective is the idea that the OFC is not a homogeneous structure but, instead consists of multiple subregions which are often broadly grouped into orbital and medial networks. These different networks have been consistently shown to perform different functions. Studies of human and non-human primate OFC have shown that these dichotomies fall into different categories. Medial OFC and lateral OFC have been shown to encode reward vs. punishment, response engagement vs. inhibition, credit-assignment (i.e., associating outcomes with specific choices) vs. value-guided decision-making (i.e., the ability to compare across multiple choices), and prediction error vs. reversal learning, among other dichotomies (Elliott et al., 2000; Fettes et al., 2017; Kringelbach, 2005; Noonan et al., 2017; Noonan et al., 2011; O'Doherty et al., 2001a; Rudebeck and Murray, 2011; Rushworth et al., 2011; Walton et al., 2011). In the rodent, there have been differences reported between lateral and medial OFC with respect to high- vs. low-value outcome encoding (Burton et al., 2014; Lopatina et al., 2016; Lopatina et al., 2017) as well as response inhibition vs. reward representation (Dalton et al., 2016; Gourley et al., 2010; Gourley et al., 2016; Mar et al., 2011; Stopper et al., 2014). There are also anterior vs. posterior differences in OFC signaling, e.g., abstract vs. concrete reinforcement (Kringelbach, 2005; O'Doherty et al., 2001a) or response selection vs. outcome-based updating (Murray et al., 2015). Thus both medial/lateral and anterior/posterior subregions exhibit a high degree of functional heterogeneity, and even these descriptions likely underestimate its extent. Clearly future work should be directed at understanding precise functions associated with OFC subregions, and probably even specific circuits within subregions. The number of recent publications addressing this issue, as those discussed above, suggests that these studies are underway.

In summary, the OFC plays a comprehensive set of roles in guiding flexible, goal-directed behavior. These go from representing sensory aspects of cues and outcomes, to facilitating shifts in behavior after outcome evaluation, and what appears to be each stage in between. The brief overview of OFC function above does not capture the entirety of contributions of OFC and its subregions to behavior. Instead, it lays out a number of functions that are tied to processes associated with alcohol use and which, if damaged or disrupted by chronic alcohol use, could result in both behavioral deficits observed in chronic alcohol users as well as in the continued use of alcohol despite negative associated outcomes as seen in AUDs. In particular, two major observations connect native OFC function with alcohol use and AUDs. First, the relationship between OFC and outcomes or value, particularly with respect to ingested rewards, indicates that this system could be redirected, via use-associated neural plasticity, to hyperactively value alcohol after prolonged use, resulting in compulsive

seeking. Second, the association between OFC and behavioral flexibility and decision-making is possibly very sensitive to disruption via prolonged alcohol exposure. As discussed further below, chronic alcohol use has profound impacts on OFC structure and function, the results of which could be substantially detrimental to the aspects of cognitive control that are necessary to regulate alcohol use and prevent AUDs. As we see in section 4, below, investigations of human alcohol users and AUD patients support this hypothesis.

3. Overview of OFC and non-Alcohol Drugs of Abuse

Given the prominent role played by the OFC in reward-motivated decision-making, it is intuitive that the region and/or its dysregulation should be a major contributor to drug-seeking and related behaviors, including those associated with alcohol. Before focusing exclusively on contributions of OFC to alcohol use and AUDs, it is worth considering what is known about the role of OFC in substance use disorders (SUDs) more generally, particularly since the contributions of OFC dysfunction to non-alcohol drugs of abuse are more commonly appreciated than they are with respect to alcohol. A considerable amount of information relating changes in OFC structure and function to SUDs has been revealed in a variety of patient populations and animal models. Consequently, a number of excellent reviews on the have been written on the topic (Dom et al., 2005; Everitt et al., 2007; Fettes et al., 2017; London et al., 2000; Lucantonio et al., 2014a; Porrino and Lyons, 2000; Schoenbaum and Shaham, 2008; Volkow and Fowler, 2000; Winstanley, 2007). Here I summarize some general observations and principles that may underlie shared contributions of the OFC to disorders associated with alcohol and other substances of abuse.

3.1. Anatomical and functional rationale for considering OFC as an important node in regulating drug use

The OFC is anatomically well-positioned to regulate drug-seeking behaviors. If is heavily interconnected with other brain regions associated with reward and motivation, emotional regulation, and cognitive control, all of which play a significant role in SUDs. In particular, its connectivity with striatum, amygdala, other prefrontal cortical regions, ventral tegmental area, and hypothalamus, as discussed in section 2.1 above, strongly indicate that it should be considered a node in the network of regions regulating drug use. Furthermore, many of these anatomical relationships are bidirectional. For example, the interaction between OFC and amygdala, in addition to being robust and reciprocal, plays a key role in the service of normal decision-making (Barbas and Pandya, 1984; Baxter et al., 2000; Carmichael and Price, 1995a; Cavada et al., 2000; Churchwell et al., 2009; Fiuzat et al., 2017; Hoover and Vertes, 2011; Lichtenberg et al., 2017; Murray and Izquierdo, 2007; Pickens et al., 2003; Price et al., 1996; Rudebeck et al., 2017; Saddoris et al., 2005; Sharpe and Schoenbaum, 2016; Stolyarova and Izquierdo, 2017; Zeeb and Winstanley, 2013) as well as during drug seeking (Arguello et al., 2017; Lasseter et al., 2011).

Multiple aspects of normal OFC function contribute to the hypothesis that disrupted OFC may contribute significantly to drug use and dependence. As described in section 2.2 above, one of the major functions of the OFC is reward valuation and outcome prediction. Given the potent motivational influence of drugs of abuse, as well as drug-associated cues that

elicit craving and seeking, it is a small leap to presume that aspects of cue and outcome signaling could be redirected towards drugs of abuse. Furthermore, there is reason to suspect that OFC systems come to signal drugs as rewards in addition to signaling cues that predict drugs, in the same way that the system would for natural rewards otherwise.

3.2. Effects of non-alcohol drug use on OFC-associated behavior, OFC structure, and OFC function in humans

Chronic drug use appears to disrupt OFC neuronal integrity, morphology, and function, potentially resulting in diminished control over flexible goal-directed behaviors. Disruption of OFC-associated functions, such as outcome expectancy, value representation, decision confidence, and reward risk, all of which allow natural flexible motivated behavior, may underlie aspects of compulsive drug seeking. Patients with SUDs exhibit inflexible behavior and impaired motivated decision-making, both with respect to drug-associated choices, as well as in laboratory tests (Bechara et al., 2001; Bolla et al., 2003; Ersche et al., 2008; Everitt et al., 2007; Garavan and Hester, 2007; Grant et al., 2000; O'Malley et al., 1992; Rogers et al., 1999a). These behavioral disorders map onto those seen in patients with damage to the OFC (Bechara, 2004; Bechara et al., 2000; Bechara et al., 2001; Fellows, 2011; Glascher et al., 2012). Furthermore, when performing laboratory-based decision-making tasks, chronic drug users exhibit disrupted OFC activation (Bolla et al., 2003; Bolla et al., 2005; Ersche et al., 2005). Such functional deficits were observable in long-abstinent drug users, in some cases 10 years following last drug use, indicating potentially long-lasting effects of drug use on OFC-mediated cognition.

That chronic drug use results in OFC dysregulation is supported by studies of SUD patients in which structural and functional disruptions of the OFC are apparent. Although there are widespread alterations in cortical gray matter after chronic drug use, frontal cortex, and particularly OFC, seem particularly sensitive to drug-associated tissue damage or loss (Franklin et al., 2002; Matochik et al., 2003). OFC gray matter decreases appear to correlate with extent of drug use (Ersche et al., 2011). Along with structural disruptions, SUD patients also exhibit hypoactivation of OFC after chronic drug use and detoxification, both during baseline conditions and during decision-making tasks not involving drugs of abuse (Dom et al., 2005; Goldstein and Volkow, 2002).

In contrast to structural damage and decreased basal activation, OFC is strongly activated by drugs of abuse and drug-paired cues in heavy users and addiction patients, and this OFC activation is significantly associated with craving (Bonson et al., 2002; Breiter et al., 1997; Childress et al., 1999; Garavan et al., 2000; Goldstein et al., 2007; Grant et al., 1996; Kilts et al., 2001; Kufahl et al., 2008; Kufahl et al., 2005; Langleben et al., 2008; London et al., 2000; Lyons et al., 1996; Maas et al., 1998; Risinger et al., 2005; Sell et al., 2000; Volkow and Fowler, 2000; Volkow et al., 1991; Volkow et al., 1996; Volkow et al., 1999; Wang et al., 1999). These results support the idea that, in chronic drug users, OFC circuits are disrupted, potentially even structurally, and that the remaining circuits are overly responsive to drugs and stimuli associated with drugs. This combination of strengthened drug-associated signaling with weakened support for flexible decision-related behavior has the potential to

result in a pathologically-emphasized focus on drugs, enhancing drug motivation and prolonging chronic, problematic use.

3.3. Effects of non-alcohol drug use on OFC-associated behavior, OFC structure, and OFC function in animals

A number of studies in animal models have demonstrated important contributions of OFC to drug seeking and use (Everitt et al., 2007; Schoenbaum et al., 2016; Schoenbaum and Shaham, 2008). Most relevant animal research is performed in rodent models, although there are a number of non-human primate studies of OFC and drug use. One of the earlier findings in animal models was that non-human primates self-administer amphetamine into OFC (Phillips et al., 1981), suggesting that the region is particularly sensitive to modulation by drugs of abuse. More recent studies in non-human primates have demonstrated that OFC metabolism is reduced in cocaine-exposed monkeys (Lyons et al., 1996; Porrino and Lyons, 2000) and that OFC neurons are activated in response to cocaine-associated cues (Baeg et al., 2009).

Drug treatment, particularly chronic psychostimulant use, impairs a number of OFC-dependent or – associated behaviors. Animals receiving chronic cocaine treatment exhibit habitual reward seeking following devaluation, increased impulsive and risky behavior, and deficits in behavioral flexibility such as reversal learning (Calu et al., 2007; Jentsch et al., 2002; Lucantonio et al., 2014a; Lucantonio et al., 2015; Lucantonio et al., 2012; Lucantonio et al., 2014b; Olausson et al., 2007; Roesch et al., 2007; Schoenbaum et al., 2004; Schoenbaum and Setlow, 2005; Stalnaker et al., 2009; Wied et al., 2013). Furthermore, chronic cocaine or amphetamine influences OFC neuron basal activity as well as activity during non-drug tasks, ultimately resulting in a profound disruption of the ability of the region to influence decision-making (Homayoun and Moghaddam, 2006; Moghaddam and Homayoun, 2008; Stalnaker et al., 2007). These disruptive effects of psychostimulants on OFC-associated behaviors were also observed after heroin, but not morphine, self-administration (Lucantonio et al., 2015). These drug-induced disruptions in decision-making have been summarized overall as a chronic drug-induced transition from model-based to model-free behavior (Lucantonio et al., 2014a). This transition is likely due in part to the detrimental effects of chronic drug exposure on OFC neurons, which usually support flexible decision-making processes underlying model-based behavior, as described in section 2.2. above.

Experimenter-induced disruption of OFC function in rodents reduces aspects of drug seeking. OFC lesions block cocaine conditioned place preference (Isaac et al., 1989). Lesions of the rat lateral/ventrolateral OFC do not block cocaine self-administration or drug-induced reinstatement, but alter response patterns and an ability to use cues to guide seeking (Capriles et al., 2003; Hutcheson and Everitt, 2003). Lateral OFC inactivation reduced cue-, shock-, and context-induced reinstatement, and lateral OFC lesions increased cocaine- and context-induced reinstatement, whereas medial OFC lesions decreased self-administration and prime-induced reinstatement and medial OFC D1 dopamine receptor antagonism reduced cue- and prime-induced reinstatement (Capriles et al., 2003; Cosme et al., 2016; Fuchs et al., 2004; Kantak et al., 2009; Kantak et al., 2013; Lasseter et al., 2009). Together

these results indicate selective effects of OFC subregions in driving drug seeking. The lateral OFC-associated findings were recently extended to demonstrate that inactivation of projections to BLA decreased cue-and context-induced reinstatement to cocaine seeking whereas inhibition of BLA projections to lateral OFC did not (Arguello et al., 2017; Lasseter et al., 2011).

OFC neurons in rodents are reliably activated by drug-associated cues and contexts in drug-conditioned animals. Self-administration and cue- or context-induced reinstatement activates OFC neurons and induces molecular markers of increased plasticity (Fanous et al., 2012; Hamlin et al., 2008; Hearing et al., 2008; Koya et al., 2006; Kuntz et al., 2008; Winstanley et al., 2009; Winstanley et al., 2007; Zavala et al., 2008). During self-administration, OFC neurons are activated by presentation of cues associated with cocaine and heroin outcomes as well as during actions leading to drug acquisition, and neuronal activation is correlated with drug preference relative to natural rewards (Guillem and Ahmed, 2017; Guillem et al., 2017; Guillem et al., 2010), similar to the association between OFC activation and craving in humans, described above. These relationships, and the fact that they appear to be preserved across species, supports the idea that OFC encodes aspects of motivation for drugs of abuse such as psychostimulants and opiates, and that hyperactivation of these networks may drive compulsive use.

Chronic drug exposure in animals also produces changes in neuronal morphology. Self-administered amphetamine and experimenter-administered nicotine decreased OFC neuron spine density, whereas morphine and sucrose self-administration increased spine density, and cocaine self-administration had no effects (Crombag et al., 2005; Kolb et al., 2004; Robinson et al., 2002). However, the effects of drug administration on OFC neuronal structure is complex, depending on factors such as species (e.g., rats vs. mice) sex, age of use, and behavioral outcomes such as the impact of chronic drug use on goal-directed behaviors (DePoy et al., 2016; DePoy et al., 2014; DePoy et al., 2017; Gourley et al., 2012). Disruptions of OFC neuronal structure and, via spine remodeling, connectivity, are very likely to have profound impacts on OFC-associated behaviors, the result of which may lead to poor decision-making associated with, and potentially facilitating, prolonged compulsive drug use.

Together, the studies presented above, among others, indicate a prominent role of the OFC in drug seeking and problematic use, although the exact contributions of OFC to drug seeking remain to be revealed. Chronic drug use disrupts OFC neuronal structure which leads to decreased basal function and diminished activation in non-drug-associated behaviors. Simultaneously, OFC neurons come to over-represent drug-associated cues after chronic exposure, implying a re-prioritization of OFC resources away from natural goal-directed behavior and towards continued drug seeking. Future studies investigating OFC disruption specifically in addiction-associated behaviors (punishment-resistance, compulsive use, etc.), as distinct from underlying reward-seeking, will be important in establishing the centrality of this region in the addiction network. Should addiction-specific functional roles of OFC be identified, mechanistic studies of the cellular correlates of this transition, probed across multiple OFC subregions and networks, will be important next steps. Such studies will be

critical in transitioning from knowledge that the system is disrupted to understanding how and what can be done to repair OFC damage.

4. OFC and Human Alcohol Use

4.1. Introduction – alcohol and OFC in humans

As discussed in section 2.2, the OFC plays an important role in regulating flexible decision-making behavior, particularly through evaluation of rewards and other outcomes. Furthermore, there is clearly an association between OFC dysfunction and drug abuse and addiction (section 3). Unsurprisingly, therefore, there is a growing indication that the OFC is particularly important in the context of motivation for alcohol, and its disruption may be a key component of AUDs. Reports of disordered human OFC structure and function in alcoholism have been consistently been published since the 1990s, and a number of groups have identified the frontal lobes, including the OFC, as the brain regions most affected by chronic alcohol use (Crews and Boettiger, 2009; Oscar-Berman, 2012; Rosenbloom and Pfefferbaum, 2008; Sullivan and Pfefferbaum, 2005; Zahr et al., 2017).

Much work has been done investigating the role of the OFC in AUDs in human patients, particularly using neuroimaging technology such as PET or MRI to identify structural or functional changes resulting from chronic alcohol use. In general, five main themes emerge from the study of human OFC in alcohol using or dependent subjects, similar to those observed in the context of other drugs of abuse. Each of these will be discussed in more detail in the paragraphs that follow. First, chronic alcohol users exhibit decreased cognitive performance on tasks associated with OFC function such as regulation of impulsive decision making, risky behavior, and behavioral flexibility. Second, there are structural changes in the OFC of chronic alcohol users. These are most frequently characterized as decreases in gray and white matter or overall volume, but alterations in connectivity between the OFC and other structures are also reported. Third, baseline activation of OFC is reduced in chronic alcohol users. Fourth, OFC exhibits significant and selective increases activation by alcohol cues in chronic alcohol users relative to light drinkers or abstainers. Fifth, imaging and analysis of OFC tissue from human patients with AUDs or heavy alcohol use reveal a number of differences in signaling pathways in OFC such as differential neurotransmitter receptor subunit expression. One important question that emerges from these studies is whether or not behavioral and OFC disruption is temporary, resolving after extended periods of abstinence, an issue discussed below.

4.2 Alcohol-induced disruptions of OFC-associated behavior and cognitive functions in humans

Chronic heavy alcohol users and patients with AUDs exhibit behavioral disruptions, particularly associated with cognitive control. The extent of these disruptions has been well characterized over decades of study and has been described extensively (Le Berre et al., 2017; Oscar-Berman and Marinkovic, 2007; Sullivan et al., 2000). Many of the affected behaviors are those that have been commonly associated with OFC function. Critically, many of the behavioral disruptions map surprisingly strongly onto those seen in patients with damage to the OFC and vmPFC.

In general, alcoholic patients demonstrate poor control over impulsive behavior, affecting the ability to inhibit responses and make appropriate decisions (Lejuez et al., 2010; Verdejo-Garcia et al., 2008). This has been quantified using classic self-report measures of impulsivity such as the Baratt Impulsivity Scale (BIS) (Mitchell et al., 2005; Wang et al., 2016). Chronic alcohol use also impairs performance in laboratory-based tasks of different aspects of impulsivity such as delay discounting (Boettiger et al., 2007; Kollins, 2003; MacKillop et al., 2010; Mitchell et al., 2005; Mitchell et al., 2007), go/nogo tasks (Kamarajan et al., 2005), stop-signal tasks (Field and Jones, 2017; Smith et al., 2014; Stavro et al., 2013), and the balloon-analogue risk task (Fein and Chang, 2008; Wang et al., 2016). There appears to be heterogeneity across subjects whereby individuals exhibit different levels of disruption across different impulsivity dimensions, and results of laboratory-based measures do not necessarily map onto self-report (Dom et al., 2006a), indicating heterogeneity in alcohol-induced neural disruptions across individuals.

Alcohol users also exhibit poor performance on reward-based decision-making tasks such as the Iowa Gambling Task, reliably choosing high-reward, high-penalty (i.e., disadvantageous) outcomes (Bechara et al., 2001; Cantrell et al., 2008; Dom et al., 2006b; Fein et al., 2004; Mazas et al., 2000; Miranda et al., 2009; Noel et al., 2007). Notably, these deficits are commonly seen in patients with damage to the OFC (Bechara et al., 1999; Bechara et al., 2001; Brevers et al., 2014; Dom et al., 2005; Mazas et al., 2000; Noel et al., 2007). These poor reward/punishment decisions may be based on an increased motivation for immediate reward and bias towards risky decisions, which interferes with working memory to diminish its ability to use previous information to guide decisions (Brevers et al., 2014).

Abstinent alcoholics and chronic heavy users exhibit deficits in tasks involving behavioral flexibility, particularly in the context of reversal learning and as measured during attentional set-shift tasks such as the Wisconsin Card Sort Task (Beatty et al., 1995; Fillmore and Rush, 2006; Goldman et al., 1985; Jenkins and Parsons, 1979; Kish et al., 1980; Parsons, 1983; Rourke and Grant, 1999; Tivis et al., 1995; Vanes et al., 2014; Yohman et al., 1985). Chronic alcohol users also exhibit impairments in reversal of classical eyeblink conditioning (Fortier et al., 2009; Fortier et al., 2008). Although different subregions of the PFC control different aspects of set-shifting tasks, the OFC likely plays some role in reversal, as described above, and recent work indicates that OFC may contribute to other aspects of flexibility in set-shifting tasks (e.g., intradimensional and extradimensional set establishment and shifting) depending on the type of paradigm employed (Chase et al., 2012; Sleezer et al., 2016; Sleezer et al., 2017).

Taken in sum, chronic alcohol use results in disruption of a broad swath of behaviors and cognitive functions, only some of which are outlined here. Many of these functions are associated with an intact OFC, such that alcohol-associated disruption of OFC structure or function could result in one or more of the observed alcohol-associated deficits. Each of these behavioral measures obviously involves the integration across multiple brain regions. However, a substantial number of these functions or metrics (e.g., performance on gambling tasks, delay discounting, reversal learning, etc.) are closely associated with OFC function, as described in section 2.2 above, indicating that the influence of chronic alcohol on the OFC may be playing a fundamental role in the disruption of many components of executive

function and decision-making. Disruptions of these behaviors have profound implications on the ability to regulate alcohol use. Inability to recognize the value of reward or penalty outcomes and a predilection for immediate risky rewards can both contribute to further alcohol use and compound this with additional risky behaviors further complicating treatment efficacy. Poor behavioral flexibility challenges the ability of subjects with AUDs to move away from patterns of problematic drinking behavior and adopt less disruptive behavioral strategies that could serve as solutions to, e.g., stress.

4.3 Alcohol-induced disruptions of OFC structure in humans

Subjects with AUDs also exhibit damage to the OFC, which may underlie aspects of these cognitive disruptions. It has been well established that the frontal lobes of chronic alcohol users undergo dramatic reductions in volume (Crews and Boettiger, 2009; Kubota et al., 2001; Rosenbloom and Pfefferbaum, 2008; Sullivan and Pfefferbaum, 2005; Zahr et al., 2017). This ultimately results in a range of chronic alcohol-induced behavioral and emotional disorders, some of which are tied to OFC functions as described above. Early studies using MRI demonstrated decreased gray matter in the prefrontal cortex of alcoholics (Jernigan et al., 1991; Pfefferbaum et al., 1988; Pfefferbaum et al., 1997; Pfefferbaum et al., 1998), and a comparison of cortical volume in Korsakoff's syndrome patients revealed a particularly high volume loss in the OFC (Jernigan et al., 1991). These decreases in prefrontal volume were significantly greater in older vs. younger alcoholics, and included both gray and white matter deficits in older alcoholics (Pfefferbaum et al., 1997).

A more precise focus on OFC specifically reveals consistent reports of decreased OFC volume in alcoholic patients and a reliable finding that OFC cortical volume is a significant predictive factor in future relapse. OFC white and gray matter volume is greater in recovering alcoholics vs. active high drinkers (Harris et al., 2008; O'Neill et al., 2001), and left OFC volume is decreased in antisocial personality subjects and the decrease is correlated with extent of alcohol use (Laakso et al., 2002). OFC volume is also decreased in prospectively relapsing alcoholics vs. those who would maintain continued abstinence for three months (Beck et al., 2012), and lateral OFC surface area and volume was decreased in prospective relapsing vs. 5–12 month abstaining patients (Durazzo et al., 2011). Abstinent recovering AUD patients exhibit increased left lateral OFC volume relative to light drinkers, and relapsing patients show decreased left and (to a lesser degree) right OFC volume (Cardenas et al., 2011). Generally speaking, the trend across studies is that OFC volume is reduced in chronic alcohol users and that the extent of reduction is a predictor of future relapse. Other groups who have reported decreased OFC volume in abstinent alcoholics, however, have shown other correlations between relapse probability and damage to additional brain areas such as dorsal medial prefrontal cortex and cingulate (Rando et al., 2011), indicating that the factors predicting future relapse to alcohol are likely multifaceted and engage multiple brain areas.

In addition to age and duration of drinking, sex may be a factor in understanding the impact of alcohol use on OFC structure and function. Some studies have found decreased OFC volume in alcoholic patients in withdrawal, but no differences between male and female patients (Demirakca et al., 2011). Other groups, however, have reported an association

between left OFC thickness and alcohol use severity, and further found that this relationship was stronger for women vs. men (Thayer et al., 2016). These and other reports indicate that a focus on sex differences in the impact of alcohol on OFC may be an important dimension to consider in future studies.

There is a relationship between alcohol-associated OFC loss, use proclivity, and deficits in cognitive function. Decreased volume in OFC and ventromedial PFC in chronic alcohol users was strongly correlated with number of years of alcoholism, number of withdrawals and poor performance on the Iowa Gambling Task (Le Berre et al., 2014). A similar relationship between medial OFC gray matter and IGT performance was observed in long-abstinent polysubstance users (Tanabe et al., 2009) and between OFC/ventromedial PFC volume and BIS-11 scores in alcohol dependent vs control subjects (Asensio et al., 2016), a relationship also seen in healthy individuals (Matsuo et al., 2009). An important consideration is whether decision impairments are influenced by extent of drinking or whether they represent a premorbid risk factor, a proposal supported by previous findings that pathological gamblers and alcohol dependent patients both perform poorly on the Iowa Gambling Task (Goudriaan et al., 2005). Other studies have observed decreased gray matter volume in the OFC of alcohol dependent patients, but did not find an association between this decrease and multiple measures of impulsivity such as BIS, delay discounting, go/nogo or Balloon Analogue Risk Task (Wang et al., 2016). Combined, these results suggest a relationship between OFC/ventromedial PFC damage, alcohol use, and decision-making, but indicate that more research is warranted.

Direct measures of tissue damage also support an impact of alcohol on OFC. Both neurons and glia were decreased in BA 47 measured in postmortem tissue taken from alcoholics (Miguel-Hidalgo et al., 2006). The density of neurons in OFC was inversely correlated with the duration of alcohol dependence, providing a particularly strong association between alcoholism in humans and OFC disruption at a cellular level. Other studies has shown increased neuronal death and pro-inflammatory enzymes in postmortem tissue OFC of human alcoholics (Qin and Crews, 2012b) as well as upregulated inflammatory cytokines and receptors such as RAGE, TLR2, TLR3, TLR4, and HMGB1 (Crews et al., 2013; Vetreno et al., 2013). Activation of these markers, which was inversely correlated with age of onset of drinking and positively correlated with overall lifetime alcohol consumption, may contribute to the observed volume and neuronal loss observed in prior studies.

Of note, in addition to OFC disruption, almost all of the reports above note decreased brain volume in a range of areas, including other prefrontal and parietal cortical areas, particularly cingulate and dorsolateral PFC, as well as in striatum, thalamus, and other subcortical areas. These studies indicate that the impact of chronic alcohol use is widespread throughout the brain. However, the consistent observation of OFC disruption demonstrates that OFC is particularly sensitive to disruption in chronic alcohol use.

OFC connectivity with other brain regions is also disrupted in heavy alcohol use and, in some cases, can predict it (Figure 1). The strength of OFC-amygdala resting-state functional connectivity, measured with fMRI in adolescents, inversely correlates with and predicts future alcohol use (Peters et al., 2015; Peters et al., 2017). This decrease in OFC

connectivity is also either maintained or exacerbated after chronic alcohol use. In alcoholics the relationship between metabolic activity in OFC and dopamine binding in the ventral striatum and putamen is disrupted, essentially demonstrating a dysregulated connectivity between prefrontal cortical areas, including OFC, and ventral striatum and dopamine neurons in the ventral tegmental area and/or substantia nigra (Volkow et al., 2007). In addition to decreased frontal gray and white matter integrity in alcohol dependent patients, there is lower resting state functional connectivity across OFC and parahippocampal gyrus, suggesting a decreased influence of these and other "higher level" cortical regions across the brain (Wang et al., 2016).

Importantly, decreases in OFC structure appear to improve over prolonged abstinence (Sullivan and Pfefferbaum, 2005). As noted above, recovering alcoholics have a larger OFC volume than active high drinkers (O'Neill et al., 2001). When compared across scans taken approximately 3 months apart, patients who relapse continue to have reduced OFC gray matter whereas those who remain abstinent see an increase in volume relative to the first scan (Demirakca et al., 2011). In addition to providing more detail on the acute impact of ethanol on OFC neural tissue, these studies also suggest that some hope maybe warranted for neural restoration, at least in OFC, in recovering alcoholics.

4.4 Alcohol-induced disruptions of OFC activation in humans

Patients with AUDs exhibit decreased OFC activation during resting or baseline conditions, or during tasks not associated with alcohol. Basal activation of left OFC, measured using cerebral blood flow, was decreased in 10-day abstinent alcoholic patients (Catafau et al., 1999). The authors also noted that OFC/PFC impairment is seen in as many as 65–67% of patients in their, and previous other, studies (Kuruoglu et al., 1996; Nicolas et al., 1993). Decreased basal OFC metabolic activity was also observed in PET scans of alcoholic patients after 8–15 days of detoxification but showed a recovery of activation to the level of healthy controls after 31–60 days (Volkow and Fowler, 1994). Another study by the same group replicated the observation of decreased OFC activation in early detoxification, but found persistent decreases in baseline activation after 8–11 weeks of detoxification, suggesting that there may be some degree of variability in recovery of function (Volkow et al., 1997). This study also reported a decreased change in OFC activation in response to the benzodiazepine lorazepam indicating potential disruption in GABA signaling in the OFC of alcoholic patients, a replication of previous work by this group (Volkow et al., 1993).

OFC activation is also decreased during cognitive tasks in subjects with AUDs. Abstinent alcoholic patients exhibited reduced OFC activity during a delay discounting task (Boettiger et al., 2007). OFC activation in this task was correlated with willingness to select the larger, delayed reward, suggesting that an impairment in OFC activation in alcoholic patients may result in an inability to consider longer-term beneficial outcomes ultimately contributing toward overall impaired decision-making. This group also demonstrated that treatment with the μ-opioid receptor antagonist naltrexone elevated OFC activity during this task and increased willingness to choose a delayed larger reward, and that these two outcomes were correlated at an individual level (Boettiger et al., 2009). The interaction between alcohol, OFC activation, and the μ-opioid receptor appears robust as discussed further below. During

performance of a monetary rewarded card-guessing task, young adults with alcohol dependence exhibit decreased lateral OFC activation and increased negative correlation between OFC and striatal responses (Forbes et al., 2014), supporting the general finding that alcohol disruption of OFC function, and its relationship with other brain areas, compromises value-driven decision-making.

4.5 Alcohol-associated OFC activation in humans

A number of studies have shown that OFC is strongly activated by alcohol-associated cues in alcohol users, particularly in heavy users and alcohol dependent patients. In alcohol dependent patients detoxified for at least seven days, visual alcohol-related cues increased activation of OFC (Wrase et al., 2002). OFC activation is also increased in response to visual alcohol cues in adolescents with AUDs (Tapert et al., 2003). Although both boys and girls with AUDs exhibited increased brain activation to alcohol cues, OFC increases were primarily found in boys. In a large sample of heavy-drinking subjects, OFC activation was increased during presentation of alcohol taste cues relative to litchi juice (Claus et al., 2011). Visual alcohol-cue-evoked increase in left OFC activation which was not impacted by treatment with the D2/D3 receptor antagonist amisulpiride (Hermann et al., 2006), though it is worth noting that craving was not significantly affected by treatment either. There is, however, a relationship between OFC activation and alcohol craving and relapse. Lateral OFC was activated during alcohol cue presentation in non-treatment-seeking alcoholics, and the strength of OFC activation was positively correlated with craving for alcohol (Myrick et al., 2004; Myrick et al., 2008). In addition, in 1–2 month abstinent alcoholics, alcohol cue-driven activation in the ventral striatum, ventral anterior cingulate, and the OFC were all positively associated with likelihood of relapse over the course of the next three months (Reinhard et al., 2015).

There is also an important role for ventromedial PFC and OFC in the intersection between stress and alcohol use (Blaine et al., 2017). In social drinkers, OFC activity was increased during presentation of alcohol-based script cues, which induced craving, and stress-based cues, which induced anxiety, in both men and women (Seo et al., 2011). Further research by this group described the combination of hyperactivity in ventromedial PFC during neutral conditions and hyporeactivity during stressful conditions as being correlated with craving and predicting relapse in alcohol dependent subjects (Blaine et al., 2017; Seo et al., 2013). They also reported hypoactivation of left lateral OFC during alcohol, stress, and neutral cues relative to healthy control subjects. These results contrast somewhat with results above describing both hypoactive OFC during rest and hyperactive OFC during cues in abstinent AUD patients, although these differences may stem from experimental design (e.g., including a stressful condition) or anatomical parcellation (ventromedial PFC/medial OFC vs. lateral OFC). However, all are broadly in line with disrupted OFC/ventromedial PFC function in patients with AUDs. Furthermore, these results indicate that the ventromedial PFC, including OFC, may be a key component of the influence of stress on problematic alcohol use (Blaine and Sinha, 2017). Clearly further studies are warranted, particularly those investigating potentially separable differences in OFC subregion activation by cues and stress.

4.6 Alcohol-associated OFC neurochemistry in humans

Studies have identified a relationship between the OFC and the μ-opioid receptor in alcohol use, as noted above (Boettiger et al., 2009; Mitchell et al., 2007). Individuals with the G (vs. A) allele of the OPRM1 gene exhibit greater motivation for and sensitivity to alcohol (Filbey et al., 2008; Ray and Hutchison, 2004, 2007; van den Wildenberg et al., 2007). Given the high density of μ-opioid receptors in OFC (Cross et al., 1987; Le Merrer et al., 2009; Zubieta et al., 2001), the relationship among these variables seems like a potentially promising avenue for treatment. OFC is activated in response to alcohol taste cues in heavy drinking or dependent subjects, and this activation is stronger in subjects with the OPRM1G allele (Filbey et al., 2008; Ray et al., 2014). OFC activation in this patient population was also correlated with responses on the Alcohol Urge Questionnaire (Filbey et al., 2008). Alcohol consumption itself increases endogenous opioid release, particularly in the OFC (Mitchell et al., 2012). The strength of this release-induced change in binding was correlated with subjects' positive reports of intoxication. This effect was stronger in heavy-drinking subjects vs. healthy controls, as was the correlation between opioid release and scores on the Alcohol Use Disorders Identification Test. Further supporting an important role for μ-opioid receptors, naltrexone reduced alcohol cue-evoked activation of OFC as well as alcohol craving (Lukas et al., 2013; Myrick et al., 2008). As noted above, naltrexone also elevates previously depressed OFC activity during non-alcohol based reward decision-making in abstinent alcoholics (Boettiger et al., 2009; Boettiger et al., 2007), indicating a potentially normalizing effect of μ-opioid receptor antagonism in the OFC of patients with AUD. In one study, naltrexone treatment had a more pronounced influence on cue-evoked lateral OFC activation in OPRM1 G-allele carriers vs. those with the A-allele though, somewhat surprisingly, this study did not report independent effects of either factor on activity (Schacht et al., 2013). Taken together, a substantial number of findings in human alcohol users indicate an important interaction between the μ-opioid receptor and orbitofrontal cortex in driving alcohol cue reactivity, motivation for alcohol, and possibly dependence.

A number of other studies have indicated that multiple neurotransmitter/neuromodulator systems may contribute to OFC activation and are disrupted in AUD. Subjects expressing the 7-repeat allele of the DRD4 variable number of tandem repeats, which has been associated with motivation for alcohol, also exhibit elevated OFC activity in response to alcohol cues (Filbey et al., 2008; Hutchison et al., 2002; Hutchison et al., 2006; Hutchison et al., 2003). As noted above, alcoholic patients exhibit disrupted DA release in the OFC and a disrupted relationship between OFC activation and striatal dopamine signaling (Volkow et al., 2007). Previous work as also shown decreased serotonin-induced activation of the OFC in alcoholic patients (Hommer et al., 1997). The nicotinic acetylcholine receptor partial agonist varenicline reduced alcohol cue-evoked activation of the lateral OFC in non-treatment-seeking heavy alcohol users, suggesting an effect of acetylcholine modulation on this system, potentially indirectly via the acetylcholine regulation of dopamine (Schacht et al., 2014). Cannabinoid type 1 receptors are upregulated in OFC (among other areas) of abstinent alcohol-dependent, but not control, subjects (Neumeister et al., 2012). Excitatory and inhibitory signaling is also disrupted in alcohol dependent patients. Alcoholics exhibit a decreased OFC response to lorazepam, indicating a decreased sensitivity to inhibitory neurotransmission during early detoxification (Volkow et al., 1993). In support of these

findings, β2 and δ GABA subunits were significantly decreased in postmortem OFC tissue taken from individuals suffering from alcohol dependence vs. those without (Jin et al., 2011). These changes were found in OFC, but not dorsolateral PFC, indicating potential selective alterations in inhibitory signaling in the OFC of chronic alcohol users. The authors also found increased GluN3A NMDA receptor subunit expression in OFC, but not dorsolateral PFC, and unlike hippocampus, no changes in other NMDA or AMPA receptor subunit expression (Jin et al., 2014). Together, these results suggest an overall disruption of excitatory/inhibitory balance in the OFC of patients with AUD, potentially concomitant with disruption of neuromodulatory signaling pathways.

4.7 Summary – alcohol and OFC in humans

In general, there is support across multiple domains that human OFC structure and function is disrupted following, and potentially leading up to, chronic alcohol use. Caveats with respect to the results presented above include the fact that OFC is almost never the only region associated with alcohol craving, relapse, or disorders, and in some cases OFC activation is not observed as a main factor. This variability in results may derive from heterogeneity across study subjects resulting from drinking history, abstinence duration, use of other drugs of abuse or other concomitant neuropsychiatric disorders, or other relevant factors. Ultimately this variability emphasizes the complexity of AUD as a diagnosis and suggests that multiple clusters of patient types, with multiple possible treatment routes, exist. However, it is clear that across a number of research groups and different subject cohorts, the OFC is frequently identified as a structure that is associated with alcohol use and dependence. This association may be particularly important in specific cohorts of patients with AUD such as those with OPRM1 gene variants, as described above. This association hints that attention to OFC hypo- and hyperactivation may produce biomarkers and potential personalized treatments for subtypes of AUDs.

5 OFC and Animal Models of Alcohol Use

5.1 Studying alcohol use in animals

As work in human alcohol users and alcohol dependent patients shows, the OFC is consistently involved in motivation for alcohol and is sensitive to disruption following chronic alcohol use. Understanding the role of the OFC in alcohol use and dependence from a cellular perspective has significant potential to further identify its specific contributions to alcohol motivation, how it is dysregulated in AUD, and potential treatments with OFC as a target (Barker et al., 2015). In order to develop a mechanistic understanding of OFC contributions animal models are of critical importance. In recent years, studies involving animal model research focusing specifically on the contributions of OFC has increased, but there is clearly more work to be done.

When considering the role of OFC in animal models of alcohol use, it is worth briefly noting the different techniques used to study the topic. The most common method of investigation, particularly in rodent models, involves exposure to an ethanol solution to drink in the home cage. Ethanol percentages generally range from 1% to 20%. There is variability in alcohol consumption across rodents, with some strains consuming relatively low levels and others

consuming higher amounts on average (Crabbe, 2014; Crabbe et al., 2010; Griffin, 2014; Vendruscolo and Roberts, 2014; Vengeliene et al., 2014; Vengeliene et al., 2005). Additional steps are sometimes required to induce or enhance alcohol drinking. Ethanol can be combined with sucrose or other palatable substances to facilitate acquisition (Carrillo et al., 2008; Koob and Weiss, 1990; Samson, 1986). The frequency and duration of alcohol access varies across studies, and certain strategies, such as alcohol deprivation, drinking-in-the-dark, or intermittent access presentation structures are used to increase alcohol consumption and model binge (Bell et al., 2014; Rhodes et al., 2005; Sinclair and Senter, 1968; Thiele and Navarro, 2014; Vengeliene et al., 2014). Selectively-bred rodents, such as P rats or HAD rats, are often used to facilitate drinking studies (Bell et al., 2006; Colombo et al., 2006; Gessa, 2016; McBride et al., 2014; Sommer et al., 2006). Chronic access to alcohol, either through the use of prolonged home cage drinking or intermittent exposure to alcohol vapor is frequently used to induce dependence-like states (Becker and Lopez, 2004; Griffin, 2014; Hopf et al., 2010; Hopf and Lesscher, 2014; Roberts et al., 2000; Rogers et al., 1979). These manipulations both increase drinking levels and generate aspects of alcohol use, such as prolonged withdrawal and punishment-resistance, that more faithfully reflect human alcohol use disorders (Hopf and Lesscher, 2014). Various forms of stress are also incorporated in order to produce a more human-like dependence state as well (Becker et al., 2011; Butler et al., 2016; Le and Shaham, 2002; Liu and Weiss, 2002; Lopez et al., 2016; Norman et al., 2015; Spanagel et al., 2014). In addition to home cage consumption, other behavioral tests, such as operant self-administration of oral alcohol delivery or conditioned place preference, are used to investigate aspects of alcohol preference and motivation, similar to other drugs of abuse (Le and Shaham, 2002; Lopez and Becker, 2014; Mahler et al., 2012; Vendruscolo and Roberts, 2014). As discussed further below, OFC may be differentially or selectively involved in regulated vs. binge or dependence-associate drinking or, as seen for other drugs of abuse, reinstatement or relapse. Alcohol-induced OFC disruption may also influence decision-making or other cognitive functions associated with optimal behavioral control. In general, therefore, when investigating the involvement of OFC in regulating alcohol use, details of which aspects of seeking, motivation, preference, or consumption are important to factor into experimental design and interpretation.

5.2 Alcohol-associated alterations in non-human primate OFC

Although the majority of animal studies of alcohol use employ rodents, a number of studies focus on non-human primates, and a small number of primate studies have investigated the role of the OFC and/or its dysregulation in alcohol use. The relative similarities between human and non-human primate frontal cortex as compared to rodents (Preuss, 1995) indicate that non-human primate studies are particularly valuable for understanding the OFC and alcohol. Acute alcohol administration induced deficits in macaque monkeys in a reversal task (Jedema et al., 2011). Given the association between OFC and reversal learning as well as the significant effects at relatively low and moderate alcohol concentrations, the authors proposed that the OFC may be particularly sensitive to alcohol use, a conclusion supported by human research, as described in section 4.2 above. Chronic alcohol use (~1.5 years) in cynomolgus monkeys resulted in decreased mRNA expression for GABA receptor a2 and a4, and b1 and b3 subunits in chronic drinking monkeys (Hemby et al., 2006). These results support the overall theme of GABAergic dysfunction in OFC of human alcoholics (Volkow

et al., 1993) and overlap to some degree with GABAergic dysregulation seen in human postmortem tissue (Jin et al., 2011). In a study of glutamate receptor dysregulation in the frontal cortex, again after chronic ethanol self-administration in cynomolgus monkeys, this group found decreased GRIN 1–1 and increased GRIN 1–2 NMDA receptor subunit mRNA expression, as well as a positive correlation between GRIN2B subunit mRNA expression and overall ethanol intake (Acosta et al., 2010). In a recent study, pyramidal neuron activity was recorded in OFC slices taken from chronically high-drinking cynomolgus monkeys (Nimitvilai et al., 2017b). The authors found decreased evoked firing, but increased amplitude and frequency of postsynaptic currents, and found that ethanol applied to OFC sections decreased neuronal firing in slices taken from control, but not alcohol-drinking monkeys. They also performed quantitative screening of synaptic proteins taken from OFC of a separate group of ~6 month-drinking monkeys and reported changes in expression of 57 proteins in high-drinking monkeys relative to controls. Of note, they report increased GluA1 AMPA receptor subunit expression in OFC neurons, potentially underlying the observed electrophysiological observations. Functional ramifications of the additional proteins will undoubtedly reveal further functional impacts of chronic alcohol on OFC function. These results support the sensitivity of the primate OFC to chronic alcohol exposure.

5.3 Alcohol-induced alterations in OFC-associated behaviors in rodents

As with other drugs of abuse, there are more rodent studies that have investigated associations between OFC and alcohol use. A number of these studies have demonstrated deficits in reversal learning and other aspects of OFC-mediated behavioral flexibility. Rats receiving four days of binge ethanol treatment exhibit selective deficits in reversal learning (as opposed to spatial reference memory or spatial working memory) in a Morris water maze task along with widespread cortical neuronal death and microglial proliferation, although OFC was not reported in this study (Obernier et al., 2002). Additional studies by this research group demonstrated reversal learning deficits in mice given intragastric binge ethanol in adolescence and also showed diminished expression of D4 dopamine receptor mRNA and protein in the OFC (Coleman et al., 2011). In a more recent study, reversal deficits on a Barnes maze in mice receiving adolescent binge ethanol was associated with increased OFC volume driven by increased extracellular matrix proteins which, it was proposed, result in decreased plasticity in OFC circuits (Coleman et al., 2014). After chronic intermittent access to ethanol vapor (CIE), adult mice exhibited decreased reversal performance in a set-shifting task (Badanich et al., 2011), potentially driven by a number of disruptions in OFC physiology, described further below. Intragastric binge-model alcohol treatment in rats for 13 days significantly impaired reversal in a similar task (Fernandez et al., 2017). Other aspects of behavioral flexibility are impacted by alcohol exposure. Both adolescent and adult CIE resulted in decreased behavioral flexibility in an operant set-shifting task, whereas other aspects of operant behavior (task learning, progressive ratio for natural reinforcers) were undisturbed (Gass et al., 2014; Trantham-Davidson et al., 2014). Similar results were found in mice: CIE exposure resulted in deficits in attentional set-shifting in a maze-based task (Hu et al., 2015; Kroener et al., 2012), and in a traditional pot-digging attentional set-shifting task, combined stress and CIE exposure also disrupted attentional set shifting (Rodberg et al., 2017). Reversal learning was not affected in these studies, in contrast to other studies described above, which suggests that both OFC and

medial PFC are disrupted following CIE treatment, likely in addition to other structures. Other groups found no effect in rats of adolescent alcohol use on operant reversal learning (McMurray et al., 2014), whereas others actually found enhanced reversal learning after CIE treatment in mice, an effect attributed to enhanced dorsolateral striatal plasticity given that no ethanol-induced alterations in dendritic morphology of OFC neurons were observed (DePoy et al., 2013). This overall set of results supports altered flexible behavior in rodents treated with chronic ethanol, but indicates that experimental differences across studies may result in different specific behavioral outcomes.

A number of studies have also demonstrated that chronic alcohol use, particularly in adolescent alcohol intake models, results in elevated risky decision-making (Boutros et al., 2014; Clark et al., 2012; McMurray et al., 2014, 2016; Nasrallah et al., 2011; Nasrallah et al., 2009; Schindler et al., 2014). These studies consistently find that adolescent alcohol exposure in rats induces increased choices on a risky lever (low probability of large reward) during operant probabilistic discounting tasks, either when tested as adolescents or adults. Increased risky behavior is stronger in high-drinking vs. low-drinking rats (McMurray et al., 2014, 2016). These effects may be selective for adolescent as opposed to adult alcohol exposure (Schindler et al., 2014). Given that risk probability and preference appears to be encoded by the activity of OFC neurons (Roitman and Roitman, 2010; Schultz et al., 2011) and that human risk taking is influenced by OFC damage (Bechara, 2004; Bechara et al., 2000; Hsu et al., 2005), one potential source of ethanol-induced altered risk-taking may be disrupted OFC processing. In fact, OFC neuronal activity signaling reward outcome in a risky-decision-making task was disrupted in adult rats with adolescent exposure to alcohol (McMurray et al., 2016). Combined, these results support an important role for the OFC in alcohol-disrupted decision-making, particularly when chronic alcohol use occurs in adolescence. A recent report testing the effects of adolescent alcohol intake on a punishment-based risky decision-making task (Simon et al., 2009) demonstrated no influence of adolescent alcohol intake in rats (Miller, K.M. et al., 2017). Instead the authors found increased delays in making choices in alcohol-exposed rats. These results suggest that the impact of chronic alcohol on risky decision-making should take into consideration the nature of the risk, whether reward- or punishment-based, and that neural systems underlying each type of decision may be differentially influenced by chronic alcohol.

In summary, there appears to be a strong degree of concordance between alcohol-associated behavioral and cognitive disruptions in humans and rodents. These include increased impulsivity, impaired decision-making, particularly value-associated decision-making, and reductions in behavioral flexibility. Together, these similarities strengthen the use of translational models in studying the role of OFC in AUDs, and pinpoint specific behavioral and cognitive frameworks to focus on in future work.

5.4 Alcohol-induced alterations in OFC structure in rodents

In addition to disrupting OFC-associated behaviors, chronic alcohol in animals produces structural and functional disruptions in OFC itself. In addition to describing neuroinflammation and neurodegeneration in the human alcoholic OFC, as described in section 4.3 above, a number of studies have described similar results in the OFC of mice and

rats given adolescent binge-like alcohol treatment (Coleman et al., 2011; Coleman et al., 2014; Crews and Boettiger, 2009; Crews et al., 2013; Qin and Crews, 2012a, b; Vetreno et al., 2013), indicating the high sensitivity of rodent OFC to adolescent alcohol exposure and supporting the predictive value of rodent OFC in comparison with human OFC in studies of chronic alcohol. In adult mice seven, but not zero, days withdrawal from CIE, increased spine density in lateral OFC layer II/III neurons, and this increase was largely driven by an increase of long, thin spines (McGuier et al., 2015). In contrast, other studies found no changes in OFC spine density in mice studied three days after alcohol vapor exposure, although differences were observed in mPFC (DePoy et al., 2013; Holmes et al., 2012). As with ethanol-induced behaviors above, divergent findings across studies may derive from experimental differences such as duration of withdrawal time or differences in subregion of OFC from which tissue was sampled (e.g., more lateral vs. medial or anterior vs. posterior).

5.5 Alcohol-induced alterations in OFC function in rodents

OFC neuronal activation is profoundly influenced by both acute and chronic alcohol. c-Fos and EGR1 expression (used measures of neuronal activation) was increased in OFC, among other areas, following an acute ethanol challenge, and adolescent alcohol exposure significantly blunted this increase (Liu and Crews, 2015). This study also reported decreased pERK1/2 in adolescent alcohol exposed rats, independent of whether or not they received an ethanol challenge as adults, suggesting a constitutive decrease in OFC excitability after chronic alcohol use, as suggested by human studies described in section 4.4 above. The acute influence of ethanol on OFC c-Fos was also reported by other studies (Knapp et al., 2001; Ryabinin et al., 1997; Vilpoux et al., 2009). A history of chronic ethanol vapor exposure also decreased acute-ethanol evoked induction of c-Fos and EGR1 in OFC, and this decrease in signaling was driven through mitogen-activated/extracellular regulated kinase (MEK) and extracellular signal-regulated protein kinase (ERK) pathways, as c-Fos/EGR1 expression was restored following administration of the MEK inhibitor UO126 (Hansson et al., 2008). Thus, acute alcohol appears to activate OFC neurons, as measured by immediate early genes such as c-Fos, and this activation is blunted by previous chronic exposure to alcohol.

The OFC is also activated during alcohol seeking in animals. c-Fos expression in the OFC (in addition to other prefrontal areas) was elevated during reinstatement of alcohol seeking, and both reinstatement and OFC c-Fos expression were reduced with treatment of the orexin receptor-1 antagonist SB-334860 (Jupp et al., 2011). Cue-induced reactivation of alcohol-seeking memories also appears to be driven, in part, through plasticity in the OFC. Cues that evoked memories of alcohol seeking increased mTORC1 signaling (measured as phosphorylation of 4E-BP, S6K, and S6) in the OFC, as well as in central amygdala and medial PFC (Barak et al., 2013). This study also reported increased Arc, GluR1, and PSD-95 expression in OFC and amygdala, indicating that excitatory synaptic plasticity in these regions plays a role in regulating alcohol-seeking memories. When the same group investigated increased alcohol drinking using an intermittent-access binge model, they found increased AKT and S6 phosphorylation in OFC, but not mPFC, of rats and mice (Laguesse et al., 2016). Neither moderate alcohol intake nor sucrose consumption produced the same changes in OFC, indicating a specific role for OFC in highly-motivated alcohol seeking as

evoked by binge-model access, and in line with cue-evoked craving associations seen in humans, as described in section 4.5 above.

Whereas many animal studies implicating OFC in alcohol motivation or alcohol-induced impairment have done so as part of a broader assessment of brain structures, a number of recent studies have focused specifically on targeting the OFC to understand its relationship to alcohol use. In slice recordings of regular spiking neurons from mouse lateral OFC, acute exposure to ethanol decreased OFC neuron excitability via a glycine receptor dependent mechanism and inhibited NMDA EPSCs, both of which lend strong support for an inhibitory influence of alcohol on OFC neuronal function (Badanich et al., 2013). Further work by this group demonstrated that chronic exposure to ethanol vapor increases the excitability of mouse OFC neurons in vitro (Nimitvilai et al., 2016). Pyramidal neurons exhibited increased current-evoked firing, reduced afterhyperpolarization, decreased SK channel function, increased AMPA/NMDA ratio, increased GluA1/A2 AMPA receptor subunit and reduced GluN2B NMDA receptor subunit expression. Neurons also displayed persistent LTP and a decreased sensitivity to ethanol application, all of which support the finding that chronic ethanol exposure results in an increase in excitability of OFC neurons. The effects were stronger after shorter vs. longer withdrawal periods, highlighting potential recovery of function following prolonged abstinence. In a separate report, mice receiving CIE exhibited upregulated alcohol seeking as well as increased mRNA for GluN1 and GluN2A NMDA receptor subunits and increased evoked NMDA-receptor mediated currents in medial OFC neurons (Radke et al., 2017). In addition to glutamatergic mechanisms, enhanced OFC excitability in mice receiving chronic alcohol treatment may result from changes in modulation of pyramidal neurons. Dopamine, norepinephrine, and serotonin each decreased current-evoked spiking in lateral OFC neurons via activation of inhibitory GIRK channels (Nimitvilai et al., 2017a). In CIE-treated mice, the inhibitory effects of these monoamines was lost, ultimately adding another mechanism to the influence of chronic alcohol on the hyperexcitability of OFC neurons. Given the robust monoaminergic innervation of OFC and dependence of monoaminergic regulation of this structure for natural behavior (Agster et al., 2013; Clarke et al., 2014; Clarke et al., 2007; Evers et al., 2005; Furr et al., 2012; Kahnt and Tobler, 2017; Sadacca et al., 2017; Winstanley et al., 2006; Zeeb et al., 2010), these results reveal an additional mechanism whereby native OFC-associated functions such as flexible decision-making may be disrupted after chronic ethanol. Together, multiple studies across research groups indicate that OFC neuron physiology is sensitive to both acute and chronic alcohol. Consistent findings across studies include an inhibitory influence of acute ethanol application and an excitatory influence of chronic alcohol exposure.

To some degree the physiological results appear to run counter to those results seen using immediate early gene (IEG) measures of activation in OFC, which support an excitatory effect of acute alcohol administration on OFC neurons in vivo, and suppression of activation by a history of chronic alcohol use. They also diverge somewhat with findings from human studies, in which OFC tends to be hypoactive in chronic alcohol users, as described in section 4.4 above. Multiple potential explanations may account for these differences. Measurements of activity with IEGs such as c-Fos are indirect and may not necessarily correlate directly with electrophysiological activation. Additionally, IEG activation may result from indirect influences of alcohol on OFC neurons via neuromodulators or

neuropeptides such as dopamine, serotonin, norepinephrine, orexin, or other factors. IEG expression may also be impacted by non-pharmacological influences such as stress, contextual information, or learning. Along the same lines, measurement of OFC activation in humans relies on metabolism or blood flow, which indirectly measures neuronal excitability and may reflect the influence of inputs to the region of interest (Logothetis et al., 2001; Logothetis and Wandell, 2004). Further, measurements in humans likely incorporate combined contributions from both glutamtergic and GABAergic neurons whereas physiological studies to date have focused primarily on changes in glutamatergic pyramidal neuron activity. Timing of physiological measurement may also be an important factor in understanding excitatory vs. inhibitory influences of alcohol on OFC neuron activity. For example, in most mouse studies, CIE followed by withdrawal produces increased OFC excitability. In contrast, in the OFC of mice and macaque monkeys studied within two hours of ethanol, OFC neurons exhibit no change in excitability (mice) or exhibit a combination of decreased evoked firing and increased (presumably AMPA-based) spontaneous postsynaptic currents (Nimitvilai et al., 2017b). These differences, both human and non-human primate vs. rodent, may also result from anatomical differences across species or overall framework of experimental study (*in vivo* vs. *ex vivo* methods of analysis). Ultimately, the influence of alcohol on OFC function is complex and becomes even more complex when attempts to integrate across species and testing paradigms. Further studies that bridge these divides, such as *in vivo* analysis in rodent models, will help disentangle these potential explanations.

One of the first studies to test the impact of OFC manipulation on alcohol motivation in behaving animals probed the effects of either lesions or DREADD-mediated inhibition of lateral OFC on alcohol consumption in CIE- or air-treated mice (den Hartog et al., 2016). Lesions and DREADD inhibition of OFC produced increases in consumption relative to sham- or vehicle treated groups, even when aversive quinine was added to the alcohol. This effect, however, was only present in mice that had undergone CIE, but not air, treatment. These results argue against a role for lateral OFC in driving all aspects of alcohol motivation, but instead suggest that disruption of OFC may release control over alcohol drinking, potentially transitioning the animal from a goal-directed to habitual state, (Gremel and Costa, 2013). Future work investigating these effects in other behavioral paradigms such as self-administration or reinstatement will be useful in further characterizing the nature of the behavioral deficits following OFC disruption, similar to that seen in studies of cocaine seeking (Arguello et al., 2017; Fuchs et al., 2004; Lasseter et al., 2009; Lasseter et al., 2010).

Recently our lab has been probing the direct effect of alcohol seeking on activation of OFC neurons *in vivo*, using single-neuron electrophysiological recording (Hernandez and Moorman, 2016). After a month of intermittent home cage access to 20% ethanol, rats were trained to self-administer ethanol and sucrose. OFC neurons were recorded during blocked or interleaved trials of ethanol and/or sucrose seeking. Although the results are still being analyzed, they demonstrate a clear modulation of OFC activity during alcohol seeking in a surprisingly high number of neurons (25%–50% depending on the context). More neurons were more strongly modulated during sucrose seeking, as might be expected from previous studies (Guillem et al., 2017). However, our preliminary work clearly shows that a population of OFC neurons is modulated during alcohol seeking and the activation of these neurons may be a potential substrate for compulsive seeking after chronic alcohol use. We

are actively pursuing this line of investigation using a number of strategies including recording in other alcohol-associated behavioral contexts as well as manipulations of OFC activity to characterize the causal impact of OFC activation of alcohol seeking (Hernandez et al., 2017).

Finally, it is important to note that any influence of alcohol use on OFC or vice versa does not occur in isolation. As noted in human studies in section 4, many of the reports presented here demonstrate a role for OFC in alcohol-disrupted or – mediated behaviors in conjunction with a range of other brain regions. Thus, any impact of chronic alcohol use on behavior or neural systems driving motivation for alcohol should be considered in the framework of extended neural networks (Barker et al., 2015). With respect to the placement of OFC in these networks in animal models, adult rats exposed to adolescent intermittent intragastric alcohol exhibited disrupted resting state connectivity as measured by fMRI (Broadwater et al., 2017). Among the disrupted connections, the investigators observed diminished functional connectivity between OFC and infralimbic prefrontal cortex, nucleus accumbens, and caudate/putamen. These connections, which represent only a subset of those observed to be disrupted, are of particular interest as they are in line with similar types of disrupted connectivity seen in humans after chronic alcohol use (Volkow et al., 2007; Wang et al., 2016).

6. Summary, Conclusions, and Future Directions

The goal of this review was to present an account of what is known to date regarding the relationship between OFC function/dysfunction and alcohol use. These findings are summarized in Table 1. What is clear from a survey of the literature is that there is a clear association between the OFC and alcohol use. This interaction is potentially bi-directional – with alcohol influencing OFC structure and function and OFC activation regulating aspects of alcohol use. The precise nature of this interaction, however, is still not clear. A number of first-pass conclusions can be drawn from both human and animal studies, although considerably more research needs to be done to refine each of these preliminary summaries.

First, both humans and animals exhibit cognitive and emotional dysregulation following chronic alcohol use and, in many cases this dysregulation involves functions that are subserved by the OFC. Examples of this include behavioral flexibility, risky decision-making, and other aspects of impulse control. Chronic alcohol use impacts a large number of functions, including many associated with additional brain regions, indicating that there is likely not a single brain area that is specifically drives or is disrupted in AUDs. Regardless, the influence of alcohol on OFC associated functions is of consequence for preventing future alcohol use and other negative consequences associated with disrupted decision-making.

Second, chronic alcohol use and/or alcohol binge use, both in humans and animal models, influences OFC structure. This can be seen by decreased volume in human chronic alcohol users and animals exposed to alcohol access. Furthermore, chronic alcohol results in both gray and white matter disruption, indicating not only local dysregulation of cell bodies, but disruption of communication between the OFC and other brain areas. There are cellular correlates of neuroinflammation and neurodegeneration in the OFC of both human

alcoholics and in animals with chronic alcohol access, indicating a potential mechanism of this structural damage and potentially revealing possible treatment or prevention targets. The question of whether OFC structural disruption recovers during abstinence from alcohol remains an open question with profound implications for treatment.

Third, these structural changes in OFC are paralleled by functional changes. In humans with a history of heavy alcohol use, there appears to be an overall decrease in OFC activation during resting and, importantly, during behaviors not associated with alcohol, including some of the decision-making associated behaviors described in section 4.2 above. This implies that alcohol-induced cellular disruption of OFC impacts the kinds of cognitive functions that may protect the individual from problematic alcohol (or other drug) use and other types of risky behaviors. In animal models, acute alcohol appears to have an inhibitory effect on OFC activity, whereas a history of alcohol increases OFC neuron excitability, as measured by *ex vivo* electrophysiological recording. These physiological changes are supported, in some cases, by alterations in glutamatergic receptor profiles, excitatory plasticity, and spine structure, though there is some heterogeneity in these results. In contrast, studies using IEGs as markers for neuronal function show the opposite effect – increased activation following alcohol exposure and decreased activation after chronic use. Future studies, such as those parametrically manipulating or tracking duration of alcohol exposure and withdrawal, and those monitoring OFC activity *in vivo* during alcohol use, will be critical in disentangling these complex constellation of results.

Fourth, there are also effects of alcohol-associated cues and craving on OFC function. In general, the OFC of human heavy alcohol users is strongly activated during presentation of cues associated with alcohol. This increase in OFC activation parallels an increase in craving suggesting that the induction of cue-induced craving is a major function associated with OFC activation. Whether these craving-associated changes in OFC activation have causal implications remains to be determined. Some studies in animal models have begun to address this question, by recording the activity of OFC neurons during alcohol seeking and manipulating OFC neuron activity through the use of pharmacology and DREADDs. This line of research supports an involvement of OFC in alcohol use, but the exact nature of the relationship remains to be determined.

Fifth, and particularly intriguing from a clinical perspective, there are associations between OFC function and genetic variations in neurotransmitter receptors in human alcohol users. Examples include A-G allele variants in the OPRM1 receptor and the 7-repeat allele of the DRD4 receptor, though other receptors and signaling systems such as glutamate and GABA receptors and receptor subunits, which exhibit alcohol-associated neural plasticity, are potentially equally influential. These associations are clinically interesting in part because they permit enhanced focus on genetic/neural-activation biomarkers for potential alcohol misuse which could be identified in individuals to prevent alcohol abuse. In addition, specific neural networks, as defined by the confluence of brain region and receptor profile, may be future targets for treatment. Many caveats go along with this consideration, including the fact that a large number of brain regions in addition to the OFC likely play an important role in driving alcohol use, as well as the fact that targeting circuits in the OFC is still a challenge for novel treatments. Future work characterizing the precise contributions of

OFC in different genetic populations will at least reveal what role the region plays in alcohol use, likely in tandem with other brain networks.

Because the understanding of the contributions of OFC to alcohol use and abuse is in its early days, there are numerous outstanding questions that need to be addressed to fully understand the importance of this relationship. One major issue that is raised across studies is that of regional heterogeneity. As noted in section 2.1 above, the OFC is a large area made up of medial, lateral, rostral, and caudal subregions. In some cases we have begun to understand what roles medial vs. lateral OFC, in both humans and non-humans, play in driving non-drug/alcohol-associated behaviors, but the disruption or activation of selective subregions related to alcohol use is somewhat unclear. Studies using fMRI, for example, to probe OFC activation, have isolated subregional differences in function, but a cohesive theory aligning normal function of these regions with disruptions associated with alcohol remains to be generated. This is true for studies involving both humans and animal models.

Another issue that needs to be considered is the contributions of OFC to different stages of alcohol use. What role does OFC play in driving initiation of drinking, moderate drinking, chronic use, and dependence? What effects of alcohol on OFC structure and function come about through pharmacological impacts of alcohol exposure, circuit-level plasticity, or the influence of withdrawal or abstinence? In humans, these questions are hard to address, though cross-sectional studies across drinking profiles (light drinkers, current heavy drinkers, abstinent alcoholics, etc.) are valuable, as are early steps at developing biomarkers to predict future use. These studies are particularly important in the study of adolescent drinking. Given that the PFC and OFC are still in early stages of development during adolescence and that alcohol drinking often begins during this time period (Brenhouse and Andersen, 2011; Center for Behavioral Health Statistics and Quality, 2016; Crews et al., 2007; Galvan et al., 2006), as well as the fact that the PFC and OFC are strikingly sensitive to alcohol exposure as described in sections 4 and 5 above, a thorough understanding of the OFC in the developing brain, both in the presence and absence of alcohol, is of critical importance for preventing the development of AUDs. Animal models will also be particularly valuable here, as a means of determining the contributions of the OFC and associated areas to the transition from regulated to compulsive alcohol use (Hopf et al., 2010; Hopf and Lesscher, 2014; Seif et al., 2013), both in adolescent and adult animals. The study of the developing brain is facilitated by a shortened developmental timecourse in animals such as rodents, in which the impact of adolescent alcohol exposure on adult OFC function and related behaviors has been demonstrated. Given the possible control available in animal models, a wide range of influences across time can be accessed, and the relationship to each question noted above can be addressed. Coordination of testing paradigms across research groups, or at least a consideration of similarities and differences in this case has the potential to facilitate advances by allowing reliable comparisons across duration and route of alcohol exposure, duration of abstinence, and other important parameters.

In addition to developmental and exposure-associated questions, there are other factors that need to be taken into consideration. A major parameter that needs to be considered is that of sex differences, both in the context of alcohol use broadly, and specifically with respect to

the impact of sex on neural circuits driving alcohol use and dependence. There are clearly sex differences in alcohol use, both in humans and in animal models (Almeida et al., 1998; Becker and Koob, 2016; Blanchard et al., 1993; Ceylan-Isik et al., 2010; Erol and Karpyak, 2015; Fillmore and Weafer, 2004; Greenfield, 2002; Juarez and Barrios de Tomasi, 1999; Lancaster et al., 1996; Lancaster and Spiegel, 1992; Schramm-Sapyta et al., 2014; Vetter-O'Hagen et al., 2009; Vetter et al., 2007; Wilsnack et al., 2000; York and Welte, 1994). Any study of the mechanisms underlying motivation for alcohol will need to consider the fact that systems may be structured differently and differentially contribute to motivated behaviors in males and females. Other factors that contribute to individual differences should also be taken into consideration in future studies of alcohol-associated neural plasticity and function. Individual differences in early-life experience, both in humans and animals, can differentially impact the future use of alcohol and other drugs of abuse (Enoch, 2011; Spear, 2015; Varlinskaya and Spear, 2015). The neural correlates of experience, in the OFC and elsewhere, likely play a critical role in defining the framework with which alcohol exposure interacts to produce resultant behaviors. Along these lines, AUDs do not always exist independently of other mental disease. OFC disruption is implicated in a number of psychiatric diseases, notably impulse control disorders and obsessive compulsive disorder (Ahmari and Dougherty, 2015; Fettes et al., 2017; Meunier et al., 2012; Milad and Rauch, 2012). Studies have reported comorbidity between substance abuse and a number of psychiatric diseases, notably including impulse control and obsessive compulsive disorders (Brady et al., 2007; Mancebo et al., 2009). An important strategy going forward will be to understand similarities and differences across diseases to identify neural changes underlying their development. If, for example AUDs, impulse control disorders, and obsessive compulsive disorders share common features of behavioral control as well as a shared neural correlate of disrupted OFC function, the specific contributions of this brain area to each disorder might be more clearly revealed.

The structure, connectivity, and function of the OFC identify this region as a likely key player in regulating alcohol use. Its role in motivation, decision-making, and behavioral flexibility all indicate that it contributes to the maintenance of alcohol use after chronic exposure, and potentially to the initiation of use. Furthermore, the sensitivity of this area to chronic alcohol means that native functions of the area are disrupted in AUDs, resulting in a damaging feedforward cycle of increased problematic use. Current studies have begun to establish formal relationships between alcohol and the OFC, though there is much work to be done. The research presented here, and additional research underway, clearly indicates that this brain region should be considered an important node in the extended network driving alcohol use. In total, these studies indicate that a thorough understanding of the OFC has substantial potential to reveal novel details about and treatments for addiction to alcohol and other drugs of abuse.

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Highlights

- Orbitofrontal cortex (OFC) guides flexible motivated behaviors
- OFC contributes to and is disrupted in drug abuse and addiction
- Although not as well-studied, OFC is also associated with alcohol use disorders
- This review addresses what is known regarding OFC and alcohol use and dependence

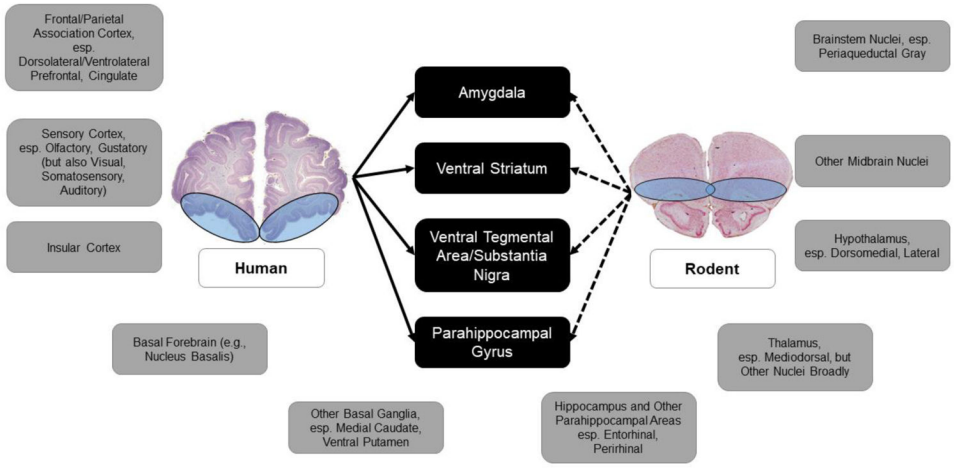

Figure 1.

Anatomical connectivity between OFC and other brain regions with respect to alcohol use and dependence. Nissl-stained coronal sections taken from human (left) and rat (right) brain. Blue-shaded areas represent approximate location of OFC. Black boxes are regions whose connectivity with OFC has been shown to be influenced by alcohol use (see references in section 4.3). Solid lines show that these connections have been exclusively shown in humans. Dashed lines indicate that strong connections are also seen in rodents, but have not been explored in alcohol-related studies (though (Seif et al., 2013) demonstrated a role in compulsive alcohol use for projections to the nucleus accumbens from the anterior insula, which is often grouped with lateral OFC regions). Gray boxes indicate brain regions that have been shown to exhibit connectivity with human and/or rodent OFC, but the relationship between these brain regions and OFC have not studied in the context of alcohol use. Note that these overly general regional characterizations obscure subtle differences across species and across OFC regional networks. See sections 2.1 and 4.3 for references that provide more detail. Human brain image provided by the Brain Biodiversity Bank at Michigan State University (https://msu.edu/~brains/), supported by the National Science Foundation.

Table 1

Studies reported OFC-associated changes after alcohol exposure or use

General overview of findings associated with OFC activation or disruption after acute or chronic alcohol in humans or animal models. Specific studies included in Reference lists are discussed in more detail in the main text.

Category	Human	References	Animal	References
Behavioral/Cognitive	Increased impulsivity	Boettiger et al., 2007; Dom et al., 2006a; Fein and Chang, 2008; Field and Jones, 2017; Kamarajan et al., 2005; Kollins, 2003; Lejuez et al., 2010; MacKillop et al., 2010; Mitchell et al., 2005; Mitchell et al., 2007; Smith et al., 2014; Stavro et al., 2013; Verdejo-Garcia et al., 2008; Wang et al., 2016	Disrupted impulsivity/decision-making	Boutros et al., 2014; Clark et al., 2012; McMurray et al., 2014, 2016; Miller, K.M. et al., 2017; Nasrallah et al., 2011; Nasrallah et al., 2009; Schindler et al., 2014
	Impaired decision-making	Bechara et al., 1999; Bechara et al., 2001; Brevers et al., 2014; Cantrell et al., 2008; Dom et al., 2006b; Dom et al., 2005; Fein et al., 2004; Mazas et al., 2000; Miranda et al., 2009; Noel et al., 2007.		
	Decreased behavioral flexibility	Beatty et al., 1995; Fillmore and Rush, 2006; Fortier et al., 2009; Fortier et al., 2008; Goldman et al., 1985; Jenkins and Parsons, 1979; Kish et al., 1980; Parsons, 1983; Rourke and Grant, 1999; Tivis et al., 1995; Vanes et al., 2014; Yohman et al., 1985	Decreased behavioral flexibility	Badanich et al., 2011; Coleman et al., 2011; Coleman et al., 2014; DePoy et al., 2013; Fernandez et al., 2017; Gass et al., 2014; Hu et al., 2015; Jedema et al., 2011; Kroener et al., 2012; McMurray et al., 2014; Obernier et al., 2002; Rodberg et al., 2017; Trantham-Davidson et al., 2014
Structural	Decreased volume	Asensio et al., 2016; Beck et al., 2012; Cardenas et al., 2011; Crews and Boettiger, 2009; Demirakca et al., 2011; Durazzo et al., 2011; Harris et al., 2008;		

Category	Human	References	Animal	References
		Jernigan et al., 1991; Kubota et al., 2001; Laakso et al., 2002; Le Berre et al., 2014; Matsuo et al., 2009; O'Neill et al., 2001; Pfefferbaum et al., 1988; Pfefferbaum et al., 1997; Pfefferbaum et al., 1998; Rando et al., 2011; Rosenbloom and Pfefferbaum, 2008; Sullivan and Pfefferbaum, 2005; Tanabe et al., 2009; Thayer et al., 2016; Wang et al., 2016; Zahr et al., 2017		
	Decreased neurons and glia	Miguel-Hidalgo et al., 2006	Increased spine density	McGuier et al., 2015; though see DePoy et al., 2013; Holmes et al., 2012
	Increased neuroinflammation	Crews et al., 2013; Qin and Crews, 2012b; Vetreno et al., 2013	Increased neuroinflammation	Coleman et al., 2011; Coleman et al., 2014; Crews and Boettiger, 2009; Crews et al., 2013; Qin and Crews, 2012a, b; Vetreno et al., 2013
	Disrupted connectivity	Peters et al., 2015; Peters et al., 2017; Volkow et al., 2007; Wang et al., 2016	Disrupted connectivity	Broadwater et al., 2017
Functional	Disrupted baseline or non-alcohol-associated function	Boettiger et al., 2009; Boettiger et al., 2007; Catafau et al., 1999; Forbes et al., 2014; Kuruoglu et al., 1996; Nicolas et al., 1993; Volkow and Fowler, 1994; Volkow et al., 1997	c-Fos or other IEGs increased during acute or seeking; decreased after chronic	Barak et al., 2013; Hansson et al., 2008; Jupp et al., 2011; Knapp et al., 2001; Laguesse et al., 2016; Liu and Crews, 2015; Ryabinin et al., 1997; Vilpoux et al., 2009
	Alcohol-associated activation	Blaine et al., 2017; Blaine and Sinha, 2017; Claus et al., 2011; Hermann et al., 2006; Myrick et al., 2004; Myrick et al., 2008; Reinhard et al., 2015; Seo et al., 2011; Seo et al., 2013; Tapert et al., 2003; Wrase et al., 2002	Electrophysiology inhibition after acute, excitation/less inhibition after chronic	Badanich et al., 2013; Nimitvilai et al., 2016, 2017a; Nimitvilai et al., 2017b; Radke et al., 2017

Category	Human	References	Animal	References
Neurochemical	Glu/GABA	Jin et al., 2011; Jin et al., 2014; Volkow et al., 1993	Glu/GABA/Gly	Acosta et al., 2010; Badanich et al., 2013; Barak et al., 2013; Hemby et al., 2006; Nimitvilai et al., 2016; Nimitvilai et al., 2017b; Radke et al., 2017
	DA, 5HT	Filbey et al., 2008; Hutchison et al., 2002; Hutchison et al., 2006; Hutchison et al., 2003; Volkow et al., 2007	DA, NE, 5HT	Nimitvilai et al., 2017a
	ACh	Schacht et al., 2014	ORX/HCRT	Jupp et al., 2011
	CB	Neumeister et al., 2012		
	Mu-opioid	Boettiger et al., 2009; Filbey et al., 2008; Mitchell et al., 2012; Mitchell et al., 2007; Ray et al., 2014; Ray and Hutchison, 2004, 2007; van den Wildenberg et al., 2007 Boettiger et al., 2009; Boettiger et al., 2007; Lukas et al., 2013; Myrick et al., 2008; Schacht et al., 2013		