

Glossary

Complement: The complement system is an essential component of the innate immune system, which is activated on recognition of microbial patterns, cellular abnormalities or modified extracellular molecules. This proteolytic cascade tags the activating structure for elimination and at the same time elicits an inflammatory response, thereby recruiting additional immune cells.

Opsonization: The process whereby deposition of molecules, such as activation products of the complement cascade, on the surface of a target marks that target for recognition and uptake by a phagocytic cell.

Golgi-Cox method: A histological method based on metallic impregnation of neurons that allows distinct visualization of cell soma, axons, dendrites and spines.

Of note, a recent study that compared complement component expression and activation in the hippocampi of patients with multiple sclerosis corroborated this notion (Michailidou *et al.*, 2015). In accordance with the findings of Jürgens and co-workers, synaptic density was decreased in demyelinated but also in myelinated hippocampi compared to control brains. Additionally, the complement components C1q and the C3 activation products localized to synapses that were within reach of microglial cellular processes, implicating active synaptic elimination of complement-tagged synapses in multiple sclerosis.

Taken together, these results indicate that synaptic loss occurs widely and independently of demyelination and axonal degeneration in the grey matter of multiple sclerosis brains. While the pathophysiology remains enigmatic, there is circumstantial evidence that continuous and diffuse activation of the classical complement cascade might be involved in this process, which could drive neuronal loss and disability progression. This

exciting finding warrants additional mechanistic investigations.

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Cerebellar damage limits reinforcement learning

This scientific commentary refers to 'Effective reinforcement learning following cerebellar damage requires a balance between exploration and motor noise', by Therrien *et al.* (doi:10.1093/brain/awv329).

An exciting challenge for research in motor learning is to disentangle the

multiple processes involved, and to tie these down to distinct neural systems. About 17 years ago, Doya proposed that the cerebellum, basal ganglia and cerebral cortex were separately responsible for supervised learning, reinforcement learning, and unsupervised learning, respectively (Doya, 1999, 2000). Supervised

learning is driven, unsurprisingly, by signals provided by a 'supervisor' and is typically equated with error-based learning: after an action, an error in performance is processed, and subsequent actions are adjusted to try to minimize the error. Reinforcement learning is driven by rewards and punishments: exploratory actions are tried

out and each action's outcome is evaluated; learning aims to maximize the value of future action choices. Unsupervised learning occurs in the face of repeated experience of the environment, and generates a mapping of its statistical regularities: it can be driven by Hebbian learning so that, for example, similar sensory events become associated with one another. In the motor domain this can equate to yet another form of learning, use-dependent learning, where there is a bias to produce actions more similar to previous ones. For many years, these learning processes were thought of as functionally and anatomically independent. However, huge efforts are now being made to understand how these various processes interact. In this issue of *Brain*, Therrien, Wolpert and Bastian have added to these efforts by testing and modelling how patients with cerebellar ataxia differ from healthy controls in performing error- and reinforcement-learning tasks (Therrien *et al.*, 2015). Using a mechanistic model, they show that optimal learning with reinforcement feedback requires subjects to balance the variability in their exploration of the task with their uncontrollable motor variability (noise). While patients with ataxia showed normal levels of exploration variability and were able to learn through reinforcement feedback, their high levels of motor noise limited the extent of this learning.

In more detail, participants performed a reaching task that required them to adapt to a visuomotor displacement, such that visual or reward feedback on the reaching movement was displaced from the hand's true position. In two related experiments, healthy young adults, or patients with cerebellar ataxia and age-matched controls either received error feedback at the end of each movement ('error-based feedback' - see Glossary); or they received a reward signal indicating good performance if they landed close to the target (termed 'open-loop', a condition only tested on the younger group). In a third condition, they were rewarded if they performed

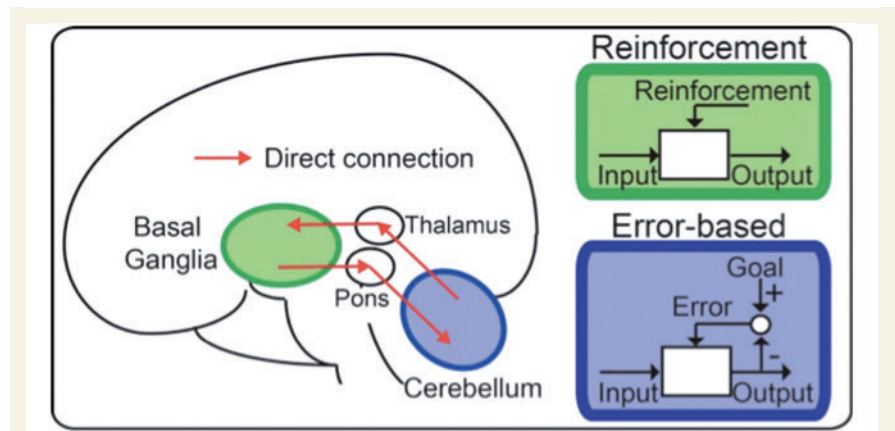


Figure 1 The basal ganglia (green) and cerebellum (blue) have historically been associated with independent roles in reinforcement- and error-based learning, respectively. However, the work of Therrien *et al.* (2015) suggests that cerebellar damage limits reinforcement learning. Could the direct connections between the cerebellum and basal ganglia reported by Bostan and Strick (2010) provide an anatomical explanation for this result? Figure adapted from Doya (2000).

better than the average of the last 10 movements ('closed-loop' reward feedback, as the feedback reflected prior performance). Participants with ataxia and healthy controls showed learning under both error-based and reward feedback conditions. But while reward feedback led to near perfect retention of the learned behaviour during a post-learning test phase, error feedback learning was not retained and decayed in the test phase. These differences between error and reward feedback are in line with previous findings (Shmuelof *et al.*, 2012). The normal learning with error feedback in the ataxia group is, at face value, inconsistent with Doya's theory. However, the complete lack of retention of this adaptive response led Therrien *et al.* to suggest that the apparent learning may in fact have been a result of non-cerebellar online correction processes (Tseng *et al.*, 2007).

The key finding of this paper, however, is that patients with ataxia did show substantial learning and retention under reinforcement (reward) conditions. With support from a mechanistic model of the learning process, Therrien *et al.* suggest that reinforcement learning depends on a balance between exploration variability and motor noise. While the patients with ataxia showed similar

levels of exploration variability to age-matched controls, their increased level of motor noise meant they learnt less through reinforcement.

This paper is interesting, and its conclusions are in line with other work suggesting that one consequence of cerebellar damage is degradation of the brain's ability to estimate the state of the motor system, i.e. loss of predictive knowledge regarding the outcome of motor commands that would normally be used to update a representation of the motor system's state (Miall *et al.*, 2007; Tseng *et al.*, 2007). However, the modelling work did seem to predict a relationship between exploration noise and motor noise that was only an approximate match to the group results. In fact, none of the participants fell within the 'sweet spot' that would produce optimal reinforcement learning. This suggests that other unknown factors may limit exploration noise, or (as with the ataxia group) covertly increase motor noise.

There is also a need for illumination of the neural mechanism that underpins the relationship between cerebellar-dependent motor noise and reinforcement learning. Recent work has provided anatomical evidence for direct bidirectional links between the cerebellum and the basal ganglia (Fig. 1) (Bostan and Strick, 2010). It is

Glossary

Error correction: Feedback of errors can be used to directly improve performance. In supervised or error-based learning the error vector gives both the magnitude and the direction of the error; and the learning system then shifts subsequent performance in the opposite direction, with the intention to reduce the error on subsequent trials.

Hebbian learning: In 1949 Donald Hebb proposed that if a neuron is causally involved in activating one of its neighbours, then some metabolic or growth process will make it more effective in activating that neighbouring cell. Although this has been reduced to the statement that ‘cells that fire together, wire together’, the causal chain from one cell to the next is important.

Open and closed loops: If the outputs of a dynamical system affect its inputs, the system can be called a ‘closed loop’, otherwise it is an ‘open loop’.

Reinforcement learning: The process by which an animal or artificial system can learn to optimize its behaviour using rewards and/or punishments. The value of actions reinforces those behaviours that maximize reward or minimize punishment. However, the feedback reward or punishment does not dictate how to improve performance.

State estimation: Dynamical systems transform inputs into outputs, but the outputs do not necessarily fully reflect the state of the system, or do not provide feedback about the state variables that must be controlled. An estimate of the system’s state, updated based on its last known state and on inputs, can provide valuable ‘model based’ control.

possible that the cerebellum could predict the sensory state of an action and feed it forward to the basal ganglia, which in turn could estimate the value of the new state through reinforcement processes. Without the cerebellum, predicted action outcomes may be poorly represented, or even unknown, and so linking them to reward values would be more difficult. This increased (motor) noise in predicting movement outcomes could lead to greater uncertainty within the basal ganglia with respect to reward-based predictions and thus a reduced ability to adapt behaviour. However, another thing to mention from the Therrien *et al.* study is that although their patients with ataxia showed almost double the motor noise of age-matched controls, the differences in reinforcement learning were small. This suggests that the cerebellum may not have a dominant influence on basal ganglia-dependent reinforcement learning. What the reverse connections from basal ganglia to cerebellum might convey is less clear. One possibility, driven by recent evidence that reward and punishment differentially influence motor learning (Galea *et al.*, 2015), is that the reinforcement signals might modulate the cerebellum’s sensitivity to incoming error signals. In other words, the basal ganglia might prime the cerebellum to weight its predictions (or to update its forward models), based on predicted reward or punishment. These bilateral connections may thus ensure that the basal

ganglia and cerebellum work together, so that reward predictions and state estimates are both tuned to reflect confidence levels in each prediction.

We suggest that a fruitful way to test these interactions would be to manipulate exploratory and motor noise at several different levels in the system and examine their effects on the tasks and model described by Therrien *et al.* One could inject motor noise peripherally, by electrical stimulation of the muscles during action, or centrally, for example by transcranial random current stimulation over the motor or premotor cortex. One might inject variability into the state estimation process by adding noise to the feedback after each action, either visual or proprioceptive, or by testing participants with sensory loss. And one might mimic the effects of poor state estimation in the cerebellum by transcranial electrical or magnetic stimulation (Miall *et al.*, 2007). The goal would be to understand in which scenarios motor noise has a detrimental effect on reinforcement learning. If increased motor noise must originate from the cerebellum, this may indicate that the direct connection from the cerebellum to the basal ganglia plays a specific role in motor-based reinforcement learning.

Can one also manipulate exploration noise? Until recently, there was no direct evidence that reward-based exploration during a motor task was dopamine- or basal ganglia-

dependent, despite much speculation (Izawa and Shadmehr, 2011). However, it has now been shown that patients with Parkinson’s disease, in whom dopamine levels are reduced, exhibit impaired exploration variability during a motor reinforcement task (Pekny *et al.*, 2015). Therefore, a strong prediction is that patients with Parkinson’s disease would show impaired exploration variability but normal motor noise within the current task. This could also be tested in a more sensitive manner with drug studies that either block D1/D2 dopamine receptors (haloperidol) or specifically block D2 receptors (sulpiride). Finally, there might be exciting opportunities through the use of deep brain stimulation to centrally block reinforcement learning or to add exploration noise. One idea would be to compare patients with deep brain stimulators implanted either in the basal ganglia (Parkinson’s disease) or thalamus (for dystonia). As the thalamus provides a link between the cerebellum and basal ganglia, one might predict that basal ganglia deep brain stimulation would manipulate reinforcement learning through changes in exploration variability, whereas thalamic deep brain stimulation may alter reinforcement learning through changes in motor noise.

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What lies beneath grey matter atrophy in multiple sclerosis?

This scientific commentary refers to ‘Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant’, by Steenwijk *et al.* (doi:10.1093/brain/awv337).

Over the last 20 years, there have been remarkable advances in our understanding of pathogenic mechanisms in multiple sclerosis, particularly those responsible for relapses and remissions. Over the same period a series of increasingly effective treatments have become available that suppress relapses. However, there has been a conspicuous lack of success in treating progressive multiple sclerosis, which most people with the condition eventually develop, and which is associated with the greatest disability. This has led to a reappraisal of pathological processes underlying progressive multiple sclerosis, and the recognition that pathology is more extensive and complicated than formerly thought. In this issue of *Brain*, Steenwijk and co-workers look specifically at cortical atrophy in patients with long-standing multiple sclerosis, and reveal that such atrophy occurs in largely non-

random patterns (Steenwijk *et al.*, 2016).

Previously, a commonly held view of multiple sclerosis was of a multifocal and multi-phasic immune-mediated white matter inflammatory demyelinating disorder, and indeed the suppression of such a process has underpinned the major progress in disease-modifying treatment to date. However, it is now abundantly clear that in progressive multiple sclerosis, demyelinating lesions may be as extensive in grey matter as they are in white matter, and that there is substantial and widespread neuro-axonal loss, not only in white matter lesions but also in normal-appearing white matter, and in both the cortical and deep grey matter. It is also clear that grey matter pathology is present in early relapsing-remitting multiple sclerosis and increases with time. Neuro-axonal loss is now thought to be responsible for a major proportion of irreversible progressive disability in multiple sclerosis, but its causes are poorly understood, particularly when it occurs in the grey matter.

Brain atrophy in multiple sclerosis, as measured during life by MRI, is likely to reflect neuro-axonal loss (although other factors that can affect brain tissue volumes should be borne in mind, especially when assessing short-term changes). Loss of brain tissue does not occur uniformly, and in progressive multiple sclerosis it is most apparent in brain grey matter, affecting some cortical and deep grey matter regions more than others (Bendfeldt *et al.*, 2011). *In vivo* MRI-clinical correlation studies have identified significant associations of grey matter atrophy with cognitive impairment, physical disability and progressive multiple sclerosis that are independent of associations with other imaging abnormalities, such as white matter lesion load. All-in-all, there are compelling reasons to try to better understand the mechanisms of grey matter atrophy and the neurodegeneration that it reflects.

In this issue of *Brain*, Steenwijk and colleagues report on their work looking at patterns of cortical grey matter atrophy in multiple sclerosis (Steenwijk *et al.*, 2016). They used