the activity of hippocampal neurons during slow wave sleep could further contribute to this memory erasing in the hippocampus[7]. Thus, replay activity during sleep could erase the recently learned information from the highly plastic hippocampal matrix, and to a smaller extent from the visual cortical synaptic matrix, which is presumed to be less plastic. This could explain why the replay probability decays to baseline levels after 1 h of sleep[1,11]. Another possibility is that the hypothesized asymmetric synaptic changes during behavior, which make place fields asymmetric, are short lived, and decay via homeostatic mechanisms over a period of an hour following experience. Removal of recent memory traces from the hippocampus during post-experience sleep would result in the observed resetting of place cell asymmetry to baseline levels within a day[12,13].

If sequential activation were encoded in visual cortex and hippocampus during behavior, why would there be a need for consolidation during sleep? The pattern of activity in sleep may be involved in integrating previously learned information in the neocortex with newly learned information from the hippocampus, while simultaneously erasing recently learned information from the hippocampus so that hippocampal synapses are left labile to encode new experiences. The sleep replay in the visual cortex observed in pre-experience sleep suggests that the behavioral trace may not be erased by the sleep activity in the visual cortex, perhaps because of lower levels of adult neocortical plasticity or because of consolidation from hippocampus to visual cortex.

It is also possible that the site of consolidation is a region other than visual cortex. The hippocampus and visual cortex are separated by many synapses, and thus it may be more plausible to suppose that the replay activity in both areas is driven by a third site that has yet to be identified. The entorhinal cortex, which is reciprocally connected to neocortex and hippocampus, is one candidate. Measurement of up-down state activity of the multiple processing stages in the cortico-hippocampal circuit would shed some light on these issues.

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Knowing without doing

Alexander Lerchner, Giancarlo La Camera & Barry Richmond

Is it possible to know what to do without being able to act upon this knowledge? In a recent study, Atallah *et al.* show clear evidence that learning a new skill and expressing it are two separate steps that can be dissociated.

Imagine going on a vacation in a country where cars are driven on the other side of the road. To get into the driver's seat, your initial tendency will be to approach the car from the wrong side. With practice, you will progressively improve and soon approach the correct side of the car consistently. In terms of learning theory, it will take a number of attempts, or trials, before a correct stimulus-response habit is successfully established. Reinforcement learning is a theoretical framework that attempts to describe how such incremental learning happens, with the basic idea that the correct response (approaching the car from the correct side) gets reinforced through the reward (positive outcome of the approach) that follows it.

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In the above scenario, the number of successes increases gradually with practice. Experiments designed to probe learning and memory use measures of outward behavior, such as the fraction of correct responses, to make direct inferences about internal learning processes. The implicit assumption is that doing it right more often is equivalent to having learned it better. However, in a new study in this issue[1], Atallah *et al.* show that this assumption is not always correct. When a part of the striatum is selectively inactivated, internal learning of a new task can happen even when there is no improvement in the animal's behavior. Such a dissociation has been previously observed in classical conditioning[2] and saccadic adaptation[3], though not in instrumental learning (that is, learning of action strategies that increase rewards).

The striatum is the major input region to the basal ganglia, which are a collection of nuclei deep below the white matter of cerebral cortex. The basal ganglia are associated with a variety of functions, such as motor control, cognition, emotions and reinforcement learning. The theoretical framework of reinforcement learning can be implemented in different ways; one popular implementation is known as the actor-critic architecture, consisting of two interacting computational components. In this framework, the critic tries to predict future rewards given a set of possible states and actions, whereas the actor uses the information from the critic to learn and perform more rewarding action strategies[4]. Attempts to map the components of these computational approaches to brain anatomy have indicated that the ventral striatum could play the role of the critic and the dorsal striatum the role of the actor[5] (but see also refs. 6,7).

Atallah *et al.*[1] set out to reassess the roles of the ventral and dorsal striatum in a cleverly designed experiment. They trained rats on a two-alternative, forced-choice task in a Y-maze, where the rats were given the opportunity to enter one of two boxes placed side by side. By entering the box marked with odor A, the rat earned a food reward. If it entered the box marked with odor B, it got removed from that box and placed in the A box, where it was

allowed to consume the reward. The locations of the boxes were switched randomly from trial to trial. The skill of choosing box A over B increased gradually over three 20-trial training sessions until it was well established, as evidenced by good performance in a fourth session.

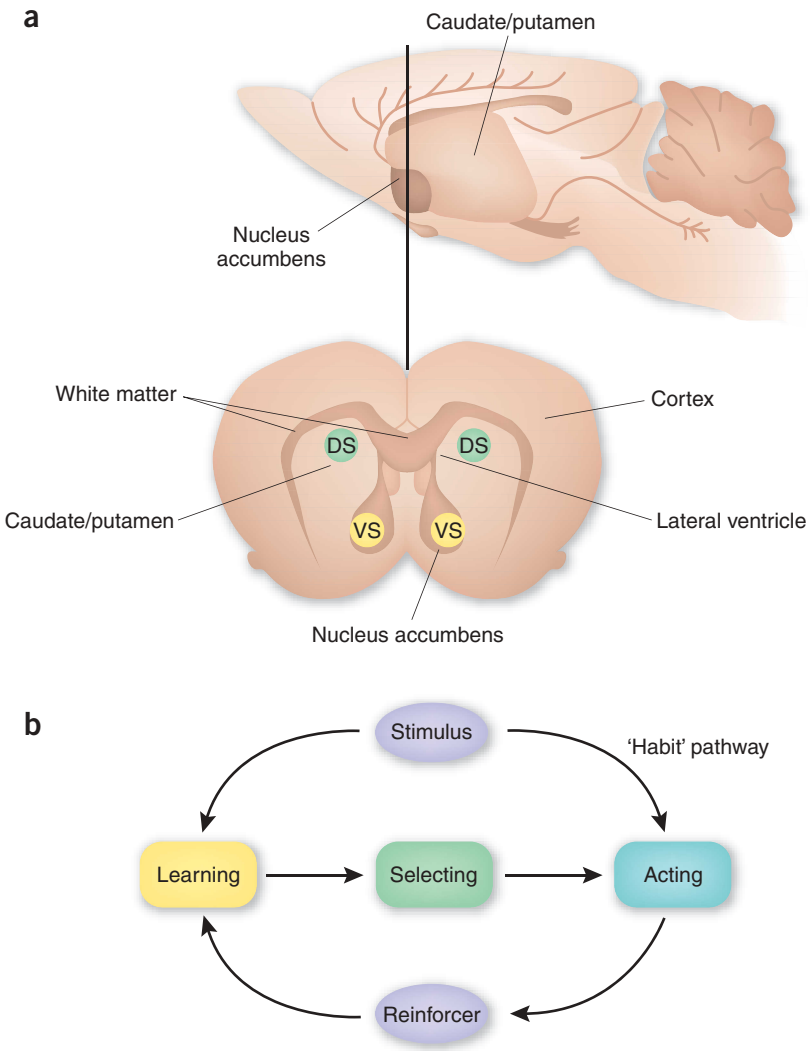
To investigate the roles of the ventral and dorsal striatum in the learning and performance of this task, the authors injected one of two drugs, muscimol and AP-5, either during the first three 'learning' sessions, or during the fourth and final 'test' session. Muscimol is a $GABA_A$ receptor agonist that temporarily inactivates the affected area, and AP-5 is an NMDA receptor antagonist that blocks a prominent mechanism of synaptic plasticity widely believed to underlie learning.

Injections of these agents into the two regions of the striatum produced strikingly different results. In the ventral striatum, both muscimol and AP-5 injections blocked learning of the task: injections during the first three sessions resulted in minimal improvements in performance, and performance remained poor in the fourth and final session even without the drug. This result implies that the ventral striatum needs to be active for learning to occur, and in particular that learning depends on NMDA receptors in the ventral striatum. Muscimol inactivation of the dorsal striatum during the first three sessions similarly blocked improvements in performance of the task during these sessions. In contrast to the effect in the ventral striatum, however, performance in the fourth session was high, comparable to that of control rats whose performance had gradually improved over the four sessions. This indicates that learning had occurred during the first three sessions, even without any visible improvement in performance. Moreover, muscimol injection into dorsal striatum after training without the drug resulted in relatively unimpaired performance, suggesting that the area is not needed to maintain a previously acquired level of performance.

To appreciate the meaning of the results, imagine the analogous effect of temporarily deactivating the dorsal striatum in our example of learning to approach the car from the correct side. As long as the dorsal striatum is inactive, you might be able to notice your mistakes and even grow frustrated with your inability to adjust to the situation. When the dorsal striatum becomes active again, your behavior will suddenly switch, and you can finally make use of your internally acquired knowledge and consistently approach the car from the correct side.

What makes this study so important is that the data show that inactivation of a specific area disconnects learning from its expression. This shows that there must be a functional chain of brain areas connecting 'learning what action to perform' and 'performing the action' that can be interrupted in the middle. What this means for the actor-critic architecture is that the actor is necessarily spread out over several brain regions, and that it is possible to interfere with one part of its function ('doing the right thing') while keeping another part intact ('learning what the right thing to do is').

A straightforward way to explain these results is with a chain of three functional modules for acquiring the task: learning-selecting-acting (**Fig. 1**). The first module learns the values of actions, the second module selects an action based on the values in the first module and, finally, the third module performs the action. In addition, the third module can carry out a standard response, a 'habit', if it is not instructed otherwise by the second module. The habit may be thought of as the action or strategy currently associated with the sensory trigger. In this hypothetical chain, the ventral striatum is part of the 'learning' module and the (affected area of the) dorsal striatum is part of the 'selecting' module, which is responsible neither for learning nor for acting per se. Temporary deactivation of



Kimberly Caesar

Figure 1 Anatomical structures and logical relationships behind 'knowing without doing'. (**a**) Rat brain anatomy. Colored ovals indicate approximate locations of injection sites in the ventral striatum (VS) and dorsal striatum (DS) in the study by Atallah *et al.*[1] (**b**) Schematic representation of the learning-selecting-acting chain. Yellow, the role of the 'learning' module is to learn correct stimulus-response associations based on information about the stimulus and the outcome of the response ('reinforcer'). The ventral striatum is part of the learning module. Inactivation of the ventral striatum or disrupting learning in the ventral striatum prevents acquisition of the task. Green, the role of the 'selecting' module is to select actions based on information from the learning module. The dorsal striatum is part of the selecting module. Inactivation of the dorsal striatum leaves learning intact but disables action selection based on learning, and leaves previously established stimulus-response pairings intact. Blue, the role of the 'acting' module is to perform actions based on information from the selecting module. Without input from the selecting module, the acting module performs a standard response ('habit'), based on a previously established stimulus-response association via a hypothetical 'habit' pathway.

the selecting module would not prevent learning but would keep the performance at the previously attained level. Reactivation of the selecting module would make the knowledge acquired by the learning immediately available to the acting module, causing a jump in performance.

The study by Atallah *et al.*[1] adds exciting new information on the role of the striatum, while raising a number of important questions. How localized was the affected area in the dorsal striatum? If the manipulations in the dorsal striatum affected the entire area, as the authors suggest, then the results call into question the role of the basal ganglia in habit formation[8] and make cortical areas more likely candidates. If, however, some lateral parts of the dorsal striatum were still functional during inactivation, then these could support habit formation, as other studies imply[9,10]. Another open question is how the ventral and dorsal striatum interact given that these two areas are not directly connected. It has been suggested that they could interact by way of the prefrontal cortex[11] or by way of the dopamine system[12]. There is likely to be a lively debate over these results, which will stimulate further exploration of the mechanisms and pathways underlying this important type of instrumental learning, and fuel development of more refined models.

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PARsing the events of myelination

Carla Taveggia & James L Salzer

A recent paper in *Science* reports that for Schwann cells to initiate myelination, the Par-3 polarity protein must interact with the neurotrophin receptor p75^{NTR} and relocate it to membrane domains of glia-axon contact.

The myelin sheath, one of the most striking of all structures in cell biology, forms when a glial cell—a Schwann cell or an oligodendrocyte—wraps a membrane around an axon (**Fig. 1**). Schwann cells are highly polarized cells, reflecting the asymmetric interactions mediated by their different membrane surfaces[1]. Thus, an inner, 'adaxonal' membrane contacts the axon and an outer, 'abaxonal' membrane contacts the basal lamina. These membranes contain distinct sets of proteins, including receptors that transduce promyelinating signals from the axon and basal lamina, respectively[2,3]. In contrast to the familiar apical-basolateral polarity of epithelial cells[4], these polarized Schwann cell surfaces acquire a radial organization owing to the spiral wrapping of the myelin membrane around the axon. Establishment of this polarized organization is thought to be crucial for the subsequent events of myelination[1], but direct evidence for this, as well as about the mechanisms responsible for establishing asymmetry, have been elusive. In a recent report[5], Chan *et al.* have taken a significant step toward both goals.

The authors demonstrate that Par-3, a component of the Par polarity complex, becomes localized to the inner glial membrane adjacent to the axon at the onset of myelination. They further show that Par-3 has a key role in promoting myelination, in part by recruiting the p75 neurotrophin receptor (p75^{NTR}) to this site after it has been activated by BDNF stimulation. These results directly implicate cell polarity as a key event in the initiation of myelination.

Par-3 is part of the Par-aPKC system, a multiprotein complex that has been remarkably well conserved during evolution[6]. It controls diverse aspects of cell polarity, including asymmetric cell division, directed cell migration and the establishment of cell polarity in epithelial and neuronal cells[6,7]. The complex contains three proteins: two scaffolding proteins containing PDZ binding domains, Par-3 and Par-6, and atypical protein kinase C (aPKC), a serine-threonine kinase that is thought to be the main effector of the complex, although its downstream signaling has not yet been elucidated[7]. Although the complex operates as a functional unit, the physical interaction of the components, particularly that of Par-3 with aPKC–Par-6, is dynamic[6]. The complex is activated by interaction with small GTPases, including Rac-1, its guanine exchange factor Tiam-1, and Cdc42, in response to extracellular cues, including cell contact and growth factors[7,8].

Par-3 accumulates at sites of Schwann cell contact with the axon before myelination, co-localizing with N-cadherin, which mediates initial axon–Schwann cell interactions[9]. When Schwann cells are cultured without axons, Par-3 remains diffusely distributed. To address the key question of whether Par-3 localization is important for initiating myelination, the authors manipulated Par-3 levels through retroviral transduction of Schwann cells co-cultured with sensory neurons. They overexpressed Par-3, resulting in a broad distribution in Schwann cells beyond just the point of axon contact; they also used short hairpin (sh) RNAs, which target mRNAs for degradation, to knock down Par-3 expression. In both instances, Schwann cells aligned properly with sensory neurites, but myelination was significantly impaired. Overexpression of Par-6 similarly inhibited myelination but not axon association. The persistent alignment of Schwann cells with axons, despite disruption of Par abundance, suggests that adhesion molecules, such as N-cadherin, independently mediate interactions with the axon. Together, these results suggest that all components of the Par complex are likely to have a crucial role in myelination.

To investigate how Par-3 might be directly involved in myelination, the authors focused on the p75^{NTR} neurotrophin receptor. Neurotrophins (reviewed in ref. 10), together with neuregulin-1 (ref. 2), are important axonal signals controlling myelination. The neurotrophins are a family of growth factors that mediate a wide array of effects on neurons and glia. They include nerve growth factor (NGF), brain-derived neurotrophic

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