Addiction: A striatal roller-coaster

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

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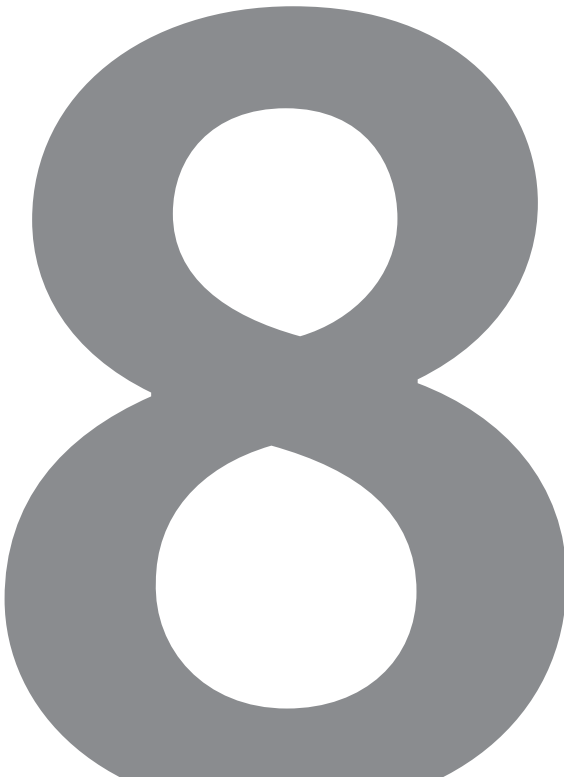
Summary and general discussion



The general aim of the work presented in this thesis was to investigate several proposed mechanisms underlying compulsive behavior in addiction. We focused on neurocognitive associative learning mechanisms related to compulsive behaviors, such as cognitive flexibility, reward processing, and habits. Across several studies, patients with alcohol use disorder (AUD) and gambling disorder (GD) were compared to matched controls. Associative learning mechanisms were assessed using different experimental paradigms while participants underwent functional Magnetic Resonance Imaging (fMRI) to measure brain activity in relation to these processes. Many theories of addiction distinguish different stages in the addiction cycle, with associated transitions at the neurobiological level – both in relation to habitual control of behavior and reward processing. By including a relatively large number of AUD patients (n=50), we investigated whether there was a link between these processes and several factors possibly associated with this shift, such as duration of dependence and addiction severity. The inclusion of an AUD group and a GD group further allowed us to distinguish neurotoxic effects from addictive behavior. Additionally, we investigated associations with total lifetime alcohol use within the relatively large group AUD patients.

In this final chapter, I first summarize the main results presented in Chapters 2-7, followed by several methodological limitations. In the General Discussion, I interpret our findings in a broader context, discuss the clinical implications and present directions for future research.

Summary of main findings

In **Chapter 2**, we systematically reviewed the literature for studies assessing neurocognitive functioning related to compulsivity in GD. A total of 29 studies, comprising 39 datasets, were identified that met our inclusion criteria. Following a previously proposed framework of compulsivity (Fineberg et al., 2010, 2014), different neurocognitive tasks were subdivided into four separate domains representing different components of compulsive behavior: Contingency-related cognitive flexibility, Task/attentional set-shifting, Attentional bias/disengagement, and Habit learning. Meta-analyses were conducted if there were more than three studies using the same task. These analyses revealed that, across most of the included tasks and domains, patients with GD showed significantly worse performance than HCs – supporting the idea that GD is characterized by compulsivity-related neurocognitive impairments. Finally, our systematic review indicated a complete lack of studies assessing habitual control in GD.

In **Chapter 3**, we evaluated the balance between goal-directed and habitual responding in patients with GD. To this end, we used a two-step reinforcement learning task (Daw et al., 2011), which offers a computational approach to studying instrumental learning. Specifically, the task allows distinguishing between two computational systems

that control instrumental actions: a "model-free" system and a "model-based" system, the computational analogs of, respectively, habitual and goal-directed control. Because stress is known to increase both habitual control (Schwabe and Wolf, 2009, 2010; Otto et al., 2013; Radenbach et al., 2015) and (escalation of and relapse to) addictive behaviors (Koob and Le Moal, 2008; Sinha, 2008), we wanted to test whether acute stress would differentially affect goal-directed decision making in GD. Using a within-subject crossover design, we tested the effect of stress on the balance between model-free and model-based decision making in patients with GD and HCs. Logistic regression indicated that GD patients' decisions were less driven by whether the previous trial was rewarding than HCs. To see if this was driven by a higher reliance on a model-free strategy, computational analyses were conducted according to Daw et al. (2011). These revealed that, contrary to our expectations, there was no significant group difference in the balance between goal-directed and habitual control, nor did stress affect behavior differently across groups. Moreover, there was no significant relationship between goal-directed and habitual control and gambling severity in patients with GD. Instead, computational analyses indicated that the lower main effect of reward in GD patients – putatively a reflection of model-free control – was explained by lower beta values, which capture how reliable choices are. Patients with GD thus made more random choices. Computational fMRI analyses further revealed no significant difference in the striatal reward prediction error learning signal in GD patients compared HCs, either during baseline or after acute stress. To conclude, the main conclusion from this chapter is that goal-directed control in GD patients was intact and stress did not differentially affect this ability.

In addition to the existing gap in the GD literature, to the best of our knowledge, there was just one study at the start of this PhD project that tested habit learning in AUD (Sjoerds et al., 2013). Additionally, the influence of contextual stimuli on instrumental behavior, referred to as Pavlovian-Instrumental transfer or simply transfer, had not been directly evaluated in patients with addictions. In **Chapter 4,** we set out to test these associative learning processes in a sample of AUD patients. Specifically, we investigated whether AUD is characterized by behavioral or neurobiological deficits in (i) the integration of Pavlovian and instrumental values and (ii) goal-directed control; and (iii) whether duration or severity of AUD was associated with such deficits. We used a previously developed task that involved learning associations between cues (different colors on a vending machine), actions (left/right button press) and outcomes (different food snacks). The influence of cues predicting food rewards on instrumental action was assessed in a Pavlovian-to-instrumental transfer test, measuring both specific and general transfer. Contrary to our hypotheses, the performance of AUD patients was very similar to control participants. Instead, both groups showed pronounced specific and general transfer effects which were mediated by distinct corticostriatal signals. Following the transfer phase, an outcome-devaluation task assessed

whether performance was under goal-directed control; this was the case in both groups, with no significant differences between groups. Addiction duration or severity were not related to any of these behavioral or neurobiological processes. These findings indicate that, contrary to our expectations, corticostriatal control of associative learning mechanisms was intact in AUD patents.

In **Chapter 5**, we tested striatal dysfunction, a key characteristic of addictive behaviors, in both AUD and GD patients. Disrupted mesolimbic reward processing is central to several theories of addiction. However, the predicted direction of the deficiency diverges between theories (e.g. reward deficiency and incentive sensitization) and research findings have been inconsistent, as both hypo- and hyperactivations have been reported. In GD, for example, two studies published in the same issue of the journal Biological Psychiatry found diminished (Balodis et al., 2012b) and increased (van Holst et al., 2012c) striatal reward processing in patients with GD compared to controls. A Correspondence followed with Leyton & Vezina (Leyton and Vezina, 2012), who proposed that the *presence* versus *absence* of addiction-related cues, respectively could serve as an explanation for the striatal hypoactivations in Balodis et al. and hyperactivations in van Holst et al. The authors went on to formalize the proposed explanation in an integrative neurobiological 'striatal ups and downs' model (Leyton and Vezina, 2013, 2014). In this theory, disorder-related stimuli gain motivational value through repeated association with the rewarding effects of addictive behaviors, thus eliciting sensitized neurobiological responses – striatal ups. Hyperactive striatal motivational states thus develop in the presence of addiction-related cues. The fact that these incentive processes become pathologically tied to a narrow set of stimuli additionally results in a progressively diminished interest towards rewards unrelated to the disorder, reflected by a hypoactive reward system – striatal downs. Indeed, factoring in the presence or absence of addiction-related cues resolves many inconsistencies in the literature (Leyton and Vezina, 2013). However, direct evidence for this theoretical framework is lacking. We therefore developed a neuroimaging task to simultaneously assesses the processing of monetary rewards, addiction-related cues, and their interaction. During monetary reward processing, hypoactivations were seen in several regions in both AUD and GD patients compared to controls, but in the striatum only in AUD patients. Hyperactivity in response to addiction-related cues was seen only in GD patients compared to controls, in the bilateral insula and dorsal striatum (putamen). AUD patients did show increased activity in regions often associated with craving, including the ACC, precuneus, insula and visual areas; however, not significantly different from controls. Directly comparing neural activation patterns between clinical groups revealed decreased ventral striatum, putamen and caudate activity in patients with AUD relative to GD during monetary reward anticipation. This finding may be interpreted as a consequence of the neurotoxic effects of alcohol. The groups did not significantly differ in their cue-reactivity response. Interestingly, a behavioral interaction was

seen between reward-magnitude and cue-type: gambling cues improved performance for big rewards but deteriorated performance for small rewards. Thus, gambling cues seem to specifically enhance the incentive value of larger reward cues. To summarize, the results provide evidence for striatal dysfunction in both GD and AUD patients, though only partially in line with the integrative 'striatal ups and downs' model.

We additionally investigated whether GD is characterized by alterations in brain connectivity. In **Chapter 6**, we used a multi-modal approach, investigating cognitive flexibility and their functional and structural brain correlates in GD. Cognitive flexibility was assessed using a 'switch'-task while being in a fMRI scanner. Additionally, diffusion tensor imaging (DTI) scans were made to assess white matter integrity. In the "switch task" participant have to change their responses based on color changes. Hence trials following a color change are switch trials, while trials followed by the same color are repeat-trials. Contrary to our expectations, task performance task was similar across patients with GD and HCs, with both groups making more errors on switch than repeat trials. Increased brain activity was seen during switch compared to repeat trials in a number of regions including the bilateral basal ganglia and ventrolateral and dorsolateral PFC, but no significant group differences were observed. Next, we investigated whether GD patients and controls differed in white matter integrity. Task-related peak activations were used to define the seed regions for probabilistic fiber tracking. Compared to HCs, GD patients showed compromised white matter integrity of corticostriatal white matter tract in the left hemisphere. Previous work has found that individual differences in cognitive flexibility can be predicted by variations in white matter microstructure of the basal ganglia projecting to prefrontal cortex (van Schouwenburg et al., 2014). Although we did not find a direct association with task-performance, these differences are expected to be related to other cognitive flexibility deficits seen in GD (see Chapter 2).

Finally, in **Chapter 7** we investigated intrinsic functional network connectivity in GD patients and controls during rest. Participants were simply asked to lie still with their eyes open and to fixate on a cross, while functional brain images were made. Data-driven independent component analyses (ICA) then revealed several common brain networks, of which we selected four with the most relevance for GD: (i) the ventral attention network, which is thought to modulate attention to internal and external stimuli; (ii) the limbic network, which is thought to be involved in processing emotions, (iii) the frontoparietal control network, implicated in adaptive control over behavior; and (iv) the default mode network, which activates during rest. Compared to controls, GD patients showed increased integration of the right middle insula within the ventral attention network. Additionally, distorted beliefs about gambling were related to increased within-network connectivity strength across a number of networks, including the insula within the default mode network. These results converge with prior work indicating increased insular activity during

near-misses (Clark et al., 2009) and a causal role for the insula in the exhibition of gambling-related cognitive distortions (Clark et al., 2014). More generally, the insula is thought to play a critical role in craving (Naqvi et al., 2014) and addiction (Naqvi and Bechara, 2009). Our results suggest that, even during rest, GD patients show increased recruitment of the insula, which correlates with gambling-related cognitive distortions.

Taken together, the findings presented in this thesis can be summarized as follows. First, GD is characterized by deficits in performance on neurocognitive tasks linked to compulsivity, such as cognitive inflexibility. Second, contrary to our hypotheses, no clear pattern of an increased reliance on habits or environmental stimuli was found in either AUD or GD. These results were surprising, given the strong evidence from animal studies for the role of habits in addiction. Third, marked but heterogeneous striatal dysfunction during reward processing was found across both gambling and AUD, with a crucial role for addiction-related cues. Finally, impaired structural corticostriatal connectivity and increased insular functional connectivity were found in patients with GD. These altered connectivity profiles may represent a neurobiological basis for decreased cognitive flexibility and increased craving and gambling distortions, respectively – key defining characteristics of GD.

Methodological considerations

several limitations need to be kept in mind when interpreting our findings. First, the included AUD and GD patients were abstinent and in treatment at the moment we tested them. Thus, our findings do not directly generalize to active users. One possibility for the absence of clear associative learning deficits is that, although present in active users, they could quickly normalize after abstinence. This, however, seems to be an unrealistic explanation for our findings for two reasons. First, we did not find a relationship with abstinence duration in any of the studies. Second, the increased reliance on habits and environmental cues are commonly thought to promote relapse, which would not converge with a quick normalization after abstinence. However, disturbed domain-general cognitive functioning– including IQ, working memory, executive functioning – is known to recover over the course abstinence (Mann et al., 1999; Stavro et al., 2013); to the best of our knowledge it is unknown if and how general associative learning processes (e.g. goal-directed control and PIT) change from active use to abstinence. More is known about adaptations in cue-induced craving that occur following withdrawal: the impact of addiction-related cues initially strengthens, leading to increased craving – until it peaks after (up to) 6 months and then declines. This process is known as the 'incubation of craving' and has been described in human nicotine, cocaine and alcohol use disorder (Li et al., 2014; Parvaz et al., 2016). As patients with alcohol use disorder were still relatively early in their abstinence (on average seven weeks), this may be an explanation for an absence of a pronounced neural cue-

reactivity effect and why this effect was stronger in patients with gambling disorder who were longer abstinent (on average 17 weeks). However, no direct evidence was found for this explanation as abstinence duration did not correlate with the cue-reactivity effect.

Moreover, the percentage of participants that were nicotine dependent was higher in both addicted groups than in the healthy control groups. It is therefore difficult to distinguish the effects of smoking addiction from alcohol or gambling addiction, which weakens our claims regarding GD as a model of addiction without the neurotoxic effects. However, smoking is highly co-morbid in GD, thus making our sample more representative than if we would have included only non-smoking GD patients. Relatedly, we excluded subjects diagnosed with other psychiatric problems, to isolate differences purely related to the addictive state. This approach somewhat limits generalizability to the average SUD patient, because addiction and other psychiatric disorders are highly comorbid (Kelly and Daley, 2013).

One methodological limitation concerns the measurement of brain activity using fMRI, specifically related to measuring BOLD signal in the orbitofrontal cortex (OFC). The OFC is known to be crucially involved in addiction (Redish et al., 2008; Schoenbaum and Shaham, 2008; Fineberg et al., 2010) and many of the processes that were of central interest to the work presented in this thesis, including goal-directed action (Valentin et al., 2007; Gremel and Costa, 2013; Gremel et al., 2016), PIT (Ostlund and Balleine, 2007) and cue reactivity (Heinz et al., 2009). Because of its location in the brain (close to the air-field sinuses), measuring the BOLD signal from the OFC is especially challenging. BOLD contrast can be improved by acquiring images at multiple echo times in combination with an algorithm that optimizes the echo weighting for each voxel to maximize BOLD contrast sensitivity (Poser et al., 2006). In the early stages of my PhD, I was involved in implementing this multi-echo sequence at the (then brand new) Spinoza Centre for Neuroimaging. We did a pilot study to compare single- and multi-echo EPI sequences directly, which indeed showed improved signal-to-noise ratios and decreased signal dropout in temporal, caudal and lower prefrontal regions, including the OFC. Despite these efforts, however, our ability to measure BOLD signal from those regions turned out to be suboptimal: the most inferior/ventral part of the OFC is missing in the functional group-level masks for the various tasks that we used. Although this is not uncommon and probably true for many fMRI studies, it is not unlikely that differences in OFC functioning in GD and AUD compared to HCs have remained unobserved.

One factor that may be viewed as a limitation of the GD studies in **Chapter 3 and 5** was the use of money as a 'natural' reward, which is an addiction-related reward for GD. We nevertheless favored money over other possible rewards (such as food, sexual cues), because (i) the magnitude of monetary rewards is easy to manipulate, (ii) money is known to robustly activate the reward circuit, (iii) it is the most commonly used type of reward in addicted populations and (iv) hypoactivations have been found in response to monetary

reward in GD (Balodis et al., 2012b). Moreover, money in gambling is not the equivalent of drugs in SUDs. Monetary rewards do not directly activate dopaminergic pathways like drugs do; instead, maximal uncertainty of reward evokes the highest dopamine release (Fiorillo et al., 2003). Reward uncertainty, not monetary rewards per se, may thus facilitate the escalation of reinforcement learning and drive compulsive gambling (Clark et al., 2018). Nevertheless, money remains a complex learned, addiction-related reinforcer in GD. The use of other natural rewards, such as erotic cues (Sescousse et al., 2013) or food rewards (**Chapter 4**) is therefore recommended in future studies.

Two limitations which deserve attention because of their broader relevance are related to the meta-analysis. First, although GD patients show significant performance deficits in compulsivity-related neuropsychological functioning, the effect sizes for the individual tasks were small to medium. Second, we did not evaluate the specificity of the results: it may be the case that patients show a general tendency to perform worse on neurocognitive tasks, perhaps as a consequence of disorder-related attentional or working-memory problems. Together, this raises the question to what extent these deficits directly contribute to the development or maintenance of the disorder. The clinical utility of these results depends on those factors; if these deficits are robust and specific, they could be clinically useful, for instance for the identification of high-risk individuals or the development of focused treatment opportunities. Alternatively, deficits in compulsivity-related neuropsychological functioning could be secondary effects of more widespread deficits in executive functioning, or the byproduct of being in a disordered state, in which case the focus of treatment should be broader. Future work should investigate the specificity of these effects, for example by looking at the effect size of neuropsychological deficits unrelated to compulsivity known to be present in GD (Goudriaan et al., 2004; van Holst et al., 2010).

Gamblers can be differentiated based on gambling preferences, and it is known that gambling subtypes show different neuropsychological phenotypes. Although we considered differentiating between GD subtypes, this would have dramatically increased the number of GD patients to be included and would have imposed further restrictions on our inclusion criteria. Unfortunately, limitations in time and resources made it unfeasible to opt for this approach. It will, however, be important for future studies to make this effort, because characteristics important for the etiology of the gambling subtype may be missed when conducting group-level comparisons with control subjects. Looking at the effect of stress on the balance between goal-directed and habitual control (**Chapter 3**), we see that there is large variability within the GD patients, which suggests that stress has a heterogeneous effect on decision making in GD patients. Within group variability in GD patients often appears to be stronger and more reliably related to clinically relevant measures than the case-control effects (Clark et al., 2018). Recent initiatives, such as the Research Domain Criteria [RDoC] project (Insel et al., 2010), have begun to address

heterogeneity within- and homogeneity between psychiatric disorders by adopting a more 'transdiagnostic' approach, using dimensions that cut across traditional psychiatric classifications. Taking into account individual variability in clinical groups will hopefully help to more effectively diagnose and treat patients and improve outcomes.

General discussion

A striatal roller-coaster?

Many, if not all, addiction theories postulate striatal dysfunctions in addiction. In this thesis, we probed various of the behavioral and cognitive processes known to be subserved by the striatum. This inspired me to refer to the striatum in the title of this thesis. The roller-coaster analogy refers to the heterogeneous role the striatum has throughout addiction: the neural transition in striatal control over behavior (the 'ventral-dorsal' shift) and the changes in the direction of striatal activity in response to natural rewards and addiction-related cues (the striatal 'ups and downs'). Obviously, the analogy also applies to the nature of addiction itself. Interestingly, our results suggest that striatal function is not as impaired as hypothesized. In AUD, the most notable striatal dysfunction was seen during monetary reward processing, which negatively correlated with craving (**Chapter 5**); we observed no striatal dysfunction during motivational processing, tested using a Pavlovian-Instrumental Transfer and outcome devaluation paradigm (**Chapter 4**). In GD, striatal hyperfunction was observed in response to gambling cues, which positively correlated with craving (**Chapter 5**); striatal activity was similar to that in HCs during monetary reward processing (**Chapter 5**), goal-directed and habitual choice (**Chapter 3**), resting state activity (**Chapter 7**) and cognitive flexibility (**Chapter 6**). Combined, our findings indicate that, although seen under some conditions, striatal dysfunction was not as ubiquitous as predicted by the various addiction-theories.

Although the striatum was the main node of interest, we did not limit our analyses to this region alone. One notable finding from the whole-brain analyses across the separate chapters was a recurrent pattern of insular dysfunction, which will be further discussed in a later section.

Associative learning mechanisms

Habits in addiction?

A major goal of this project was to evaluate the role of aberrant Pavlovian and instrumental learning mechanisms in human addiction. Various paradigms were used to probe goal-directed and habitual strategies and the influence of reward-paired cues to influence instrumental performance. In this section, I will focus on general instrumental

decision-making processes unrelated to specific addiction contexts; addiction-related cue-processing will be discussed in the next section.

Contrary to our expectations, patients with an addiction did not exhibit a clear deficit in the balance between goal-directed and habitual behavior (i.e. two-step performance in **Chapter 3** and outcome-devaluation in **Chapter 4**), nor a deficiency in the ability of reward-paired cues to acquire motivational properties and influence instrumental performance (i.e. Pavlovian-Instrumental transfer in **Chapter 4**). Even under stress, GD patients did not rely more on a habitual, model-free or less on a goal-directed, model-based strategy. Taken together, these results indicate intact goal-directed and habitual control capacities in GD and AUD.

However, we were not the only research group that recognized the need to investigate the habit theory of addiction in human patients. While there was just one study assessing habit learning (Sjoerds et al., 2013) and none investigating Pavlovian-Instrumental Transfer in human SUD at the start of my PhD project in 2014, recent years have seen a surge in studies tapping into these processes. In addicted populations, habitual control was tested in at least six other studies (Sebold et al., 2014, 2017; Voon et al., 2015b; Ersche et al., 2016; McKim et al., 2016; Pritchard et al., 2018) and transfer effects in three studies (Garbusow et al., 2014, 2016; Hogarth et al., 2018). Using the same task as the initial study by Sjoerds et al in 2013, one study reported an increased reliance on habits in cocaine-addicted patients (Ersche et al., 2016). One other study found increased habit propensity (operationalized as perseveration on a stimulus-response learning task after contingency change) in individuals with a (non-clinical) history of substance use disorders (McKim et al., 2016). No deficits were found in other studies: similar to our results of Chapter 4, Hogarth et al. (2018) found intact goal-directed control on both outcome-devaluation and Pavlovian-Instrumental transfer in treatment-seeking drug users. Using the same two-step task as in **Chapter 3**, no group differences were found in a relatively large sample (n=90) of AUD patients in the balance between model-free and model-based decision making (Sebold et al., 2017). Similarly, in a study across several 'disorders of compulsivity', an intact balance was found in AUD patients, although a higher reliance on the model-free system was seen in methamphetamine users (Voon et al., 2015b). In an earlier study by Sebold et al. (2014), a smaller group of AUD patients showed decreased model-based choice behavior. However, the group difference was no longer significant after controlling for cognitive speed, which was lower in AUD patients. Moreover, the analyses in this study relied on simple stay probabilities, which limits the interpretation of the results; using the more comprehensive computational model, as usually done with this task, would increase specificity of the underlying group difference. Two recent publications report on subtle Pavlovian-Instrumental Transfer impairments in patients with AUD. One found increased transfer effects in abstinent AUD patients using abstract Pavlovian stimuli (Garbusow et al., 2016), although the same group found no deficits in a previous study of AUD patients using this same task (Garbusow et al., 2014). Additionally, studies have

investigated the association between habit propensity and individual drug use (including alcohol and tobacco) in non-clinical populations. Although one large online study found a significant positive link with substance use (Gillan et al., 2016), five others have failed to find such a relationship (Hogarth and Chase, 2011; Hogarth, 2012; Hogarth et al., 2012b; Deserno et al., 2015; Nebe et al., 2018). Moreover, in a group at high risk for addiction (children of fathers with AUD), no evidence for altered behavioral control was found (Reiter et al., 2016). Similarly, studies have failed to provide evidence for a link between Pavlovian-Instrumental transfer strength and amount of tobacco use (Hogarth and Chase, 2011, 2012; Hogarth, 2012; Hogarth et al., 2014) and alcohol use (Martinovic et al., 2014; Hardy et al., 2017).

Synthesizing these findings, a picture arises of (at the most) subtle associative learning impairments in addicted populations. More often (6x: Hogarth et al., 2018; Sebold et al., 2014, 2017; Voon et al., 2014, **Chapter 3 and 4**) than not (5x: Ersche et al., 2016; Garbusow et al., 2016; McKim et al., 2016; Sjoerds et al., 2013; Voon et al., 2014), patients with gambling or substance use disorders perform similarly to controls on paradigms probing associative learning mechanisms. Across the various studies, addiction severity or duration were not reliably associated with habit propensity – further suggesting its relevance for addiction is limited. When comparing findings from different substance use disorders, there seems to be a pattern. Whereas methamphetamine use disorder is reliably associated with increased habit propensity (Voon et al., 2015b; Ersche et al., 2016), findings in groups of patients with different SUDs are mixed (McKim et al., 2016; Hogarth et al., 2018). In AUD, two studies found impairments (Sjoerds et al., 2013; Garbusow et al., 2016) but most (four) found intact associative learning (Sebold et al., 2014, 2017; Voon et al., 2014, **Chapter 4**). In GD – in the absence of neurotoxic effects – no altered behavioral control is observed **(Chapter 3)**. Taken together, a preliminary conclusion may be that associative learning deficits in addiction could be caused by drug-induced changes rather than being a risk-factor.

Addiction habits in context: reconciling animal and human findings

We were initially surprised by our findings, which did not match our initial predictions. However, as outlined above, they largely converge with a growing body of evidence indicating intact goal-directed control in human addiction. Thus, we currently have to conclude that findings in humans are at odds with findings in animal models of addiction. This has led some authors to conclude that habit has no role in addiction (Hogarth, 2018; Hogarth et al., 2018). In my opinion, however, it still makes sense for habit to have a role in addiction. The conflicting evidence, I propose, is a consequence of discrepancies between animal and human research: on the hand due to imperfections in animal models of addiction; on the other due to human addiction neuroscience studies investigating different habit processes. I will first specify both accounts and then give some suggestions on how future work may reconcile these seeming contradictions.

The use of nonhuman animal models gives us the exciting opportunity to investigate the neural and genetic background of psychiatric disorders, including addiction, and to develop, test, and validate drugs for treatment. However, modeling of psychiatric disorders in animals is extremely challenging (Nestler and Hyman, 2010)., Laboratory models of addiction have been relatively successful compared to other psychiatric disorders by modeling addiction-like behavior through excessive drug use. Thus, animal models have been able to incorporate some addiction-related DSM symptoms, including escalation of drug use and resistance to punishment (Vanderschuren and Ahmed, 2013). Although symptoms are useful for establishing a classification (reflect the presence of an addiction), but they are not a reflection of the causal mechanisms. Thus, the individual symptoms modeled in animal models may not have a simple, straightforward correspondence to addiction in free-living humans. This, of course, can be interpreted as a general critique on animal models of psychiatric disorders but is especially true for addiction, in which cultural, social and environmental factors also play a significant role (Heilig et al., 2016). Thus, although animal models evidently display face validity, construct validity is more questionable, which in turn leads to reduced translational value to the human situation.

Animal models of addiction have often relied on drug self-administration, which (using the right reinforcement schedule) can result in several symptoms of addictive-like, compulsive drug use, including escalation of drug use, increased motivation for drugs and continued use despite negative consequences (Deroche-Gamonet et al., 2004; Everitt and Robbins, 2005, 2015, Belin et al., 2009, 2013; Vanderschuren and Ahmed, 2013). Using this model of addiction has provided convincing evidence that the shift to compulsive addiction-like behavior *can* be characterized by increased habitual control represented by neural transitions. But are habits *necessary*? Animal models of addiction typically require animals to very frequently repeat the same actions to obtain drugs – creating drug habits by design. However, acquiring (illegal) drugs in humans often does not require frequently repeating the same action, but requires complex, goal-directed behaviors. This has often been a critique on the habit theory of addiction (Robinson and Berridge, 2008). A fascinating recent study has addressed this question using a complex procedure requiring rats to solve new 'puzzles' every day to obtain cocaine (Singer et al., 2018). This way, they circumvented creating drug-habits by design. Nevertheless, rats developed addiction-like symptoms including escalation of drug use, sensitization, compulsive drug use (continued use despite negative consequences, e.g. shocks). Some rats were more addiction-prone; interestingly, these rats showed especially pronounced cue-induced reinstatement. In line with the fact that the behavior remained 'goal-directed', dopamine in the ventral but not dorsal striatum controlled drug-seeking. These findings provide initial evidence that habits and a striatal shift are not necessary for addiction-like behavior in rats.

That is not to say that habit has no role in addiction, but its role may be more complex than suggested by animal research. Human research, on the other hand, has so far mainly focused on *domain-general* associative learning processes, whereas the evidence from animal research has proposed that *addiction-related* behaviors are under habitual control. This is a second factor that has hindered translating animal findings to humans. Although also relevant, whether individuals at risk for or with addiction are less goal-directed or more prone to develop habits *in general* is obviously an entirely different question. There is some evidence in rats suggesting that repeated drug exposure can have general habit-promoting effects, but the evidence is limited and, like human findings, somewhat mixed (Halbout et al., 2016; Ahmed, 2018). Importantly, there is no indication that such changes also result in addiction or stronger drug habits (Ahmed, 2018). A procedure that does assess addiction-specific processes is the cue-reactivity paradigm, an established procedure to investigate neural response to Pavlovian addiction-related cue-reactivation (see **Chapter 5**). According to the habit theory of addiction, the ventral-to-dorsal transition underlies a shift in control of instrumental action from goal-directed control to compulsive habits (Everitt and Robbins, 2015). However, cue-reactivity paradigms do not require instrumental responses, and are thus not suited to test instrumental control of behavior. Thus, findings from cue-reactivity studies should, in my view, not be interpreted as evidence for a habit-related striatal transition (Vollstädt-Klein et al., 2010). Some additional thoughts about cue-reactivity will be discussed in the next section.

Additionally, as shortly discussed in **Chapter 1**, it is not easy to experimentally induce and test habits in the laboratory. We spent quite some time evaluating the literature for tasks potentially fit for our purpose and we piloted various options. In the end, we convened on two tasks that had previously been used with success in clinical groups: a PIT and outcome-devaluation task involving food rewards (Morris et al., 2015) and the two-step reinforcement learning task (Daw et al., 2011). One option that we considered was a paradigm previously used to induce habit formation by overtraining instrumental behavior for three days, which showed behavioral and neurobiological results in line with animal work (Tricomi et al., 2009). Luckily, we decided not to use this paradigm, as various attempts to replicate this finding have failed (de Wit et al., 2018). However, this finding also suggests that the outcome-devaluation paradigm used in **Chapter 4** was probably not sensitive to detect deficits in the goal-directed or habitual system: if three days of overtraining is not enough to make responding habitual – i.e. insensitive to outcome-devaluation (de Wit et al., 2018) – the ~10 minute training participants received in our study definitely won't do it. Nevertheless, patients diagnosed with schizophrenia showed a complete deficit in instrumental outcome-devaluation on this same task (Morris et al., 2015). The impaired performance in schizophrenia patients may be a consequence of a general deficient ability to integrate action-outcome learning with outcome values to guide choice, instead of

reflecting increased habit propensity. The specifics of our tasks aside, it is clear that the current experimental approaches to define and assess habits are limited and require further development (Foerde, 2018; Watson and de Wit, 2018).

A final difference with basic studies of addiction is that human studies usually test patients while they are abstinent and in treatment. Acute alcohol use has been shown to impair human goal-directed action (Hogarth et al., 2012a). Such a loss of goal-directed control could make quitting an substance use disorder more difficult in active users. Moreover, neurocognitive deficits are widely described in addicted populations (Bernardin et al., 2014), and are known to recover during abstinence (Schulte et al., 2014), which can take up to a year (Stavro et al., 2013). Although we found no relation with duration of abstinence in any of our studies, it is worthwhile for future studies to investigate these processes in active users directly.

To summarize, animal models have provided a simplified version of addiction, possibly inflating the role of habits in addiction. Human addiction research has, until now, only investigated general habit propensity, but has failed to test addiction-specific habits. In the light of the findings summarized above, it seems unlikely that generally increased propensity for habit-formation is a risk factor for addiction.

Addiction-related cue reactivity

To investigate the neural mechanisms underlying addiction-related cue processing, human studies have largely relied on cue reactivity paradigms. In **Chapter 5**, we investigated neural response to Pavlovian addiction-related cue-reactivation, in combination with natural reward anticipation. Contrary to our hypothesis, the effect of addiction-related cues did not distinguish AUD patients from controls. A possible explanation could be that, due to the omnipresence of alcohol in our society, alcohol-related cues gain saliency and motivational properties in control participants too, thus leading to similar neural activation patterns in controls as AUD patients. Gambling-related cues, on the other hand, generally have not acquired similar saliency in controls and this may explain why gambling cues do lead to distinguishable brain patterns in GD patients compared to HCs.

However, this explanation does not reconcile the inconsistency with previous studies that have reported increased striatal activation patterns in AUD patients compared controls. Additionally, many cue-reactivity studies, especially from a decade or longer ago, have included relatively small numbers of subjects (often <15/group) using uncorrected statistical thresholds (which have become unacceptable now), increasing the chance of false positives. This is nicely illustrated by a 5-year old systematic review and meta-analysis of brain activation patterns across alcohol cue-reactivity studies (Schacht et al., 2013): only 6 of 28 studies included more than 15 subjects per group, and all used uncorrected thresholds (between $p<0.05$ and $p<0.001$) without FWE-correction, sometimes using cluster extent

threshold, known to increase false positives (Eklund et al., 2016). The results of this meta-analysis show that activation of the mesolimbic reward pathway does not differentiate AUD patients from controls, contrary to the tenet that cue-reactivity in AUD is a robust effect. AUD patients showed increased activity in parietal and temporal regions, including the posterior cingulate and precuneus. Additionally, informal discussions with colleagues suggest that there are quite some unpublished cue-reactivity studies with null-results, especially within AUD groups. Future collaborative efforts should address this question formally, but a (speculative) conclusion could be that, although alcohol-related cues do increase mesolimbic functioning as a consequence of learned Pavlovian conditioning, this does not distinguish pathology from normality – at least not during the passive viewing of alcohol-related pictures. A still open and relevant question, therefore, remains whether it would be possible to differentiate cases from controls by including instrumental actions (e.g. drug seeking) and real addiction-related rewards.

Future perspectives of studying learning mechanisms in addiction

As mentioned in the previous section, it is my opinion that the next step that human addiction research should make is investigating *addiction-specific* mechanisms of instrumental conditioning that produce goal-directed and stimulus-response habit learning, Pavlovian conditioning, and their interactions. This would answer questions such as: are alcohol-seeking behaviors, involving real alcoholic rewards, under habitual control, and does habitual control become stronger in AUD? What effect does a casino environment have on betting in a person with gambling problems? What is the impact of addiction-related stimuli on decision-making? Recent research has gone beyond the use of general habitual control or passive cue-induced viewing paradigms to address these questions. Studies in AUD have started to investigate instrumental responding in the context of addiction-related cues (Schad et al., 2018), even using sips of beer as outcomes (Groefsema et al., 2018). The findings in these studies have been a bit puzzling – with alcohol cues having inhibitory effects on instrumental responding in AUD patients (Schad et al., 2018) and anticipating, obtaining and tasting beer having no differential effects across light, at-risk or dependent alcohol users (Groefsema et al., 2018) – possibly related to the suboptimal use of static pictures as addiction-related stimuli. To more realistically investigate environmental impact on addiction-related decision-making, Hogarth, Field, & Rose (2013) built a bar lab where they presented participants with an alcoholic beverage. Just the expectancy of an alcoholic drink abolished goal-directed control of cigarette seeking in smokers, emphasizing the impact realistic contextual cues can have on instrumental behavior. Such a study-design is, however, not suitable for fMRI studies. Environmental stimuli may perhaps be more realistically induced in the laboratory using virtual reality. Additionally, methodological advancements may create new opportunities. For example, the development of portable

MEG devices (Boto et al., 2018) provides a way to investigate processes while people interact with and in a realistic environment.

An advantage of investigating GD is that the specifics of addiction-related decision-making itself (i.e. gambling) can be studied in detail, including (to some extent) realistic environmental factors using real monetary rewards during neuroimaging. Recently, studies have started to exploit these possibilities. With the use of realistic gambling paradigms, several factors have been shown to impact decision-making and their neural responses, such as previous choices (Brevers et al., 2017), ambiguity (Brevers et al., 2012), environmental cues (Miedl et al., 2014; Cherkasova et al., 2018), and gambling availability (Brevers et al., 2018). In some cases, sensitivity to these factors has been related to gambling severity or GD (Chase and Clark, 2010; Brevers et al., 2012; Miedl et al., 2014; van Holst et al., 2014). Future studies will have to determine whether these processes are specifically distorted in (subtypes of) GD patients, as neuroimaging studies have already done for neural responses during near-misses (Sescousse et al., 2016).

In sum, to successfully understand how associative learning deficits in the goal-directed and habit system contribute to the development and persistence of addiction, it will be essential to use a more comprehensive approach, incorporating the wider influence of environmental factors on addictive behaviors. Moreover, a better fundamental understanding is needed of habits and how to change them. Whether or not deficits in goal-directed and an overreliance on habits are present in addicted human populations has important consequences for the development of psychological treatments to prevent relapse and promote abstinence (Everitt, 2014; Everitt and Robbins, 2015; Hogarth, 2018). GD offers the unique opportunity to investigate addiction-specific processes realistically in the scanner. The combined use of neuroimaging techniques and computational modeling, using individual differences, will provide us with a more fine-grained understanding of the associative learning mechanisms that underlie addiction.

Cognitive flexibility in gambling disorder

One candidate cognitive function that may underlie the development of compulsive behavior is cognitive flexibility. To our surprise, GD patients did not reliably show cognitive flexibility problems. In the meta-analysis (**Chapter 2**) we found that GD patients did not show a significant impairment on reversal learning, part of the contingency-related cognitive flexibility domain. Reversal learning involves learning a rule and subsequently adapting one's behavior after a rule change using trial-by-trial feedback, often by (not) receiving rewards or losses. Theoretically, it makes sense that deficits in this domain would characterize GD: it is the nature of the disorder that gamblers continue to gamble despite severe losses, thus showing real-life inflexibility to change their behavior after changes in contingencies.

Interestingly, problem gamblers did show significant performance deficits on another task in this domain – the 'Card Playing Task' (CPT). On this task, participants are presented with a deck of cards and are asked if they want to turn a card. If they play, they win money if a face card is turned and lose money when a number card is turned. Unknown to the participant, the win chance is high initially but decreases slowly; an optimal strategy is to play for 40–60 trials and then quit. GD patients tend to choose a suboptimal strategy: they keep on playing for too long. It is interesting that patients with GD show this (extremely) perseverative responding on the CPT across several studies, whereas this deficit is less pronounced on reversal learning tasks testing similar cognitive skills. An explanation for this seemingly contradictory finding may be that the CPT involves playing-cards – strongly conditioned stimuli for most GD patients. Although speculative, these motivational properties of the playing-cards may alter decision making, resulting in perseverative behavior through Pavlovian-to-Instrumental Transfer.

Another explanation for the absence of a clear performance deficit on the probabilistic reversal learning task in GD patients may be the heterogeneity of the dependent measure; each of the four studies reported a different outcome measure from the PRLT. Although these behavioral summary scores should all be measures of cognitive flexibility, the inconsequent use of outcome measures may have left behavioral deficits undetected. Additionally, the outcome measures used (e.g. total money won, perseverative errors, number of correct choices) only offer a very crude reflection of behavioral performance, and more importantly, of flexibility. Recently, the development and use of computational models for analyzing these data have offered a more principled approach. Computational models provide increased precision over raw outcome measures about the different aspects that can control learning and decision making throughout the task. Different parameters in the model can define various behavioral components such as learning rate, reward sensitivity or decision noise. In this way, it is possible to distinguish between subjects with very different strategies (e.g. slow vs fast learners, sensitive to reward or punishment) – even if they make the same number of errors. Analyzing PRLT data using a computational model (EWA; (den Ouden et al., 2013), we recently found that GD patients show greater resistance to update the value of a choice with increased experience, although the error rate was not significantly different between groups (van Holst et al, in preparation).

Previous work has shown that cognitive flexibility depends on structural and functional connectivity between the basal ganglia (including striatum) and several subregions of the prefrontal cortex (including OFC, mPFC) (Cools et al., 2002, 2004, van Schouwenburg et al., 2010, 2012, 2013; van der Schaaf et al., 2013). The results from **Chapter 6** suggest decreased corticostriatal white matter integrity in GD patients, which may explain why gamblers experience difficulty to stop gambling in the face of negative consequences. However, we found no behavioral deficits or any association between white matter integrity with

individual behavioral performance on a switch task. This may be related to the fact that the switch task at hand did not involve feedback. Behavioral deficits in GD patients may be most pronounced when feedback, especially in the form of monetary rewards (Boog et al., 2014), is involved. It could thus be suggested that cognitive flexibility deficits in GD are specifically related to problems in updating choice values from feedback. This seems to be in line with the aforementioned findings, which indicate flexibility problems specifically related to the updating of choice values following increased experience in GD patients on the PRLT (van Holst et al., in preparation). In future work, we are hoping to replicate both the white matter integrity findings and extend them by finding a link with different tasks assessing cognitive flexibility. To this end, we have already collected DTI data in combination with behavioral data from the intra-extra dimensional set-shifting task [IED] (from CANTAB) and the probabilistic reversal learning task. An additional possibility is to reanalyze raw data of existing studies using more advanced computational modeling techniques to investigate the presence and specificity of such selective impairments.

Addiction chronicity

Addiction is commonly dissociated into multiple stages of the addiction cycle. Early on drug use is voluntary and goal-directed, in the end stage drug taking is constrained and compulsive (Volkow et al., 2016). The development of addiction is thought to be represented by transitions at the neural level, including the shift from prefrontal and ventral striatal control to dorsal striatal control (Everitt and Robbins, 2005). To explicitly test relationships with chronicity, we originally designed the study to include and compare a non-chronic (<2 years AUD history; <2 treatments) and chronic (>7 years AUD history; >3 treatments) AUD group. However, recruiting patients meeting these exact (and arbitrary) cut-offs for AUD history and number of treatments was not feasible. Therefore, the AUD criteria were broadened to include a range in years of AUD history, severity (number of symptoms endorsed), number of past treatments and lifetime alcohol intake. In combination with including a relatively large number of patients, this facilitated the investigation of chronicity in a dimensional way. However, across the different chapters in this thesis, we did not find evidence for neural transitions related to chronicity. In some cases (Chapter 4), Bayes Factors provided evidence against it. Only in GD patients, duration of gambling problems was related to neural sensitivity to gambling cues. One explanation for the absence of a neural 'shift' related to chronicity may be that the included patients all have a relatively high level of chronicity as they all consisted of treatment-seeking patients. Because our design was cross-sectional, however, interpretability is limited; correlations do not imply causal relationships. To identify causal changes related to the development of addictive behaviors, prospective longitudinal studies should be undertaken.

The insula as a therapeutic target?

The insula is a brain region implicated in a wide range of cognitive functions and conditions, including decision making, reward processing, body awareness and interoception (Craig, 2009). Furthermore, the insula has been highlighted as a region important for addiction and craving (Naqvi et al., 2007, 2014; Naqvi and Bechara, 2009), possibly through aberrant interoception, and specifically underlying gambling-related cognitive distortions (Clark et al., 2008, 2009, 2014). Across different chapters in this thesis, aberrant insular activity was found in both GD and AUD. During monetary reward anticipation, insular activity was decreased in AUD patients relative to HCs and was negatively related to baseline alcohol craving (**Chapter 5**). In GD patients, on the other hand, insular activity positively correlated to craving levels during both monetary reward anticipation and addiction-related cue reactivity (**Chapter 5**). During resting-state MRI, GD patients further showed increased integration of insular activity in the ventral attention network compared to HCs; within GD patients, higher gambling-related cognitive distortions was associated with increased insular integration in the default mode network (**Chapter 6**). Thus, our findings indicate abnormal insular activity in both alcohol use disorder and gambling disorder, especially in relation to craving. Future studies should investigate whether the insula could serve as a potential target for therapies for addiction, e.g. through neurostimulation, pharmacological interventions or meditative strategies such as mindfulness (Sharp et al., 2018).

Conclusion

Why do people who suffer from addiction continue to use drugs despite the devastating consequences to their lives? How is it possible that at one moment the only thing someone wants to do is quit their addiction, yet the same day they are using again? For me, these are the most interesting questions we are trying to understand in addiction research. The fact that most people can regularly use drugs, drink alcohol or gamble without any problems is important to consider: what makes that some people do develop addiction? Genetic, developmental factors like trauma and early life stress, and social factors influence the vulnerability to develop addiction. Automatic stimulus-response habits are part of the explanation for addiction, but only capture one aspect. Nevertheless, addiction is by definition the consequence of learning mechanisms: there can be no addiction without (repetitively) using drugs (or gambling). In this thesis, we have found no evidence for impairments in general associative learning mechanisms. We did find altered neural responses related to reward- and addiction-related processing in both AUD and GD, and neurocognitive performance deficits related to compulsivity, possibly caused by alterations in structural and functional connectivity profiles, in GD. This implies that changes in responsivity to rewards and changes when addiction-related cues are present influence behavior in addiction,

with diminished flexibility possibly leading to difficulty in disengaging from addiction-related cues. In order to get a more comprehensive understanding of learning mechanisms distortions in addiction, future research will have to incorporate addiction-specific contexts and take into account individual variability.