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Neurobiology of habit formation

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Our knowledge of the brain changes that enable habits to be formed continues to grow rapidly. As a key hub for habits, many studies have focused on neurobiological processes related to habits in the striatum. Attention has been paid to the contributions of the direct and indirect pathways, interneurons, dopaminergic inputs, and potential cortical and amygdala influences. We highlight this research here and conclude with a discussion of several additional topics that are also being addressed to propel our understanding of habits further forward.

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Advances in research on habits are being made in many realms. There is a growing understanding of how habit formation relates to molecular and physiological mechanisms of neuronal plasticity as well as how varieties of neurons and neural pathways contribute to habits [1–4], which we review here. Several major behavioral assays for habits have been in use in order to provide operational measures that distinguish behaviors that are habitual versus those that are purposeful or cognitively driven. One measure for habits is to show that behavior is insensitive to changes in the expected value of the earned outcome. For tasks that involve learning behaviors to achieve rewards, outcome revaluation involves a deflation or inflation of the reward value (e.g. through conditioned taste aversion, satiety, hunger) that occurs outside of the task conditions. The test is whether subjects incorporate that new knowledge about reward value into their learned task behavior routine where the changed reward is the outcome; when behavior immediately adjusts to reflect the new outcome value (e.g. is reduced when the reward has been devalued), it is thought to be goal-directed and rooted in associations that had been learned between the action and the specific outcome. When behavior remains the same as before, and is insensitive to the new outcome change, it is regarded as habitual and driven by stimulus-response associations. In some cases, habits are also inferred when a learned behavior is insensitive to changes in the received outcome. This occurs, for example, when behavior persists despite the outcome co-occurring with punishment (e.g. a footshock). Similar assays test behavioral flexibility in response to a change in the action-outcome contingency; purposeful behaviors adjust rapidly to reflect new contingencies, while habits do not. On maze tasks, habits are also inferred when navigation is driven by a response rule (e.g. turn right) rather than a place rule (e.g. use environmental cues to signal reward locations). Finally, high performance optimality and vigor can also be a marker of habits. Habitual behavior will exhibit trial-to-trial consistency in rapid and routed responses, accurate responses, and responses that lack vicarious trial-and-error head movements (i.e. deliberations toward choice options before action selection, VTEs).

The basal ganglia

Dorsal striatum

In the brain, ground-zero for habits is the dorsolateral striatum (DLS; primate putamen homologue), a basal ganglia input structure, as it has been implicated in all of the behavioral indices of habits noted above. DLS disruption causes animals to favor the use of spatial cues over response-based rules for navigation, to increase sensitivity to outcome value and action-outcome contingency changes, to reduce responding for an outcome paired with punishment, and to increase variance in action structure [1,2,5–7]. This habit promoting role is specific to the DLS within the larger striatum. In fact, an adjacent area, the dorsomedial striatum (DMS; caudate homologue), instead promotes flexibility and goal-directed behavior. For instance, disruption of DMS activity reduces outcome-sensitivity and space-based navigation, resulting in a reliance on habits instead [2]. It is unlikely that the DMS simply serves to oppose habits as neural recording and imaging studies routinely implicate activity in this brain area as signaling relationships between action choice and outcomes, suggesting an active role in goal-directed behavior [8]. Thus, the general consensus is that parallel and competing circuits exist in the brain for habits and goal-directed actions, the former DLS-related and the latter DMS-related.

A series of recent studies have attempted to uncover how activity in the DLS, and the broader circuits within which it is embedded, represent habit learning. This line of

research has begun to suggest that the DLS signals several different aspects of habits in different ways, highlighting what we have described as a multi-component structure of habitual behavior [4]. Two major distinctions include signaling related to the DLS role in performance optimization and the role in producing behavior that is insensitive to changes in outcome value or action-outcome contingency. For example, activity in DLS medium spiny neurons (MSNs), the GABAergic projection neurons of the striatum, can signal specific movements from specific body parts, likely as a consequence of major inputs arriving from the sensorimotor cortex [9]. However, as those movements are put to use in learning a task for reward, the neurons cease responding to each movement occurrence [9]. This change in neuronal signaling occurs as the movements become consistent and repetitive, suggesting a role in representing performance optimization. Yet these changes do not appear to be related to the degree of outcome-insensitivity of the behaviors. For example, the change occurs in head-related activity during a head-movement task for reward, in which head movements become outcome-insensitive, but also occurs in lick-related neurons during a licking task for reward in which licking remains outcome-sensitive [10,11]. A similar conclusion has been reached through analysis of another type of activity change in the DLS, one consistently linked with the optimality and vigor of behavior across several animal species: the emergence of a 'chunking' pattern of spiking that emphasizes the boundaries of a learned action sequence [12]. This pattern has been shown to relate closely to the vigor of a given action routine as it occurs, increasing in strength in close correspondence with an increasing fluidity and consistency of behavior as it is repeated [13,14•,15,16]. Even at the single trial level, the strength of DLS chunking activity, particularly the activity at the initiation of behavior, correlates with faster performance and, notably, an absence of VTEs that indicate purposefulness in behavior. Such findings support the notion that the chunking patterns represent the linking together of an action chain into a single habitual unit [12]. Curiously, though, the chunking pattern is not related to how sensitive the behavior is to outcome value at the trial level, but its emergence does coincide across days with the development of outcome-insensitivity that can serve to define a habit [14•]. Consistent with this, measurements of the overall magnitude of activity in the DLS during task behavior, in both human imaging and rodent neuronal recording studies, shows a positive relationship with the development of the outcome sensitivity measure of habit [17,18]. These collective findings raise the question of how to integrate signals in the DLS that represent movement vigor with the outcome-insensitivity of habits, which we touch on below.

Direct-pathway and indirect-pathway striatal neurons

Additional work has begun to dissect the habit-related contributions of different types of MSNs within the striatum. Two main MSN populations of interest include those of the basal ganglia direct pathway (striatonigral MSNs) and those of the indirect pathway (striatopallidal MSNs) [19]. Classically, the direct-pathway MSNs are thought to promote the performance of chosen movements while the indirect-pathway MSNs inhibit movement or promote alternate movement options [19]. New methodologies have paved a way for monitoring and manipulating these MSNs by capitalizing on their distinct molecular profiles. For example, direct-pathway MSNs contain the excitatory G-protein-coupled dopamine D1 receptor, while indirect pathway MSNs instead contain the inhibitory G-protein-coupled D2 receptor (as well as the adenosine A2A receptor) [20]. Traditionally, the view is that movements are facilitated by dopamine influx that increases activity in the direct-pathway (via D1 receptors) and decreases activity in the indirect pathway (via D2 receptors). Yet, for habits, the story is more nuanced.

In one study on striatum-wide signaling, reduced outcome-sensitivity that occurs after dopamine stimulation (i.e. habit enhancement, see also below) was found to be related to activity in both MSN populations. Habit enhancement was blocked by antagonism of D1 receptors, which would inhibit direct-pathway MSNs. In contrast, outcome insensitivity was augmented by antagonism of D2 receptors, which would increase activity in indirect-pathway MSNs [21]. Several additional studies report a necessary role for the indirect pathway in habit expression based on measures of both insensitivity to outcome value and action-outcome contingencies [22,23]. One recent example highlighting a potentially nuanced role for both MSN populations is an experiment that focused specifically on the DLS. Stimulation of direct-pathway MSNs increased task acquisition rate and biased behavior toward an action paired with optogenetic stimulation (i.e. enhanced performance optimality), while stimulation of indirect-pathway MSNs decreased task acquisition rate and increased non-rewarded actions [24]. Moreover, relative to one another, animals with indirect-pathway stimulation were less sensitive to action-outcome contingency degradation compared to animals with direct-pathway stimulation. These results suggest an action optimization role for direct pathway activity, and a distinct role for indirect pathway activity in diluting the representation of action-outcome contingencies. As both behavioral optimization and action-outcome insensitivity can be important features of an overall habit, these findings point toward the direct-pathway and indirect-pathway MSNs as potentially contributing distinct but complementary functions for habit formation. Indeed, there is evidence that both MSN populations can be engaged in tandem during optimized behaviors, particularly at the point of action initiation [25,26], further suggesting that both populations contribute meaningfully to habits. Intriguingly, there may be a

temporal dynamic to DLS direct and indirect MSN activity when they are both engaged during habits. A recent study found that habit strength in behavior was related *ex vivo* to stronger activity in both MSN populations, but with activity in direct-pathway MSNs preceding in time activity in indirect-pathway MSNs [27••].

There are findings from related studies suggesting that the role of the DMS in promoting goal-directed behavior also involves changes in both direct-pathway and indirect-pathway MSN activity. For example, a greater ratio of AMPA to NMDA receptors in the DMS, indicative of long-term plasticity, is increased in direct-pathway MSNs and simultaneously decreased in indirect-pathway MSNs during acquisition of a goal-directed (outcome-sensitive) lever pressing task [28]. This result suggests that activity in direct-pathway MSNs in the DMS encourages behavior to be goal-directed rather than habitual. Likewise, disruption of striatum-wide or DMS-specific adenosine A2A receptor function, which are expressed on indirect-pathway MSNs and would plausibly impede indirect-pathway plasticity, leads to habit reduction in the form of a heightened sensitivity to outcome devaluation and greater ability to adjust to action-outcome contingency changes [20,29,30].

The results above clearly show the need for additional research as the role of each MSN population may be different depending on which behavioral measure of habits is being studied, what timescale the populations are compared at, and which striatal subregion is considered. One intriguing conclusion is that the classic pro-movement (direct-pathway)/anti-movement (indirect pathway) view of the basal ganglia may not easily apply to the realm of habit control [25], considering, for example, that indirect pathway activity can oppose movement yet is also critical for habits.

Additional striatal mechanisms

There are also beginning to be signs that striatal interneurons, though few in number, play a considerable role in action learning and habits. For example, striatal fast-spiking interneurons (FSIs), thought to be GABAergic, exhibit a chunking-like representation of well-learned actions similar to what is seen in MSNs, suggesting a complementary role in encoding habits [31]. The activity of these interneurons is also necessary for habits. In a recent study, chemogenetic inhibition of DLS FSIs impaired habit expression during a lever press task following outcome devaluation [32]. Thus, despite a relative paucity of studies on FSI roles in habits, the evidence so far strongly favors them being critically involved.

Another type of striatal interneuron is the cholinergic interneuron. In the DMS, the cholinergic interneurons are critical for updating changes in established action-outcome contingencies [33], suggesting a role for the capacity of the DMS to promote goal-directed behaviors. Activation of these cells can be sufficient to elevate dopamine release in at least the ventral striatum [34], raising the possibility that they participate in the ability of dopamine input to the DLS to facilitate habitual behaviors. This possibility remains to be tested, however, leaving it unclear if cholinergic signaling in the DLS promotes habits or instead promotes goal-directed behaviors as it does in the DMS.

Finally, the striatum also has a striosome/matrix compartmentalization [35] that has not yet been studied in the habit context. Striosomal MSNs contribute to action stereotypy and have a privileged connectivity with nigral dopamine neurons [36,37], making their involvement in dopaminergic regulation of striatal function and habits seem plausible.

Dopamine input to the striatum

As noted above, a major neuromodulatory input to the DLS comes from dopaminergic neurons in the substantia nigra pars compacta. These neurons are broadly thought to modulate striatal MSN responses to excitatory inputs and also play an important role in striatal plasticity related to learning [19]. Suggestive of a role in habits, disruption of the dopaminergic neurons or their synaptic terminals in the DLS reduces several markers of habit acquisition and habit-related striatal activity [38–40], and in turn habit formation can be accelerated by increasing dopamine activity [39,41,42]. Notably, an action chunking activity pattern has been found to occur in these neurons during performance of a well-rehearsed action sequence [16]. As the chunking pattern can also predominate DLS MSN and fast-spiking interneuron activity during habitual performance, as noted above, this finding raises the possibility of a dopamine-DLS circuit for the sequencing of behavior into a habitual chunk. In support, a study has found that removing dopamine input ipsilaterally results in a deterioration of learning-related signaling in DLS MSNs in animals performing a maze running task [40].

We note that the role for nigral dopamine in habitual behavior can be dissociated from movement or general learning roles that they have. For example, in Faure *et al.*, 6-OHDA lesions to destroy DA input to DLS produced a mild delay in learning but after reaching a peak level, lesioned animals were markedly more sensitive to outcome devaluation (i.e. less habitual) as compared to controls [38]. Similarly, Nelson and Killcross found that repeated amphetamine administration to augment dopaminergic signaling led to enhanced reliance on habit (i.e. reduced outcome-sensitivity) with no change in learning rate [21]. How dopamine can both promote movement and, in a dissociable manner, promote the learning and performance of habits is an interesting topic for future study.

Beyond the basal ganglia

The basal ganglia are not the only brain areas that participate in habitual behavior. One curiosity is that an area of the neocortex, the infralimbic (IL) cortex in rodents, is also necessary for habits. Perturbations of the IL cortex reduce both habit acquisition and expression [14•,43,44,45••]. Evidence indicates that the IL cortex promotes the strategy of using a habit on-line during behavior, rather than storing the habit learning details [43,45••]. Intriguingly, the IL cortex is not known to be connected directly with the DLS [46]. This raises the question of whether multiple circuits exist in service of habits, one IL-related and one DLS-related, or whether the IL cortex could circuitously interface with the DLS as part of a larger habit-promoting network. In support of the latter possibility, the IL can modulate the central nucleus of the amygdala (CeA) [47] which in turn can project to the SNc [48], the source of DLS dopamine. Suggestive of a habit role for this circuit, Lingawi and Balleine showed that pre-training functional disconnection of the CeA with the DLS, created by making lesions to these structures contralaterally, increased outcome sensitivity in otherwise habitual animals [49••]. Murray *et al.* [50•] also found that the development of habitual characteristics of cocaine seeking, as measured by continued responding in the presence of a drug cue after prolonged training, required functional connectivity between the CeA and dopamine release in the DLS, while the CeA-DLS interaction was not as relevant to cocaine seeking prior to this stage. Moreover, the well-documented acceleration of habit formation that occurs following stress exposure [5,51] can correspond with increased functional activity in amygdala and putamen (primate DLS homologue) as measured in cue-response tasks [52,53]. A picture emerges from this work that IL cortex could serve as an early node for supporting basal-ganglia-based habits through the CeA, nigra, and DLS. One possible circuit underlying this interaction, as suggested by Lingawi and Balleine, is a disinhibitory mechanism involving projections from the IL cortex to intercalated cell masses in the amygdala, with those intercallated neurons sending inhibitory projections to the CeA. The CeA would then send inhibitory projections to nigral dopamine neurons, which would send dopaminergic efferents to DLS. However, complicating the picture of an IL-to-DLS stream of information processing is a finding in a rodent maze running task that learning-related changes in DLS neuronal activity can precede those in the IL cortex as habits are formed [14•]. Despite remaining uncertainties regarding the details, mounting evidence points to important roles for neocortex and amygdala in modulating what is presumed to be a basal-ganglia storehouse for habits.

Challenges

Habit research faces familiar neurobiology questions concerning key circuit nodes and connections, relevant neural activity dynamics, and molecular mechanisms for plasticity. We highlight a few interesting, if complex, questions that have received recent attention.

How is the strength of a habit regulated?

By virtue of gradations in behavioral and neural markers of a habit, including levels of outcome sensitivity and performance vigor, it is likely that habits can occur with graded strength. Neurally, stronger habits could arise through stronger recruitment of the habit system, weakening of the competing goal-directed system, or both. Weaker engagement of brain areas promoting cognitive control has coincided with habit strength in several studies [15,17,44,54,55], and directly dampening activity in such networks can lead to stronger habits [2,45••]. Impaired processing of action-outcome associations leading to abnormal habit-like thoughts and actions has likewise been implicated in human disorders [56,57]. It is equally possible that a waxing and waning of activity in the habit system itself can modulate habit strength [1,2,27••,58,59], though the evidence is more ambiguous. There is a link between the strength of DLS activity during performance and outcome insensitivity in some studies [17,18], while in other studies performance-related DLS activity has been found to change rapidly and in a manner unaligned with the more slowly developing outcome-insensitivity in behavior [14•,15,60]. There is at least clear evidence that the foundation of a habit can be acquired rapidly since removing functionality in the goal-directed system relatively early in task experience immediately produces a behavior that is habitual (in the sense of being independent of outcome value and action-outcome contingency) [2,45••]. Notably, in one maze study, changes in DLS signaling related to task rewards and errors occurred more slowly and in close alignment with behavioral outcome-insensitivity; these changes included a loss of error-related activity and a generalization of reward-related activity [61••]. Such results raise the possibility that plasticity in DLS related to habits can emerge at both early and late timescales. Late-phase involvement of the nigral-DLS system in behavior has also been noted to occur during drug seeking as it grows to be highly persistent [62–64]. Yet, as with the formation of basic habits, DLS activation can also precede addiction development [65]. A related issue for understanding habit strength modulation is the brain basis of its suppression or extinction, which has been tackled in part by studies showing that the DLS and IL cortex themselves can directly participate in the process [27••,44,66]. Increased engagement of cognition-promoting networks is likely to suppress habits as well [3].

How to understand action sequences?

In reality, habits are often chains of different actions. Laboratory investigations of such heterogeneous action chains support a view that sequential actions become associated with one-another, beyond their individual stimulus and reward associations, and that the encoded

goal of an initial action can be a subsequent action. This conclusion has been drawn from studies showing that devaluing the outcome of an action chain can either affect or fail to affect the chained responses together [67,68,69•]. Extinction of an element of the chain reduces responding on the other paired element, confirming that the actions themselves have become associatively linked [69•]. When action chains are affected by a revaluation of the expected outcome, actions temporally proximal to reward exhibit greater sensitivity compared to reward-distal actions, suggesting that initial actions might be the most habitual of the sequence [69•,70]. At the neural level, key questions are the conditions under which the reward proximity of an action is encoded in signaling patterns and how/whether secondary actions are represented during initial actions (and vice versa).

Do habits that are acquired through negative reinforcement work the same?

Relatively little is known about the rules governing habits that are acquired in service of avoiding negative outcomes. The noted acceleration of habits after stress and evidence that strong avoidance habits that can form in OCD patients [71,72] suggest that behaviors acquired to evade unpleasant states might become habits quite rapidly or strongly. Of note, using the response-strategy measure of navigational habits, animals trained to escape a water maze favor a habitual response strategy remarkably early on in task experience [73]. An interesting question now is the extent to which negatively and positively reinforced habits will share the same neural mechanisms.

How do we define a habit?

It is tempting to draw a line in the sand where behaviors that cross are called habits, such as any residual responding for a devalued or non-contingent reward. The notion is that if a behavior appears to lack representation of the expected outcome, then it is best explained in S-R terms. Similarly, on the neurobiological side, 'habit' is often the default interpretation of any behavior that requires the DLS. We argue that this sort of stance overlooks the growing complexity for defining habits and basal ganglia function [74,75]. For example, there can be a disconnect between measures of outcome insensitivity and measures of action optimization at the trial level [74]. Interestingly, action-chunking activity in the DLS corresponds closely to trial-level variations in performance vigor, suggesting a particularly close relationship between DLS and that habit characteristic above others [14•]. Moreover, the habit measure of a maze running response strategy (e.g. turn right) does not necessarily meet the outcome-insensitivity measure of habits, though can become outcome insensitive with over-training [76]. These mismatches between behavioral measures of habit, alongside the diversity of neural signatures for habits noted above, raise the possibility that brain mechanisms of habit may best be understood as contributing components to an overall psychological–behavioral repertoire rather than as servicing or not servicing a simple S-R association [74]. One interesting example to consider in this regard is sign-tracking behavior (a.k.a., autoshaping), in which physical Pavlovian reward cues are pursued and interacted with. Like a habit, this behavior is insensitive to outcome devaluation [77,78]. Yet, more in line with a Pavlovian conditioned response, it can also flexibly adjust yet persist in the face of reward omission and can be exquisitely sensitive to new motivational states [79,80]. Neural mechanisms of sign-tracking include limbic circuits [81] as well as the DLS [75,82]. Should we define sign-tracking as a Pavlovian motivational response or as an S-R habit? Or should we treat each brain process related to sign-tracking as potentially contributing components to the phenomenon, some of which may generate habit-like characteristics? The latter approach might be most fruitful, as would an approach to considering potential components of habits themselves.

Conclusion

It is remarkable how something as intuitively simple as a 'habit' exhibits such great complexity when probed scientifically. Recent behavioral neuroscience work has indicated that habits can occur in graded strength, compete with other strategies for control over behavior, are controlled in part moment-to-moment as they occur, and incorporate changes in neural activity across multiple timescales and brain circuits. One is left with the impression that varied types of questions might be useful to raise now, such as those highlighted in the preceding section. We additionally suggest the potential utility of using habit phenotypes as experimental variables to more fully understand how habits are sculpted and expressed by different signaling components in the brain.

Conflict of interest statement

Nothing declared.

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This study documented how habit formation was represented in activity patterns of DLS and IL neurons. A major result was that plasticity in these areas was dissociable. DLS 'chunking' activity emerged prior to outcome-insensitivity in behavior and was insensitive to restoration of outcome-sensitivity, but it closely tracked the automaticity of behavior trial to trial. In contrast, IL neurons too formed a 'chunking' pattern, but did so in close correspondence with the development and loss of outcome sensitivity. The study further showed that inhibition of IL neurons during habit formation was enough to block outcome insensitivity from emerging.

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This study simultaneously monitored neural activity in projection neurons in the DMS, a site related to goal-directed behavior, and the DLS, a habit-related site, during stages of maze learning. An early-forming and stable 'chunking' pattern was noted in the DLS, while activity accentuating decision points increased and then decreased in parallel to learning time. This result implicates changes in the engagement of goal-directed networks in the brain in the process by which behavior transitions from exploratory to habitual.

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This intriguing study focused on functional distinctions between direct-pathway and indirect-pathway MSNs of the DLS using neural activity measures related to behavioral habit versus goal-directedness in different task environments. By analyzing single-subject variations in habit strength (outcome insensitivity), it was found that habits correlated with an increase in activity of both MSN populations. However, the activity of direct-pathway MSNs tended to precede in time the activity of indirect-pathway MSNs, suggesting a major temporal component to habit representations in striatal output pathways. Moreover, a reduction of habit strength, achieved by removing reward when a response was emitted, correlated only with weakened direct-pathway MSN activity, indicating a preferential role for this pathway in habit suppression.

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