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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.

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 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

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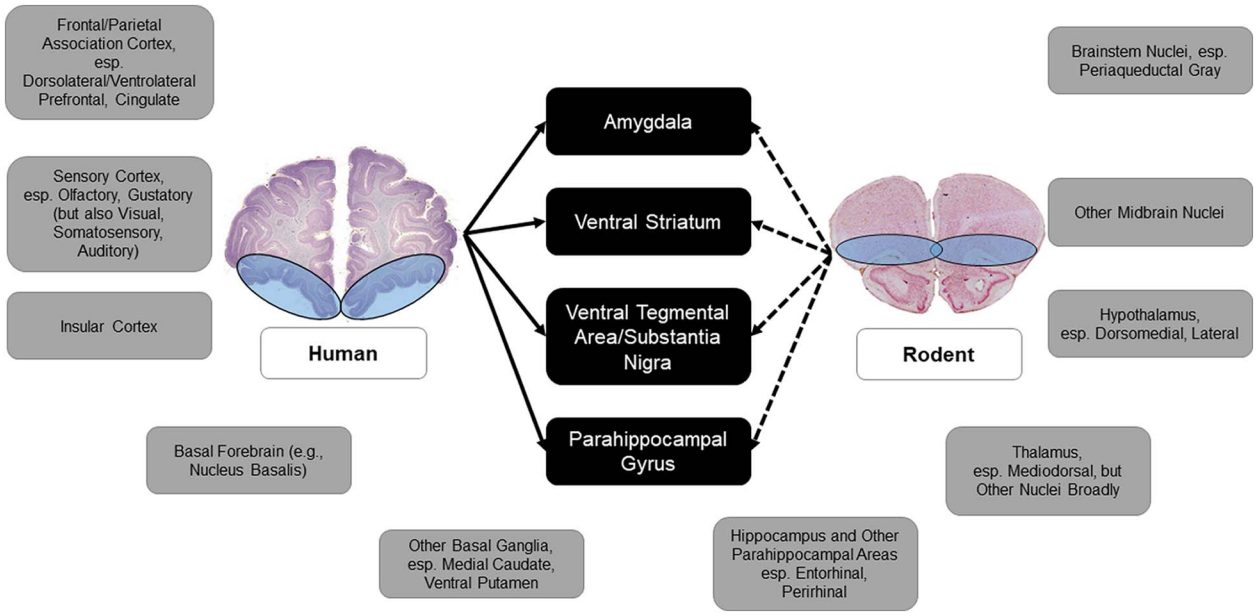

Fig. 1. Anatomical connectivity between OFC and other brain regions with respect to alcohol use and dependence. Nissl-stained coronal sections taken from human (left) and rat (right) brain. Blue-shaded areas represent approximate location of OFC. Black boxes are regions whose connectivity with OFC has 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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, 1995b, 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