Addiction: A striatal roller-coaster

On the neural and associative-learning mechanisms underlying gambling and alcohol use disorder

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Publication date
2019

Document Version
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General introduction

1

Addiction is a huge burden to individuals and society. Drug and alcohol abuse have been associated with serious public health problems, productivity loss, and public safety issues, all leading to substantial economic damage (UN Office on Drugs and Crime, 2011). Perhaps more importantly, addictive behaviors can have devastating results for the individual and their surroundings. Addiction is a very complex psychiatric disorder, and its development can have many causes including genetic, social, environmental and cultural (El-Guebaly et al., 2015). Over the past few decades, addiction is increasingly regarded as a chronic relapsing brain disorder, characterized by continued drug use despite the negative consequences (Volkow et al., 2016). People suffering from addiction increasingly focus on obtaining, using, and recovering from substances, which ultimately leads to the loss of control over the addictive behavior that defines addiction.

To better understand what drives addictive behaviors, and to improve and develop novel treatment interventions, it is of great importance to understand the mechanisms underlying loss of control. Over the last four decades, various theories have been proposed to explain addictive disorders from the perspective of the brain (Wise and Rompre, 1989; Leshner, 1997; Berridge and Robinson, 1998; Robbins and Everitt, 1999; Hyman et al., 2006; Koob and Le Moal, 2008; Redish et al., 2008; Goldstein and Volkow, 2011). Central to many of these theories are neurobiological changes related to the rewarding aspects of drug seeking and use, and the associative learning processes controlling them. In this introductory chapter, I will give an overview of the associative learning mechanisms that are thought to be involved in the development of addiction and explain why we studied alcohol and gambling addiction. Finally, an outline is given of the chapters included in this thesis. **Chapter 2**, then, expands on disruptions in neurocognitive functioning related to compulsivity that could give rise to addictive behaviors and presents a systematic review of this literature in gambling disorder.

Associative learning mechanisms in addiction

Behavioral control depends on the capacity to learn relations between actions, environments, and goals. Our brains are exceptionally well geared to learn to predict events based on contexts and to use this knowledge to act – especially when rewards are involved. This learning capacity is adaptive from an evolutionary perspective: survival is dramatically facilitated if one can learn from previous experiences where, when and what to do to maximize rewards (and avoid harm). Taking alcohol as an example, being at a party, in a bar, or in a certain mood (stimuli) is associated with drinking alcohol (actions), which will result in a pleasurable feeling, elevate your mood and a fun night out (outcomes). Learning these relationships is called associative learning, and two major types can be distinguished: instrumental (operant) and Pavlovian (classical) conditioning processes. Several theories

of addiction explain the gradually diminished control over behavior by changes in these learning processes, which involve cues predicting rewards and ascribing motivational value to actions, through the learning systems of the brain (Everitt and Robbins, 2005; Hyman, 2005; Robinson and Berridge, 2008). These changes, and the neuroadaptive changes caused by drugs, putatively lead to a loss of flexibility and increase in rigidity and thus drive compulsive behavior. Environmental factors such as trauma and stress may additionally impact these decision making processes and contribute to the development and maintenance of addiction.

In this chapter, I will particularly focus on the habit theory of addiction, which explains the development of addictive behaviors as a transition from goal-directed control to strongly formed compulsive habits (Everitt and Robbins, 2005). Much is known about the neurobiology underlying habits and their relation to addictive behaviors (Everitt and Robbins, 2015). However, most evidence for addictive behaviors as a consequence of compulsive habits comes from animal studies (Vanderschuren and Everitt, 2004; Vanderschuren et al., 2005; Belin and Everitt, 2008; Zapata et al., 2010) and evidence in humans is limited (Hogarth et al., 2018). The general lack of studies translating the evidence for the habit theory from animal models to humans inspired most of the work presented in this thesis. We have used predictions from several theories of addiction – largely developed based on animal research – to derive testable hypotheses regarding deficits in associative learning mechanisms and reward processing in human addiction.

Pavlovian conditioning, incentive sensitization and changes in reward processing

All addictive drugs are rewarding and reinforcing to the brain. Through the stimulation of dopamine transmission, drugs activate the mesolimbic brain reward system (Wise and Rompre, 1989), connected through the ventral tegmental area in the midbrain to major inputs like the nucleus accumbens (NAc), part of the (ventral) striatum in the basal ganglia, and the prefrontal cortex (PFC). With repeated exposure to the same reward, environmental stimuli that are closely associated in time and space with the pleasurable effects of the outcome of the behavior (e.g. a bar or a casino), gain 'incentive salience' through the process of Pavlovian conditioning. This strengthening of stimulus-drug associations results in the attribution of high motivational value to the stimuli that precede drug availability, causing excessive 'wanting' and craving (Robinson and Berridge, 1993). Another result of these changes is that 'natural' rewards (e.g. food or money) increasingly lose their motivational power. Additionally, the repeated use of drugs results in tolerance and releases increasingly smaller amounts of dopamine than initially was the case (Volkow and Morales, 2015).

There is much evidence supporting a role for each of the three aforementioned processes in addiction. Theoretically, it makes sense to assume that these processes

arise simultaneously. However, many studies investigate these processes in isolation. For example, 'cue reactivity' paradigms have provided evidence that addicted populations show increased activation of the brain reward system in response to addiction-related stimuli, while other studies have shown that this response is decreased for the (anticipation of) other 'natural' rewards. However, the hypothesis that these two dysfunctions co-occur was never tested directly. Thus, in **Chapter 5** we investigated the motivational impact of Pavlovian cues – both addiction-related and general – on instrumental behavior, to test the hypothesis that dysfunctions in reward processing (increased with addiction-related, decreased with general reward cues) would be present within the same individuals, and that these impairments would be related to each other, and to addiction duration and severity.

Instrumental conditioning: goal-directed and habitual control, and their relevance to addiction

In addition to the attribution of incentive, motivational salience to environmental stimuli through Pavlovian conditioning, the rewarding effects of drugs or addictive behaviors also reinforce the rate or probability of behaviors that produce them – a process known as instrumental conditioning. Instrumental conditioning thus involves reinforcement of *actions* instead of stimuli (as in Pavlovian conditioning). Such action-outcome learning can have several effects on behavior. Before turning to their relation to addiction, we will describe the general properties of these processes.

It has long been known that there are multiple competing systems controlling the performance of reward-related actions: one controlling the acquisition of goal-directed actions and the other of habits (Dickinson and Balleine, 1994; Balleine and Dickinson, 1998; Balleine and O'Doherty, 2010). The critical difference between goal-directed and habitual actions is whether or not, respectively, these are performed with regard to their consequences. The goal-directed decision-making system is guided by the value of the predicted outcome of each action, i.e. 'action-outcome' associations. This system is flexible and sensitive to environmental changes, but this comes at the cost of being relatively slow and cognitively demanding. In contrast, habitual actions do not consider their causal relationship to, nor the value of their consequences – instead, they are driven by 'stimulus-response' associations. As a consequence, habits are rapid, efficient and require minimal cognitive effort, but are also rigid and inflexible in the face of environmental changes. Whereas goal-directed actions are initially controlling behavior, habitual performance strengthens through behavioral repetition. On a neural level, evidence in both humans and rodents indicates that goal-directed and habitual actions are mediated by distinct parts of a corticostriatal circuitry (Balleine and O'Doherty, 2010). Goal-directed learning is controlled by the medial prefrontal cortex (mPFC), including the orbitofrontal cortex (OFC) and the

anterior caudate nucleus, part of the ventral striatum. Habitual control of behavior, on the other hand, is dependent on the putamen, a more dorsal part of the striatum (Yin and Knowlton, 2006).

Although habits are very functional in efficiently executing behaviors that repeatedly occur, their inflexible nature can result in unwanted behaviors if the outcome value changes. Thus, habits are hard to extinguish. There are clear similarities between the transition from goal-directed to habitual control and the development of addiction. Indeed, habit has been suggested as key mechanism in addiction (Tiffany, 1990; Robbins and Everitt, 1999). Initially, drinking alcohol, using drugs or gambling money is done for its rewarding, hedonic effects. For many people, these behaviors remain 'goal-directed': having a beer with friends to blow off some steam after work, smoking weed to enjoy going to the movies or going to the casino to feel the rush of the roulette wheel spinning. Similar to the development of a habit, repetition may yield these behaviors outcome-independent such that they are no longer performed for the rewarding effects. This becomes most pronounced in the face of negative consequences, such as health-related problems or trouble at work or at home. The habit theory of addiction proposes that over the course of extended drug use, addictive behaviors become more and more ingrained and automatic and ultimately compulsive (Everitt et al., 2001; Everitt and Robbins, 2005, 2013, 2015). While initially dependent on instrumental action-outcome associations, drug seeking and taking is thus increasingly controlled by Pavlovian stimulus-response habits. At the neural level, this switch from voluntary to habitual drug seeking is thought to be mediated by a progression from prefrontal to striatal control, and more specifically ventral to dorsal striatal control over the addictive behavior. Animal studies modeling the development of addictive behaviors have provided causal evidence for this neural transition (Everitt et al., 2008). However, it is unclear to what extent human addiction is characterized by aberrant goal-directed and habitual decision making and their neural representations. In **Chapter 3** and **Chapter 4** we tested the hypothesis that gambling disorder and alcohol use disorder, respectively, would be characterized by an increased reliance on habitual control of behavior, associated with decreased ventral and increased dorsal striatal control.

The influence of Pavlovian values on decision making

Pavlovian processes can also modulate instrumental choice. For example, contextual cues (e.g. a bar) gain general motivational properties that can directly influence and motivate actions (e.g. to have a beer) – a process known as Pavlovian-to-Instrumental Transfer [PIT] (Cartoni et al., 2016). Thus, PIT describes the ability of Pavlovian cues to enhance (or inhibit) instrumental action for an outcome, even when the instrumental (i.e. action-outcome) and Pavlovian (i.e. stimulus-outcome) associations have been created independently. For example, you may have planned to visit Rome's Colosseum

for the first time, but a green Heineken sign catches your attention and you decide to sit down at the terrace to have a beer – even though this is the first time you are visiting Rome in your life. This process can have two fundamentally different forms: outcome-specific transfer and general transfer. Specific transfer is demonstrated by the ability of specific reward-related cues to bias choice toward actions earning the same reward: e.g. the Heineken sign that motivates you to have a Heineken. Relying too much on environmental factors to guide decisions, could thus lead to always drinking Heineken on city trips (my advice: Try a local beer!). General transfer describes the general motivation of Pavlovian cues to enhance instrumental actions independent of the outcome: the Heineken sign may also motivate your decision to grab the bottle of water from your bag.

Lesion studies in animals have found that distinct neural structures mediate general and specific PIT, with dissociable roles for the basolateral and central amygdala (Corbit and Balleine, 2005) and the nucleus accumbens core and shell (Corbit and Balleine, 2011), respectively. Although most human neuroimaging studies have not distinguished general and specific transfer (Bray et al., 2008; Talmi et al., 2008; Mendelsohn et al., 2014), the two studies that did, implicate the medial OFC in general transfer and different parts of the amygdala and ventral striatum in both general and specific transfer (Prévost et al., 2012; Morris and Balleine, 2015). Importantly, failures to integrate these processes may result in poor control of goal-directed action and could thus facilitate drug seeking and relapse (Hogarth et al., 2013a; Balleine et al., 2015; Cartoni et al., 2016; Corbit and Janak, 2016a). That the development of addiction importantly depends on these transfer effects (Everitt and Robbins, 2005), with some convergent roles for both types of transfer (Hogarth et al., 2013a). Again, however, very limited work in humans had investigated transfer in humans, and none had dissociated between specific and general PIT. In **Chapter 4**, we therefore tested whether patients with alcohol use disorder show aberrant Pavlovian-to-instrumental transfer effects and associated differential brain functioning.

Stress, addiction, habits and their interaction

Stress is a well-known risk factor in the development and maintenance of addiction (Sinha, 2008). Both acute and chronic stress can increase the motivation to engage in and the escalation of addictive behaviors; using alcohol, for example, may serve as a coping strategy to deal with stress or to decrease withdrawal-related distress. Stress may also increase craving states that are predictive of relapse. Neurobiological models emphasize the neurotoxic effects of drugs, which cause long-term, persistent dysregulation of brain reward, learning, and stress pathways (Koob, 2008; Robinson and Berridge, 2008). These alterations have been hypothesized to cause a negative emotional state when the hedonic effects of drugs wear out, which in turn drive the negative reinforcement of addiction that serves as an opponent motivational process (Koob and Le Moal, 2005). This explanation of

compulsive drug use through negative reinforcement complements the habit theory of addiction (Everitt and Robbins, 2015).

Interestingly, human studies using classical associative learning paradigms have shown that acute stress biases behavior towards habits (Schwabe and Wolf, 2009, 2010) through increases in cortisol levels (Otto et al., 2013; Smeets et al., 2018) and interacts with chronic stress (Radenbach et al., 2015). Despite these separate lines of research indicating that stress can increase both (vulnerability for and relapse to) addiction and habitual control, there is still a knowledge gap regarding the effect of stress on habitual control in addicted populations. In **Chapter 3**, we therefore tested the hypothesis that patients with gambling disorder show an increased reliance on habitual strategies under stress.

Testing habits in the laboratory

As outlined above, there is considerable reason to believe that addiction in part reflects a dysregulation in two separate learning processes: one system controlling goal-directed and one controlling habitual actions. But how can we distinguish which system controls performance? A classical test to examine which system controls responding is by decreasing the value of the reward – a procedure known as outcome devaluation (Adams and Dickinson, 1981). Food rewards are often used because they are valuable for (often food deprived) animals and because the value can easily be manipulated, for example by pairing the consumption with illness or satiation. If actions are goal-directed, this value devaluation should cause a reduction of responding for that outcome. If actions are habitual, however, responding should continue even if it no longer produces a valuable reward (or even leads to aversive outcomes). In humans, various tasks have been developed relying on the mechanisms of outcome devaluation (Valentin et al., 2007; Tricomi et al., 2009), including the slips-of-action task that was used in the only study of habit in human addiction (Sjoerds et al., 2013). In **Chapter 4** we have used an outcome devaluation procedure involving real snack foods to test goal-directed and habitual control of action. Furthermore, the use of different food rewards made it possible to learn distinct stimulus-outcome and response-outcome associations, thus facilitating the assessment of specific and general transfer effects.

A separate, more recent line of research regarding goal-directed and habitual learning has been developed from the computational theory of reinforcement learning (Daw et al., 2005; Gläscher et al., 2010). These computational models have described the goal-directed and habitual system as arising from two distinct forms of reinforcement learning, known as 'model-based' and 'model-free' learning (Daw et al., 2011). Compared to the classical assay of goal-directed control – which requires participants to (over)learn associations to form habits and then probe which system controls behavior using outcome-devaluation – this task provides a relatively quick and easy way to differentiate between these systems.

Additionally, the learning-based approach makes the task well suited for dynamic neuroimaging studies. For these reasons, the task has been increasingly used in clinical populations (Voon et al., 2017). Although questions remain about the validity of equating these computational reinforcement learning models to goal-directed and habitual learning (Dezfouli and Balleine, 2013), studies have shown that especially decreased model-based (not model-free) decision-making correlates with traditional indexes of habitual behavior (Friedel et al., 2014; Gillan et al., 2015; Sjoerds et al., 2016). These studies generally indicate that decreased model-based control correlates with increased habitual control, as indexed with outcome devaluation or slips-of-action, but also with increased PIT effects (Sebold et al., 2016). Similarly, studies in clinical populations indicate reduced model-based control in schizophrenia (Culbreth et al., 2016) and across a range of 'compulsive' disorders (Gillan et al., 2016) including obsessive-compulsive disorder (Voon et al., 2015a), binge eating disorder, and methamphetamine dependence (Voon et al., 2015b). In **Chapter 3**, we therefore implemented the two-step task, measuring model-free versus model-based decision making in gambling disordered patients. We hypothesized that patients with gambling disorder rely more on habitual (model-free) and less on goal-directed (model-based) strategies under stress.

Brain connectivity

The experimental chapters in this thesis mainly focus on the cortical and striatal regions that are known to subserve goal-directed and habitual behavior, decision making and reward processing. Obviously, however, brain areas do not operate in isolation; in order to process and integrate all kinds of information, they must interact. The striatum is known as a central hub that receives inputs from and projects back to several cortical and subcortical regions (Haber and Knutson, 2010). Reward processing, decision making and goal-directed action are crucially dependent on this corticostriatal network (Haber and Knutson, 2010; de Wit et al., 2012; Gerraty et al., 2018) and thus, impairments in these connections may cause dysfunction. In investigating brain connectivity, we largely distinguish two levels: structural and functional connectivity. Structural connectivity refers to the anatomical connections between (grey matter) brain areas and is composed of white matter bundles. By carrying action potentials, these tracts coordinate communication between different brain regions. Using a specific type of MRI sequence – called diffusion-weighted imaging (DTI) – it is possible to map white matter tractography in the brain. Functional connectivity, on the other hand, describes the simultaneous (de-)activation of spatially separated brain areas, which can be interpreted as long-range communication between these regions. Functional connectivity can be investigated using functional MRI (fMRI) by looking at patterns of fluctuations in brain activity, as represented by temporal coherency in the BOLD signal. The

presence of such statistical relationships between neural activity in two regions, then, is thought to reflect functional connectivity between them.

Investigating brain connectivity can thus provide crucial information for understanding distorted patterns of brain network mechanisms in addiction. To obtain a more thorough picture of impairments that characterize the addicted brain, we thus investigated abnormalities in both structural and functional brain connectivity in patients with gambling disorder. In **Chapter 6**, we investigated *structural* connectivity using DTI by looking at the integrity of white matter tracts in gambling disordered patients. We specifically looked at corticostriatal white matter connections that are known to mediate cognitive flexibility (van Schouwenburg et al., 2014). In **Chapter 7**, we investigated *functional* connectivity during rest (known as 'resting-state fMRI') using independent component analysis (ICA), a data-driven method that detects spatially and temporally independent patterns of coherent fMRI activity. This method enables the detection of robust networks of brain areas, which can be used to investigate alterations between addicted groups and healthy control participants. In this study, we compared network connectivity strength within four well-known networks between patients with gambling disorder and healthy controls.

Why study alcohol use disorder and gambling disorder?

Alcohol consumption is omnipresent in our society and alcohol use disorder is among the most prevalent mental disorders worldwide: the prevalence of alcohol use disorder is estimated to be 4% in Europe (WHO, 2010) and 14% in the United States (Grant et al., 2015). This high prevalence not only makes it a very relevant disorder to study, but also has a practical advantage: patients at addiction clinics are most commonly in treatment for alcohol use disorder, which makes the recruitment of participants more feasible. In order to be able to investigate the effects of addiction duration, severity and lifetime alcohol use we decided to include a relatively large number of patients with alcohol use disorder. Although the development of compulsive drug use is often attributed to the effects of drugs, an increased propensity to form habits may also be a vulnerability factor for or a consequence of the addictive behavior itself. Formally teasing these factors apart would require difficult, expensive and longitudinal studies with large numbers of subjects. An alternative way (and importantly, one that is feasible for a PhD-project), is to use gambling disorder as a model for addiction without the confounding neurotoxic effects of drug use. The prevalence of problem gambling is considerably lower than alcohol use disorder, with an estimated 0.22-0.15% in the Netherlands (Goudriaan, 2014), and 1-2% in the United States (Petry et al., 2005). Formerly listed as pathological gambling under "Impulse control disorders not elsewhere classified", gambling disorder has recently been relocated to the category "Substance-related and Addictive Disorders" in the *Diagnostic and Statistical Manual of Mental Disorders*

(5th ed.; *DSM–5*; American Psychiatric Association, 2013). This decision was taken because of evidence showing similarities in the phenomenology and biology of substance use disorders (Petry et al., 2014). Similar to substance use disorders, gambling disorder has severe consequences for the individual and their surroundings and is associated with reduced quality of life, high monetary debts, divorce and jail (Grant and Chamberlain, 2015)

Outline of this thesis

To summarize the above, in this thesis we will focus on various associative learning mechanisms and their neurobiological underpinnings related to compulsive behavior in human addiction. Largely relying on findings from basic animal research, we investigate goal-directed and habitual control over behavior, reward processing and decision making in abstinent human patients who were in treatment for either alcohol use disorder or gambling disorder. In **Chapter 2**, we start with an inquiry of the various neurocognitive tasks that may be related to compulsive behavior and systematically review the literature on this topic in gambling disorder. Compulsive behavior, as assessed by compulsivity-related neurocognitive tasks, is divided into four subdomains and the results are synthesized using meta-analyses for each domain. One important finding in reviewing the literature was the complete lack of studies in the habit-domain in gambling disorder. In **Chapter 3** we investigate the balance between goal-directed and habitual control in gambling disorder using a two-step decision task (Daw et al., 2011). Moreover, we investigate the influence of stress on this balance using a within-subject cross-over design. Analysis of this dataset involved computational modeling of the behavioral data and model-based fMRI analysis to investigate brain functioning. In **Chapter 4** we use fMRI to test corticostriatal control of goal-directed actions in patients with alcohol use disorder using a Pavlovian-to-Instrumental transfer and outcome-devaluation task. To this end, we use a task that involves learning new Pavlovian and instrumental associations with food rewards. In **Chapter 5**, we test monetary reward anticipation in the presence or absence of addiction-related cues to study striatal hyper-/hypofunction in both gambling disorder and alcohol use disorder compared to controls. In **Chapter 6** we report on cognitive flexibility in gambling disordered patients using a cognitive switch task without monetary feedback while measuring BOLD activity using fMRI. Additionally, we relate these results to white matter integrity by performing probabilistic fiber tracking on DTI scans. In **Chapter 7** we apply data-driven Independent Component Analysis (ICA) to fMRI resting-state data to compare patients with gambling disorder to healthy control participants. Finally, **Chapter 8** provides a summary and general discussion of the findings presented in the thesis.