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Neural circuits in goal-directed and habitual behavior: Implications for circuit dysfunction in obsessive-compulsive disorder

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ABSTRACT

Goal-directed and habitual actions are essential for normal functioning in everyday life. Goal-directed behaviors are actions that are executed to achieve specific goals. With repetition, such as a daily routine, these goal-directed actions become automatized and habitual. However, these useful behaviors can become aberrant, manifesting as key symptoms in several psychiatric disorders, including obsessive-compulsive disorder (OCD). A comprehensive understanding of the neural circuits underlying both aberrant and non-pathological goal-directed and habitual behaviors can lead to improved treatments for OCD. Here we review the preclinical research that has advanced our understanding of the brain structures that control goal-directed and habitual behavior and discuss their relationships to the pathophysiology of OCD.

1. Introduction

When we act to achieve a specific outcome, we are conscious of the relationship between our action and its consequence. In an ever-changing world, goal-directed behaviors allow for adaptive decision-making based on features of the outcome and its current expected value. On the other hand, after multiple repetitions of the same action to achieve the same outcome, we might stop consciously thinking about the consequence of the action and start relying on more automatized behavior. Once the habitual behavior has been formed, we execute the behavior almost reflexively. Because of this habitual stimulus-response action strategy, we can omit action planning and greatly reduce the cognitive load required for routinized actions. However, habitual behaviors are also less flexible, which can sometimes lead to maladaptive responses. For example, an inflexible behavior might be executed even if the original purpose is already achieved, a different action is required, or the action results in negative consequences. It should be noted that persistent action despite direct negative consequences is referred to as compulsive behavior, which is truly maladaptive.

Recently, the negative aspects of habitual behavior have been linked to neuropsychiatric disorders that are characterized by behavioral inflexibility, such as addiction (Everitt and Robbins, 2016), overeating (Godier and Park, 2014), obsessive-compulsive disorder (OCD; Gillan et al., 2011; Gillan and Robbins, 2014) and schizophrenia (Morris et al., 2015). These patients have difficulty suppressing their actions even though they understand that their behaviors lead to negative consequences and suffering, and treatments for these disorders are marginally effective at best. By understanding the neurobiological underpinnings of these impairments, we can find novel therapeutic targets and improve treatments. To that end, detailed study of the precise neural circuits responsible for goal-directed and habitual behavior in animal models is required in addition to clinical research. In this article, we will first review findings on the neural circuitry of non-pathological goal-directed and habitual behaviors in animal studies. Then, we will briefly review neural circuit dysfunction in OCD patients and animal models of OCD, followed by a discussion of aberrant goal-directed and habitual behaviors in OCD.

2. Outcome-specific devaluation

How can we differentiate goal-directed behavior from habitual behavior in laboratory animals? In this review, we will mainly focus on results arising from outcome-specific devaluation in instrumental conditioning, the ‘prototypical’ habit formation task (Adams, 1982; Dickinson, 1985). In this paradigm, animals are trained to execute actions such as lever pressing for a specific outcome (e.g. food reward; Fig. 1). After training sessions, devaluation of the outcome is conducted by means of outcome-specific satiety or conditioned taste aversion. In outcome-specific satiety, animals are usually allowed free access to either the food that was delivered during training as a reward or the

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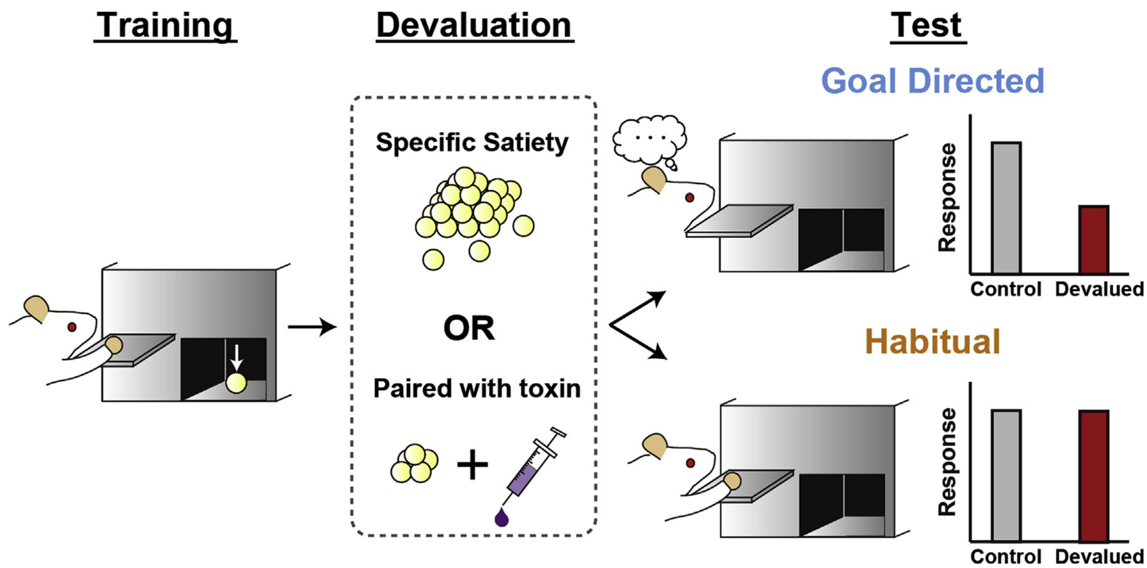

Fig. 1. Outcome-specific devaluation to test goal-directed or habitual behavior. During training, animals learn to associate a lever with a reward (e.g, sucrose pellet) and undergo lever press training for multiple days. Then, for reward devaluation testing, animals are pre-fed *ad libitum* with the lever-associated reward, or the reward is paired with an aversive substance (typically LiCl). Eventually, during devaluation testing, animals reduce their lever press response in the devalued state if their behavior is goal-directed. In contrast, they maintain lever pressing in the devalued state if their behavior is habitual. An additional testing session during non-specific satiety serves as non-devalued control.

food that was available outside of the training chamber such as in the home cage (control condition). In conditioned taste aversion, animals are given free access to the food used during training as a reward, but they receive a concurrent lithium chloride injection, which induces nausea and results in aversion to the once rewarding food. When the animals are sated or show conditioned taste aversion, their lever-press behavior is tested in the absence of reward delivery. If the animals reduce their responding in the devalued condition compared to the non-devalued condition, their reward-seeking is goal-directed, which depends on the knowledge of the relationship between action and outcome (i.e. lever press and food reward). On the other hand, if the animals respond comparably in the devalued and non-devalued conditions, their reward-seeking is habitual, which depends on the stimulus–response (i.e. lever–lever press) association rather than the action–outcome association. It should be noted that two levers choice paradigm is also commonly used to test habits. In this version, animals are typically trained for two different action–outcome contingencies (e.g. left lever press–outcome A, and right lever press–outcome B). The action is regarded as goal-directed if the animal shows more frequent lever press to non-devalued lever, compared to the devalued lever.

Two confirmation tests have been used to validate that habitual lever pressing is not just an artifact of devaluation testing that arises from an inability to distinguish sensory features of foods. One test is a feedback test, in which the food reward is delivered contingent on lever pressing, like during operant training (Furlong et al., 2017; LeBlanc et al., 2013). The other test is a food consumption test, in which the animals are allowed direct access to the lever-associated food reward itself (Furlong et al., 2014; Parkes et al., 2015).

Animals can be encouraged to develop either goal-directed or habitual lever-pressing in the reward-devaluation task by using different training session durations. Consistent with what we might expect from our everyday experiences, extended rather than short duration instrumental training sessions trigger habitual behavior in experimental animals (Adams, 1982; Dickinson, 1985; Iguchi et al., 2017; Kosaki and Dickinson, 2010). Reinforcement schedules during training can also induce either goal-directed or habitual lever pressing. Random (RR) or variable ratio (VR) schedules facilitate goal-directed behavior, whereas random (RI) or variable interval (VI) schedules facilitate habitual behavior (Dickinson et al., 1983; Yin et al., 2005).

Note that some studies referred to in this review, employed Pavlovian conditioning tasks to assess goal-directed or habitual behavior. In contrast to instrumental conditioning where reward availability depends on the execution of a voluntary action (e.g. lever pressing behavior), passive response to reward predictive cue (e.g. head entry to food cup) is typically measured in Pavlovian conditioning. Importantly, animals also show outcome-specific devaluation when tested in a Pavlovian conditioning paradigm. In this review, reward seeking behavior in both instrumental and Pavlovian paradigm is regarded as 'goal-directed' when seeking behavior is reduced after outcome specific devaluation. We mostly refer to studies that utilized instrumental conditioning, but we indicate where Pavlovian conditioning was used.

Rodent studies using the outcome-specific devaluation task have revealed that goal-directed and habitual behaviors are controlled by separate neural circuits, which we summarize in this review. Understanding the neural circuits that are critical for goal-directed and habitual behavior may lead to a better understanding of the pathophysiology of OCD and thus to more targeted treatment options that can more specifically ameliorate circuit dysfunction.

3. Brain structures involved in goal-directed and habitual reward seeking

3.1. The role of the striatum in goal-directed and habitual reward seeking

The striatum is a key brain structure in neural circuits underlying motor and action control. The striatum is part of the basal ganglia, which is a group of brain nuclei involved in the generation and control of motor patterns. Within the basal ganglia the striatum is conceptualized as an input nucleus, allowing cortical structures to facilitate action selection by specifically modulating subgroups of striatal neurons. These striatal activity patterns are then thought to control specific motor movements, associative learning, and decision making. Anatomically and functionally, the striatum can be divided into a dorsal part and a ventral part, which is typically called the nucleus accumbens (NAC). The dorsal and ventral striatum are further subcategorized into dorsomedial (DMS) and dorsolateral striatum (DLS), and NAC core and NAC shell. The striatum consists of two major types of medium-sized spiny projection neurons (MSN) that are characterized by differential

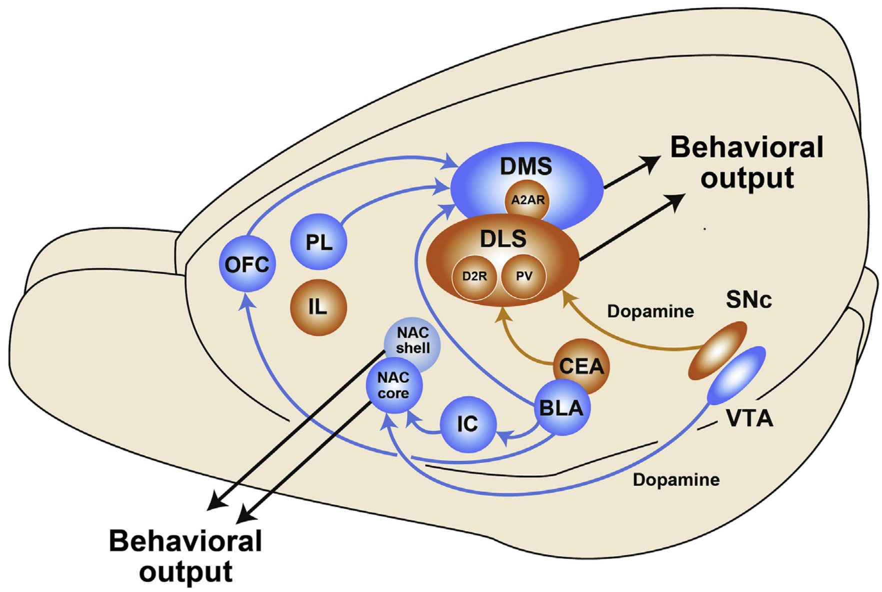

Fig. 2. Summary of brain structures involved in goal-directed or habitual behavior, as assessed in animal models with outcome-specific devaluation testing. The structures in blue contribute to goal-directed action, whereas the structures in orange play a role in habitual responding.

gene expression. One type of MSNs (D1R-MSN) expresses dopamine type-1 receptors (D1R) and substance P, whereas the other type of MSNs (D2R-MSN) expresses dopamine type-2 receptors (D2R), adenosine A2A receptors (A2AR), and enkephalin (Alexander and Crutcher, 1990; Gerfen et al., 1990). These two types of MSNs are output neurons that project to specific downstream nuclei, such as the substantia nigra and globus pallidus, to control motor output. Locally, the striatum is controlled by a small but functionally significant population (5%) of interneurons that includes fast-spiking parvalbumin (PV)-positive interneurons, low-threshold spiking somatostatin-positive interneurons, and cholinergic interneurons (Kawaguchi, 1993). Importantly, studies employing outcome-specific devaluation paradigms have revealed opposing functional roles of different striatal subregions and different striatal neuron types in goal-directed and habitual behaviors.

The DMS is an essential structure for goal-directed behavior (Fig. 2). Excitotoxic lesion of this area increased habit-like responding in mice (Gremel and Costa, 2013) and rats (Corbit and Janak, 2010; Yin et al., 2005), suggesting that DMS function is required for goal-directed action. Interestingly though, animals with specific knockdown of A2AR, which are expressed in D2R-MSNs throughout the striatum, did not develop habitual responding in the outcome-specific devaluation task, as their lever-press behavior remained goal-directed (Yu et al., 2009). Furthermore, optogenetic activation of A2AR signaling in A2AR-positive neurons specifically in the DMS facilitated habit formation (Li et al., 2016). Together, these findings suggest that although the DMS is necessary for the execution of goal-directed behavior, altering its activity can also facilitate habitual behavior via A2AR signaling.

While the DMS is especially relevant for goal-directed behavior, the DLS is thought to be an essential brain region for habitual behavior (Fig. 2). Excitotoxic lesioning of the DLS in mice and rats changes habitual reward seeking into goal-directed actions, while it does not alter goal-directed behavior itself (Gremel and Costa, 2013; Yin et al., 2004). However, one study shows that pharmacological inactivation of the DLS impairs outcome devaluation when tested in Pavlovian conditioning, but not in an instrumental task, suggesting that the DLS is involved in cue-guided goal-directed behaviors in addition to its prominent role in habitual instrumental behavior (Corbit and Janak, 2010). Supporting the significance of DLS in habitual behavior, infusion of AMPAR or D1R antagonists into the DLS reversed habitual responding for palatable food to goal-directed responding (Furlong et al., 2014). Similarly, the infusion of AMPAR, D1R or D2R antagonists impaired habitual ethanol seeking (Corbit et al., 2014). These findings suggest that both glutamate and dopamine signaling in the DLS are necessary for habitual reward seeking. Importantly, a recent study showed that activation of fast-spiking PV-interneurons in the DLS facilitates habit formation, suggesting that DLS PV-interneurons also mediate habitual behavior (O'Hare et al., 2017). Ex vivo synaptic plasticity experiments have also pointed to a key role for the DLS in habit formation. RI schedule training, which promotes habitual responding (Dickinson et al., 1983), results in decreased miniature excitatory postsynaptic currents specifically in D2R-expressing neurons in DLS, and this plasticity is dependent on the activity of D2R and the ion channel TRPV1 (Shan et al., 2015). Furthermore, the strength of cortical excitatory synapses on D1R- and D2R-expressing MSNs in the DLS is correlated with the extent of habitual reward seeking behavior (O'Hare et al., 2016). Although it is not fully resolved yet how the DLS contributes to the formation of habits on a cellular and microcircuit level, these studies show consistently that the DLS is a key brain structure for habits.

In the ventral striatum of rats, excitotoxic lesion of the NAC core impaired the expression of outcome devaluation but not instrumental learning itself, suggesting that the core is important for goal-directed actions in instrumental conditioning (Corbit et al., 2001, Fig. 2). Furthermore, local infusions of μ-, but not ∂-opioid receptor antagonists impaired the expression of goal-directed lever pressing, suggesting that the opioid system in the NAC core is involved in goal-directed actions (Laurent et al., 2012). Excitotoxic lesion of the NAC core also impaired outcome-specific devaluation when rats were tested in a cue-guided Pavlovian paradigm (Singh et al., 2010). Specifically, the NAC core might encode cue-association that triggers a goal-directed response, which is supported by the findings of an in-vivo electrophysiology study employing an operant task where the instrumental response was guided by a cue-light. They found that the larger the population of NAC core neurons that were responsive to a reward-predicting cue during training, the stronger the suppression of lever pressing after reward devaluation during testing (West and Carelli, 2016). It should be noted that NAC core neuronal activity did not change under devalued condition compared to the non-devalued condition, suggesting that the NAC core is not involved in the representation of changed reward value if a cue is present. Collectively, these studies suggest that the NAC core plays a role in goal-directed instrumental action, probably by encoding a Pavlovian association to a cue. The role of the NAC shell in goal-directed or habitual behaviors is less clear. One study showed that excitotoxic lesion in NAC shell does not impair goal-directed behavior when assessed by instrumental behavior (i.e. lever press; Corbit et al., 2001), but another study found that shell lesions did impair goal-directed behavior when assessed by cue-guided Pavlovian conditioned response (i.e. head entry into reward delivery port; Singh et al., 2010). In vivo electrophysiology studies in the shell have shown that the number of neurons that are responsive to a reward-predicting cue were reduced after devaluation compared to the non-devalued condition, supporting a role of the NAC shell in cue-guided reward seeking (West and Carelli, 2016). More research is required to fully understand the role of NAC shell in goal-directed behavior.

3.2. The role of the cortex in goal-directed and habitual reward seeking

Cortical regions interact with various projection targets to control aspects of behavioral flexibility, including goal-directed and habitual behaviors (Fig. 2). One important cortical projection target is the dorsal striatum, but many studies have investigated the role of different cortical regions in goal-directed and habitual behaviors independent of their downstream targets. The medial prefrontal cortex (mPFC), especially the prelimbic (PL) and infralimbic (IL) subregions, has been widely investigated in the context of behavioral flexibility. Evidence suggests that the PL is especially important for goal-directed behavior. Excitotoxic lesions in the PL made before initial operant training impaired goal-directed behavior in an outcome-specific devaluation task (Balleine and Dickinson, 1998; Killcross and Coutureau, 2003; Ostlund and Balleine, 2005). However, animals were spared this deficit when the lesions were made after significant training, suggesting that the PL is important for encoding the action-outcome association, but not for retrieving this association during the execution of goal-directed behavior (Ostlund and Balleine, 2005). This idea has also been supported by pharmacological inactivation of the PL (Tran-Tu-Yen et al., 2009) and by a study that showed that MAPK activity in the PL is important for encoding the action-outcome association (Hart and Balleine, 2016).

The PL projects to several brain areas, but the posterior part of the DMS (pDMS) is one of the critical downstream targets for the control of goal-directed behavior. After operant training, pERK levels were increased in pDMS-projecting PL neurons, suggesting that these neurons are preferentially active during operant training (Hart and Balleine, 2016). Furthermore, asymmetrical lesions in the PL and pDMS impaired goral-directed behavior (Hart et al., 2018). This finding is especially convincing because asymmetric lesions disconnect these regions from each other without compromising overall function of either in relation to other downstream targets. In contrast to the PL, the IL seems to be especially critical for habitual behavior. Studies have shown that excitotoxic lesion of the IL results in goal-directed behavior in overtrained rats (Killcross and Coutureau, 2003) and cocaine treated mice (Schmitzer-Torbert et al., 2015), which are conditions that favor habitual behavior in control mice. The IL sends its projections to the DMS and many other brain areas, but it remains unknown which projection is functionally important to regulate habitual behavior.

The gustatory region of the insular cortex (IC) is another important cortical area for goal-directed behavior. Chemogenetic inhibition of the IC during free-access feeding or during devaluation testing impaired goal-directed behavior, while this inhibition had no effect during initial training (Parkes et al., 2018). Furthermore, local IC infusion of the NMDA receptor antagonist ifenprodil impaired goal-directed behavior, whether it was infused before reward devaluation or before devaluation testing (Parkes and Balleine, 2013). The same study further showed that the sequential disconnection between amygdala and IC results in a deficit in goal-directed behavior when the amygdala was inactivated during the devaluation and the IC was inactivated during testing, but not when the order of drug infusions was opposite (see also 3.3). Together, these results suggest that IC activity is required for the retrieval of the altered value during testing, but not for the encoding and storage of the action-outcome association itself. Interestingly, the NAC core seems to be an important downstream target of the IC for the execution of goal-directed behavior, as evidenced by a study showing that asymmetrical pharmacological inactivation of the IC and the NAC core just prior to devaluation testing impaired subsequent goal-directed behavior (Parkes et al., 2015).

The orbitofrontal cortex (OFC), has also been shown to be important for flexible behavior, which is critical for goal-directed behavior. Excitotoxic lesions of the OFC impaired goal-directed behavior in mice (Gremel and Costa, 2013), rats (Pickens et al., 2003), and monkeys (Rhodes and Murray, 2013; Rudebeck et al., 2017). Importantly, Gremel and Costa (2013) also showed that chemogenetic inhibition of OFC pyramidal cells impaired goal-directed behavior and that chemogenetic inhibition specifically targeted to DMS-projecting OFC neurons induced the same deficit in goal-directed behavior without affecting habitual reward seeking. They also found that knockdown of endocannabinoid receptors specifically in the OFC-to-DMS pathway led to goal-directed behavior, even in animals trained under a RI reinforcement schedule that induced habitual behavior in control mice (Gremel and Costa, 2013). These results suggest that OFC activity is required for goal-directed behavior through downstream signaling to the DMS, and that signaling through endocannabinoid receptors in the OFC-to-DMS pathway is involved in habit formation. In line with this conclusion, Renteria et al. (2018) found that chronic intermittent ethanol exposure facilitates habitual behavior and is accompanied by decreased excitability of OFC projection neurons and reduced probability of neurotransmitter release from OFC terminals onto D1-MSNs in the DMS. This finding indicates that reduced activity in the OFC-DMS pathway coincides with reduced goal-directed responding. Additionally, chemogenetic activation of the OFC shifts the behavior of these ethanol-exposed animals from habitual to goal-directed. It should be noted that some studies using excitotoxic lesions or chemogenetic inhibition of the OFC have failed to produce deficits in goal-directed behavior (Lichtenberg et al., 2017; Ostlund and Balleine, 2007; Parkes et al., 2018); however, these studies did show deficits in goal-directed behavior when a Pavlovian cue-guided reward delivery port entry rather than instrumental lever press behavior was assessed (Lichtenberg et al., 2017), and also found a similar deficit when the action-outcome association was changed by switching the lever associated with food (Parkes et al., 2018). Note that all these studies targeted the ventral, ventrolateral and lateral subregions of the OFC. Although less studied, the medial OFC, especially its anterior part, may also play a role in goal-directed behavior, as excitotoxic lesion of this region impairs (Bradfield et al., 2015, 2018), while chemogenetic activation of this region facilitates goal-directed behavior (Gourley et al., 2016), but much more work is required to fully understand its contribution.

3.3. The role of the amygdala in goal-directed and habitual reward seeking

The amygdala is an important limbic structure for learning and memory that are triggered by emotionally salient experience such as fear or reward. However, amygdala also have essential function to flexibly control reward-seeking strategies through its projections to the cortex and the striatum (Fig. 2). Excitotoxic lesions of the basolateral amygdala (BLA) impaired goal-directed behavior (Corbit and Balleine, 2005), and infusion of the NMDA receptor antagonist ifenprodil into the BLA prior to reward devaluation, but not prior to devaluation testing, impaired goal-directed behavior (Parkes and Balleine, 2013). These results suggest that BLA activity is necessary for updating outcome value but not for retrieving the updated outcome value. Additionally, asymmetric inhibition of the BLA and the IC via local infusion of ifenprodil indicated that the BLA-to-IC projection specifically is important for updating the outcome value that triggers devaluation (Parkes and Balleine, 2013). The involvement of the BLA-to-IC projection in outcome value updating after devaluation (Parkes and Balleine, 2013) and the relevance of the IC-to-NAC core projection for the expression of outcome devaluation (Parkes et al., 2015) suggests that the BLA-to-IC-to-NAC core circuit could be an important functional sequence for goal-directed behavior. Indeed, pharmacological disconnection experiments have also shown that the projection from the BLA to the NAC core has functional relevance for outcome-specific devaluation (Shiflett and Balleine, 2010) supporting this possibility. The BLA also projects to the OFC, and chemogenetic inhibition of BLA terminals in the OFC impaired goal-directed behavior in a Pavlovian task but not in an operant task. Inhibition of this pathway in the opposite direction (OFC to BLA) did not affect behavioral responses (Lichtenberg et al., 2017), suggesting that the BLA-to-OFC, but not the OFC-to-BLA, pathway is necessary for the expression of cue-guided goal-directed behavior.

The BLA also influences goal-directed behavior through its projections to the DMS. Pharmacological disconnection between the BLA and the DMS during initial training impaired goal-directed behavior, suggesting that the BLA-to-DMS circuit is required for the acquisition of the action-outcome association (Corbit et al., 2013). BLA-to-DMS disconnection immediately before devaluation testing also disrupted goal-directed behavior, suggesting that the BLA-to-DMS projection is also important for the retrieval of the action-outcome association (Corbit et al., 2013).

In contrast to the BLA, the central nucleus of the amygdala (CEA) facilitates habit formation, particularly through projections to the DLS. Bilateral lesions of the anterior CEA, but not the posterior CEA, resulted in goal-directed behavior in over-trained rats while sham lesions resulted in the habitual behavior typical for this training paradigm (Lingawi and Balleine, 2012). The same study also showed that asymmetrical lesions of the CEA and DLS have the same disruptive effect on habitual behavior (Lingawi and Balleine, 2012). Taken together, these results suggest that BLA contributes to goal-directed behavior through its projection to cortex and striatum whereas CEA facilitates habitual behavior. Considering variety of neural projections from these regions and cell types, further studies are necessary for deeper understanding of the regulatory mechanism.

3.4. The role of the dopaminergic system in goal-directed and habitual reward seeking

Dopamine, a neurotransmitter involved in motivation and movement, controls a variety of reward seeking behaviors, including both conditioned and unconditioned reward seeking. Midbrain dopamine neurons originating in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) send strong projections to the ventral and dorsal striatum, respectively. 6-OHDA-induced dopamine depletion in the NAC impaired goal-directed behavior in a Pavlovian context but not in an instrumental context (Lex and Hauber, 2010b, Fig. 2), indicating the involvement of NAC dopamine in modulating goal-directed behavior. Consistent with this result, cue-evoked DA release in NAC is decreased after outcome-specific satiety (Aitken et al., 2016; Papageorgiou et al., 2016). Interestingly, dopamine depletion in the pDMS did not affect outcome-specific devaluation (Lex and Hauber, 2010a), but more research is needed before excluding a role for pDMS dopamine signaling in goal-directed behaviors. Dopamine neurons also project to the frontal cortex, but the role of cortical dopamine release in outcome-devaluation has remained widely untested. However, a couple of studies have shown that dopamine depletion in the PL and IL does not affect outcome devaluation in an operant task (Lex and Hauber, 2010a; Naneix et al., 2009), indicating that cortical dopamine signaling may be less influential in controlling goal-directed behavior.

Dopamine is also important for habitual reward seeking. Dopamine depletion in the DLS impaired habitual reward seeking and facilitated goal-directed behavior (Faure et al., 2005). Knockout of NMDA receptors selectively in midbrain dopamine neurons also impaired habitual behavior (Wang et al., 2011), suggesting that dopamine neuron activity is integral to habitual responding. Supporting this, dopamine receptor blockade into DLS impaired habitual cocaine seeking in which animals are extensively trained (Murray et al., 2015). Consistent with this idea, electrophysiological recordings from monkeys that respond to visual cues with habitual saccades have shown that the substantia nigra dopamine neurons that project to the caudate tail remain responsive to previously reward-associated cues, even if the cues no longer predict a reward (Kim et al., 2015). So far, the data suggest that NAC dopamine may be more important for goal-directed behaviors, while DLS dopamine may be more important for habitual behaviors, but this area is ripe for further investigation.

4. Implications for OCD

4.1. Impaired goal-directed or excessive habitual behavior in OCD

As much as habits can be useful for a daily routine, excessive engagement in habitual processes can become pathological as the inflexibility of habitual behaviors can become an obstacle. Several psychiatric disorders are thought to rely on aberrant habit formation, including OCD, Tourette's syndrome, drug addiction, and binge-eating disorder (Robbins and Costa, 2017), but we will focus on the pathophysiology of OCD. OCD affects 1–2% of the population (Kessler et al., 2012), and according to the DSM-5 (American Psychiatric Association, 2013), diagnosis requires 1) the experience of obsession and/or compulsion symptoms and 2) that obsessions or compulsions are time consuming ($>$ 1 h a day), stressful, or impair the patient's functioning in everyday life. Anxiety symptoms are also frequent in OCD patients.

Compulsive behavior (continued behavior despite negative consequences) in OCD patients has long been explained as an avoidance action to relieve the anxiety that arises from obsessive thoughts (Pauls et al., 2014). This explanation implied that compulsive behavior is conducted in a goal-directed manner (e.g., washing hands to relieve the fear of contamination). However, it has also been proposed that compulsive behavior in OCD patients could arise from maladaptive stimulus-response learning and, as a consequence, facilitated habitual behavior (Gillan and Robbins, 2014; Graybiel and Rauch, 2000). This psychological view seems to contrast with the understanding of goal-directed behavior to relieve anxiety and could benefit from further investigation, nevertheless, conclusive studies show excessive formation of habits in OCD patients. In an appetitive learning task, OCD patients showed impairment in goal-directed actions, indicating that their habit learning system is more engaged than in healthy control subjects (Gillan et al., 2011). Impaired goal-directed behavior in OCD patients was also reported in a study that employed an economic choice paradigm (Gillan et al., 2014a). The reliance on the habit system in OCD patients was even more evident in an avoidance learning task (Gillan et al., 2014b). In this study, OCD patients and healthy controls were trained to respond to a stimulus that predicted a mild electric shock to the hand that could be avoided by a correct response. After overtraining, the subjects' responses were tested in the devalued state, during which there was no connection to the device delivering the electric shock. OCD patients showed significantly more unnecessary avoidance responses than control subjects, suggesting that the OCD patients learned the avoidance habits more readily than the healthy controls. Interestingly, the OCD patients also reported a subjective urge to respond to the stimulus. This indicates that for OCD patients, forming a habit is not only an automated motor program triggered by a stimulus, but that the stimulus-response is accompanied by the awareness that the behavior is being performed. A major difference between naturally formed habits and aberrant habits in OCD patients could be that, in the pathological situation, habits are accompanied by the urge to respond to a stimulus, whereas in normal habits a cognitive reflection or an emotional component of the stimulus-response action is absent. However, this requires further investigation. Overall, the excessive habit formation observed in OCD patients may be explained by an imbalance of action-outcome vs. stimulus-response learning, favoring stimulus-response learning due to an impairment in goal-directed learning (Gillan et al., 2015). A recent study in rats provided evidence that the presence of salient stimuli significantly accelerates the formation of habits (Vandaele et al., 2017). OCD patients might in general be particularly responsive to stimuli and therefore form habits readily.

Likely, facilitated or inappropriate habit formation is a symptom of OCD, but cannot explain the complete spectrum of compulsive behavior in OCD. Nevertheless, the cognitive and behavioral inflexibility that goes along with the aberrant habit formation can be debilitating for OCD patients that are heavily affected by these deficits, and certainly requires specific attention. These OCD patients might also benefit from different treatment than OCD patients with anxiety as core symptom, for example, targeting the glutamate system rather than the serotonin system. However, the number of studies investigating inflexible, habitual behavior in OCD are still low. We summarized in the paragraphs below briefly circuit dysfunction in OCD patients that might be related to aberrant habits, and, in more details, animal models of OCD which can be particularly useful to investigate aberrant habits and behavioral inflexibility related to OCD.

4.2. Cortico-striatal circuit dysfunction in OCD patients

If OCD is a disorder characterized by aberrant habit formation due to impaired goal-directed learning, then OCD patients should have abnormalities in the neural circuits that have been shown to contribute to these types of behaviors. Indeed, dysfunction of the cortico-striatal-thalamic-cortical (CSTC) circuit (Milad and Rauch, 2012; Rotge et al., 2009) is a key element in the current understanding of OCD pathophysiology (Pauls et al., 2014; Saxena and Rauch, 2000). Imaging studies with OCD patients have consistently reported abnormal functioning of brain areas in the CSTC circuit. Increased activity and metabolism during a resting state were found consistently in the OFC, anterior cingulate cortex (which includes BA32, the human homolog of the rodent PL), caudate and putamen (human homolog of the dorsal striatum), and thalamus of OCD patients compared to healthy participants (Brennan et al., 2013; Menzies et al., 2008; Saxena and Rauch, 2000). Conversely, during the engagement of a task such as reversal learning, OCD patients show hypoactivity in the OFC (Chamberlain et al., 2008; Wood and Ahmari, 2015). This is comparable to animal research that showed the importance of the OFC for goal-directed behavior (see 3.2). Altogether, the brain areas that have been implicated in OCD pathology overlap extensively with the circuits that control goal-directed or habit behavior in animal studies. Furthermore, changes in serotonin and dopamine signaling have been suggested in the pathophysiology in OCD (Denys et al., 2004; Figee et al., 2016), however, probably due to the complexity of these neuromodulatory systems, the role of serotonin and dopamine in OCD-like compulsivity is still not quite clear. Likely, hyposerotonergic and hyperdopaminergic states contribute to OCD symptoms.

4.3. Cortico-striatal circuit dysfunction in animal models of OCD

Mouse models can be instrumental for an in-depth understanding of the circuit abnormalities present in OCD, since they allow for synaptic and mechanistic investigations of pathological circuit dysfunction that would not be possible in human participants (Piantadosi, 2015). In mice, neuronal activity patterns can be recorded during behavior, and brain circuits can be selectively manipulated. Furthermore, to investigate synaptic dysfunction, *ex vivo* analyses using electrophysiological techniques are indispensable. We recognize that OCD is a human pathology and we do not have means to reveal (obsessive) thoughts in animal models of OCD, nevertheless, OCD-like behavior can be induced and observed in animals, including mice. OCD-like behaviors in mice have been assessed by testing for anxiety, habitual motor responses (e.g., approaching a previously reward-associated area in a maze), repetitive behaviors, and stereotypic self-grooming. Of note is the idea that stimulus-response learning that favors habitual action can occur without underlying obsessive thoughts in OCD patients (Gillan et al., 2014b) reinforces the translational validity of mouse models of OCD, although we cannot know whether mice are experiencing obsessive thoughts. Therefore the habit formation task that we described in detail above is a translational behavioral phenotype that could be useful in further validating animal models of OCD; but despite its potential, the habit formation task has not yet been tested in typical OCD models.

There are several genetic mouse models of OCD (e.g., *Slitrk5*-KO, *HoxB8*-KO, *Slc1a1*-KO), but a prominent, standard model is the *Sapap3*-KO mouse, whose most pronounced behavioral phenotype is stereotypic self-grooming. In these mice, grooming continues to the point that the animals develop skin lesions but nevertheless continue self-grooming. This grooming behavior despite the negative consequence of skin lesions may be comparable to the compulsive hand-washing seen in OCD patients. These mice lack SAPAP3, a protein abundant at excitatory synapses that maintains their normal functioning. Although the consequences of the *Sapap3*-KO on circuit function is not fully understood, the *Sapap3*-KO mouse has become a standard mouse model of OCD, likely due to its strong validity (Zike et al., 2017). Construct validity for the *Sapap3*-KO model is indicated by mutations of *Sapap3* in OCD patients (Zuchner et al., 2009), and face validity is indicated by the remarkable phenotype of compulsive grooming. Most importantly, the efficacy of chronic fluoxetine-treatment in normalizing the aberrant over-grooming parallels the efficacy of this treatment in OCD patients and thus supports the predictive validity of the model (Welch et al., 2007). The absence of the postsynaptic density protein SAPAP3 in the dorsal striatum underlies the behavioral phenotype of anxiety and compulsive grooming in *Sapap3*-KO mice (Welch et al., 2007), which not only links these OCD-like behaviors to circuits that control goal-directed and habitual behaviors, but also further links this animal model to OCD patients, who show basal ganglia abnormalities. Note that OCD-like phenotypes can also be pharmacologically induced in wild-type animals with dopaminergic and serotonergic drugs (Zike et al., 2017), which is consistent with the findings implicating dopamine signaling in goal-directed and habitual behaviors and with the centrality of these behaviors to OCD symptoms. Furthermore, dysregulation of the serotonin and dopamine system were detected in *Sapap3*-KO animals (Wood et al., 2018), which further implicates a contribution of these neurotransmitters to OCD-like phenotypes in animal models.

Although the *Sapap3*-KO mouse model has been initially described over a decade ago, no study to date has assessed the behavior of these mice in a habit formation task. However, three recent studies have tested *Sapap3*-KO mice on behavioral flexibility. In behavioral flexibility paradigms, mice first have to learn an instrumental or a Pavlovian stimulus-reward contingency. Then, the contingency (e.g., active lever in instrumental tasks or cue in Pavlovian paradigms) is changed. Behaviorally flexible animals will readily learn the new contingency, whereas behavioral inflexibility is reflected in a failure or delay of adapting the new contingency. *Sapap3*-KO mice show deficits in adapting to a new contingency in instrumental (Benzina, 2019; Manning et al., 2018) and Pavlovian paradigms (Van den Boom et al., 2019). This finding is consistent with the idea that OCD is a disorder with underlying aberrant habitual behavior, here reflected in an excessively persistent original response, even when stimulus-reward contingencies have changed (Gruner and Pittenger, 2017). Interestingly, Manning et al. (2018) found that roughly half of the tested *Sapap3*-KO mice did not differ from wild-type in acquiring a new instrumental contingency, whereas the other half of the *Sapap3*-KO animals completely failed to learn the new contingency. Similarly, Benzina et al. (2019) found that only a subgroup of *Sapap3*-KO showed behavioral inflexibility. This suggests that the genetic deletion of *Sapap3* is not sufficient to cause this behavioral phenotype, but that other, so far unknown factors can provoke behavioral inflexibility in animals with deletion of *Sapap3*.

Animal models of OCD allow to explore circuit dysfunction on an experimental level that is not feasible in clinical research with OCD patients. A growing body of basic research found corticostriatal circuit dysfunction in OCD mouse models and point to specific circuits and synaptic changes involved in OCD-like behavior. In wild-type mice, OCD-like grooming can be optogenetically induced by delivering repeated 10-Hz stimulation to medial OFC terminals in the ventromedial striatum (Ahmari et al., 2013). This manipulation of the OFC-to-ventromedial striatum projection resulted in enhanced sensitivity of striatal neurons in response to subsequent OFC stimulation (Ahmari et al., 2013). In the *Sapap3*-KO mice, the AMPA receptor currents are decreased relative to the NMDA receptor currents (AMPA/NMDA ratio) at cortico-striatal synapses, which is indicative of reduced synaptic strength at this connection (Wan et al., 2011). A recent study employed optogenetics to specifically compare the corticostriatal projections from the OFC and the secondary motor area (M2; human homolog = presupplementary motor area) and found that in *Sapap3*-KO, compared to wild-type littermates, the M2 to central striatum projection is strengthened, whereas the OFC projection is weakened, expressed by post-synaptic changes in AMPA and NMDA receptor function (Corbit et al., 2019). A decrease in OFC projections indicates that *Sapap3*-KO mice could be more prone to form habits or be impaired in goal-directed behavior (see section 3.2. in this review). Hyperactivity in the DMS (human homolog = caudate nucleus; Burguiere et al., 2013) and an imbalance between direct and indirect pathway neuron activity in the DLS (human homolog = putamen; Ade et al., 2016) have also been described in *Sapap3*-KO animals, which might also be a result from abnormal cortical top-down control, mediated through changes at corticostriatal synapses. Similar circuit/synaptic pathologies have been described in other models of compulsion. *Slitrk5*-KO mice showed deficits in corticostriatal transmission and OFC hyperactivity, as measured by FosB expression (Shmelkov et al., 2010). OFC hyperactivity and potentiated OFC-to-dorsal striatum synapses are also evident in mice that compulsively self-stimulate dopamine neurons, which is a model of drug addiction (Pascoli et al., 2015, 2018). Future research employing OCD mouse models, optogenetics, cell-type specific assessment of neuronal activity, *ex-vivo* patch-clamp electrophysiology, and other tools will lead to a more detailed understanding of the circuit and cellular pathologies underlying OCD-like behavior. In addition, these approaches can causally link circuit abnormalities with behavioral outcomes.

4.4. Deep brain stimulation (DBS) treatment of OCD

Ideally, treatments for OCD would specifically target the neural circuits that are dysfunctional. However, current treatments are limited and cannot be directed to specific circuits. Selective serotonin reuptake inhibitors (SSRI) such as fluoxetine, are the main pharmacological treatments for OCD. They are typically administered at high doses, sometimes in combination with antipsychotic agents (Pittenger and Bloch, 2014). SSRIs take weeks to have any ameliorative effect on OCD symptoms, and many patients respond only partially or not at all to treatment. Deep brain stimulation (DBS) can be a more effective alternative treatment for OCD and is typically reserved for patients that do not respond to standard pharmacological and behavioral therapies (Alonso et al., 2015; Kisely et al., 2014; Mallet et al., 2002). For OCD treatment, the subthalamic nucleus (STN), a nucleus involved in action control downstream of the striatum, is targeted and continuously stimulated at a high frequency ($>$ 100 Hz).

In animal models of OCD, DBS can effectively reduce OCD-like behavior. For example, DBS targeting the internal capsule, which contains the descending and ascending projections between the cortex and basal-ganglia, acutely reduced grooming in *Sapap3*-KO mice (Pinhal et al., 2018). The same DBS protocol also reduced grooming when the dorsal part of the ventral striatum was targeted, but this was less effective than targeting the internal capsule. DBS in the STN effectively prevented 'compulsive' lever pressing in rats subjected to a signal-attenuation task (Klavir et al., 2009). High frequency DBS is thought to act by inducing a temporary lesion (acute inactivation for the time of the stimulation) and thus disrupting aberrant circuit function (Mulders et al., 2016). By targeting the STN for DBS, we intervene at a downstream level in the circuit, as the STN is an output nucleus of the globus pallidus externa, which itself is an output nucleus of the striatum. Intervention at a more upstream level of the circuit could be beneficial for patients by restoring normal functioning of more of the aberrant circuit. Preclinical research will be useful for the optimization of DBS targets and stimulation protocols, and will allow us to achieve a mechanism-based reversal of the circuit pathology, similar to DBS to reverse drug-adaptive plasticity (Creed et al., 2015).

5. Conclusion and perspectives

Preclinical and clinical studies have been complementary in the investigation of the basic circuit mechanisms that underlie goal-directed behavior and habitual responses and in the identification of pathological circuits present in OCD. In animal models, direct manipulation of brain circuits can reveal the roles of those circuits in specific behaviors, such as habitual responding to a stimulus. The translational validity of findings from animal experiments has been enhanced by a range of clinical studies on habit formation and circuit pathology in OCD patients. DBS has been proven to be an effective treatment for OCD, but it is incredibly invasive, and continuous stimulation is required for efficiency. A better understanding of the OCD-relevant circuits can be achieved by investigating cellular activity, synaptic plasticity, and the link between synapses and behavioral outcomes may lead to improvements in therapeutic options. A causal link between OCD circuit pathology and aberrant habit formation has not yet been established, but different circuits can be probed for causality by using animal models and optogenetic/chemogenetic tools to manipulate specific circuits and cell types. Eventually, future research might propose convergent, or divergent, circuit models for psychiatric disorders with underlying aberrant habit formation, such as OCD, addiction, or binge-eating disorder.

Conflicts of interest

None.

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