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Rodent models for compulsive alcohol intake

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ABSTRACT

Continued seeking and drinking of alcohol despite adverse legal, health, economic, and societal consequences is a central hallmark of human alcohol use disorders. This compulsive drive for alcohol, defined by resistance to adverse and deleterious consequences, represents a major challenge when attempting to treat alcoholism clinically. Thus, there has long been interest in developing pre-clinical rodent models for the compulsive drug use that characterizes drug addiction. Here, we review recent studies that have attempted to model compulsive aspects of alcohol and cocaine intake in rodents, and consider technical and conceptual issues that need to be addressed when trying to recapitulate compulsive aspects of human addiction. Aversion-resistant alcohol intake has been examined by pairing intake or seeking with the bitter tastant quinine or with footshock, and exciting recent work has used these models to identify neuroadaptations in the amygdala, cortex, and striatal regions that promote compulsive intake. Thus, rodent models do seem to reflect important aspects of compulsive drives that sustain human addiction, and will likely provide critical insights into the molecular and circuit underpinnings of aversion-resistant intake as well as novel therapeutic interventions for compulsive aspects of addiction.

The need for animal models of compulsive alcohol intake

Continued seeking and drinking of alcohol despite adverse legal, health, economic, and societal consequences is a central hallmark of human alcohol use disorders (AUDs) (Ahmed, 2012; Koob & Volkow, 2010; Larimer, Palmer, & Marlatt, 1999; Lesscher & Vanderschuren, 2012; Naqvi & Bechara, 2010; Sanchis-Segura & Spanagel, 2006; Spanagel, 2009; Tiffany & Conklin, 2000). This compulsive drive for alcohol, defined by resistance to adverse and deleterious consequences, represents a major challenge when attempting to treat alcoholism clinically (Anton, 2000; Koob & Volkow, 2010; Larimer et al., 1999; Naqvi & Bechara, 2010; Sanchis-Segura & Spanagel, 2006, Spanagel, 2009; Tiffany & Conklin, 2000). Thus, there has long been interest in developing pre-clinical rodent models for the compulsive drug use that characterizes drug addiction. Indeed, rodents have been shown to develop persistent drug or alcohol consumption where intake persists despite overt pairing with aversive consequences. This aversion-resistant intake is considered to model some aspects of human compulsive drives observed in addiction (Deroche-Gamonet, Belin, & Piazza, 2004; Hopf, Chang, Sparta, Bowers, & Bonci, 2010; Lesscher, van Kerkhof, & Vanderschuren, 2010; Lesscher & Vanderschuren, 2012; Seif et al., 2013; Spanagel & Hölter, 1999; Spanagel, Hölter, Allingham, Landgraf, & Zieglgänsberger, 1996; Vanderschuren & Everitt, 2004; Vengeliene, Celerier, Chaskiel, Penzo, & Spanagel, 2009; Wolffgramm, Galli, Thimm, & Heyne, 2000; Wolffgramm & Heyne, 1991). Simple behavioral models of aversion-resistant intake in rodents would greatly facilitate the identification of circuit and molecular mechanisms that promote this pathological drinking, and could assist in the development of behavioral and pharmacological therapies to target the compulsive drives which remain a nearly intractable aspect of human addiction.

There has been considerable theorizing about the brain circuits that underlie the development of addiction and the transition from recreational drug use to habits to compulsion. Several influential groups (Everitt et al., 2008; Koob & Volkow, 2010; Pierce & Vanderschuren, 2010) have considered that self-administration is

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initially driven by mesolimbic regions including the ventral striatum (mediating the reinforcing effects of drugs of abuse) and prefrontal cortical areas (mediating goal-directed activities focusing on drug acquisition and intake). Habitual processes become more important with repeated intake, and habit-based theories of addiction (Everitt & Robbins, 2005; Pierce & Vanderschuren, 2010; Tiffany, 1990) have inspired work examining the role of the dorsal striatum in addiction. Repeated intake and withdrawal also likely lead to the development of negative reinforcement, where intake occurs to reduce negative aspects of withdrawal (Koob, 2009), effects that persist into protracted abstinence (Heilig, Egli, Crabbe, & Becker, 2010). Thus, a number of possible mechanisms could contribute to development of addiction, including conditioning processes whereby drug-related cues can promote seeking and intake. Compulsive responding for drugs of abuse may be driven in part by habitual processes, and in part by recruitment of cortical circuits that are sufficiently strong to overcome anticipation of aversive consequences (see below).

We include a glossary that describes how concepts such as habit, compulsion, aversion resistance, and other terms used for compulsive-like intake may be related to each other. We also want to clarify that we explicitly speculate that many drinking models (dependence, longer-term intermittent binge drinking, longer-term 4-bottle choice, shorter-term mouse intake) likely lead to or involve a similar set of long-term adaptive changes and neural circuits. The way these different adaptations drive a particular alcohol-related behavior may have as much to do with the cognitive requirements and context of the behavior as it does with the method by which rats came to drink alcohol. This provides a working hypothesis, and any exceptions would be as interesting as the common principles.

Although compulsion is a critical aspect of human addiction, it is also important to note that addiction can be driven by processes included in the DSM-IV that do not necessarily reflect compulsion (although they may interact with it). These include increased motivation for drugs, cortical dysfunction that reduces control over drug seeking and taking, and a negative emotional state that develops with repeated withdrawal and may promote intake through something more akin to anxiety and depression than compulsion (see Ahmed, 2012 for further discussion). When attempting to validate rodent models for addiction, it may be beneficial if multiple aspects are captured by the models that together can be considered to recapitulate different aspects of human addiction. For example, footshock-resistant cocaine seeking is present in a subpopulation of rats which also exhibit greater motivation for cocaine, greater responding even without reinforcer delivery, and greater reinstatement (Belin, Berson, Balado, Piazza, & Deroche-Gamonet, 2011; Deroche-Gamonet et al., 2004). The co-association of these behaviors with resistance to punishment is useful in establishing the potential validity of the model for humans, although it does not necessarily imply that these other behaviors reflect compulsion *per se*.

Are compulsion, habit, and other terms for compulsive-like drinking similar or different constructs?

In order to understand whether a common circuit might mediate habits versus compulsions, we must first define these terms. There are a number of semantic as well as procedural differences and uncertainties when defining constructs used to describe compulsive-like drinking (Belin, Belin-Rauscent, Murray, & Everitt, 2013; Hopf et al., 2010; Lesscher et al., 2010; Spanagel & Hölter, 1999; Spanagel, Hölter, et al., 1996; Spanagel, Putzke, Stefferl, Schöbitz, & Zieglgänsberger, 1996; Turyakibahika-Thyen & Wolffgramm, 2006; Vendruscolo et al., 2012; Vengeliene et al., 2009; Wolffgramm et al., 2000; Wolffgramm & Heyne, 1991), even in human addicts (Belin et al., 2013; Moeller et al., 2010). As addressed in depth in the Glossary below, compulsion and habit are similar in the sense of automaticity, where habits and compulsive drives seem to compel behavior without the ability to exercise control. However, we believe compulsions differ from habits in one key aspect: the cost associated with the alcohol drinking. We prefer the term aversion resistance since this operationally and experimentally defines compulsive-like drinking as the willingness to overcome an adverse consequence in order to get alcohol. Thus, although the respective circuitries that underlie habitual and compulsive responding are likely to largely overlap, there are also theoretical and recent experimental reasons to believe that they are not identical.

In this regard, prefrontal cortical areas are thought to promote compulsive behavior in humans, since craving and relapse correlate with prefrontal activity (Breese, Sinha, & Heilig, 2011; Koob & Volkow, 2010; Naqvi & Bechara, 2010; Tiffany & Conklin, 2000). Importantly, several groups (Naqvi & Bechara, 2010; Tiffany & Conklin, 2000) have suggested that cortical areas play a particular role in compulsive intake because of the presence of conflict during compulsion (i.e., continued intake despite the possibility of adverse consequences) and the role of some cortical areas in processing conflict (Koob & Volkow, 2010; Naqvi & Bechara, 2010; Roberts & Hall, 2008; Tiffany & Conklin, 2000). In contrast, this theory suggests that cortical areas contribute much less to habitual intake in the absence of conflict. Thus, cortical areas that process conflict would be selectively recruited in the face of challenge, but not recruited in the absence of challenge. In contrast, habit-related areas would support alcohol drinking with or without challenge. In support of a selective cortical recruitment with compulsion, our recent studies (Seif et al., 2013, discussed in detail in "Cortical circuits and compulsive alcohol use" section), demonstrate that aversion-resistant alcohol intake requires cortical projections to the nucleus accumbens (NAcb) core and alcohol-related enhanced NMDA receptor function under these inputs, and that alcohol intake in the absence of aversive challenge does not (Seif et al., 2013). Thus, cortico-NAcb inputs differentially sustain alcohol intake depending on the level of conflict during consumption. By contrast, recent evidence suggests that striatal areas (which are innervated by PFC areas dorsal to cortico-accumbens areas) can mediate both habitual (Everitt et al., 1999; Everitt & Robbins, 2005; Pierce & Vanderschuren, 2010; Tiffany, 1990) and compulsive drug use. However, a recent study by Jonkman, Pelloux, and Everitt (2012) shows that the most dorsal part of dorsolateral striatum (DLS) selectively promotes punishment-resistant cocaine seeking, indicative of compulsive cocaine seeking, but does not alter cocaine seeking without punishment (see the "The striatum and compulsive alcohol use" section for further discussion).

Thus, it may be that compulsions and habits are both driven by the neural circuitry of automaticity, but with a high or low cost associated with the action, respectively. In fact, there are a range of rodent paradigms considered to model aversion resistance and habits which could reflect this gradient of high to low cost paired with responding. On the high end is responding that persists despite acute pairing with an adverse consequence such as shock. Less costly than direct shock but still aversive would be persistent responding despite previous pairing of the reinforcer with a negative consequence such as lithium chloride sickness (Dickinson, Wood, & Smith, 2002) or presentation of a cue paired with a negative reinforcer (such as a footshock-paired cue) (Johnson & Kenny, 2010; Vanderschuren & Everitt, 2004). Further, three behavioral models might reflect habits under the least intense condition: 1) resistance to pre-feeding, where responding persists despite "pre-feeding" with the particular reinforcer to decrease the