

Glossary

Immune dysbalance: A state of disturbed 'immune homeostasis' characterized by increased (or decreased) pro-inflammatory activity, and/or decreased (or increased) anti-inflammatory activity.

MAIT cells: Mucosal-associated invariant T (MAIT) cells express a particular T cell receptor alpha chain (TCR V alpha 7.2). Some MAIT cells recognize bacterial metabolites. MAIT cells were first identified in the gut lamina propria (Treiner and Liblau, 2015). They are found in the blood and in multiple sclerosis brain lesions.

Multiparametric flow cytometry: A method for defining and enumerating lymphocyte populations. Cells are tagged by staining with multiple monoclonal antibodies directed against different cellular differentiation or activation molecules. Inside the flow cytometer, the mixture of labelled cells is funnelled through a laser beam, and the fluorescence signals of individual cells are recorded by sensitive photomultiplier tubes. In this way, flow cytometry provides quantitative information about the composition of the cell sample.

extreme settings such as the ones discussed here.

What is also very clear is that the new Canadian study opens up many more questions than it provides final answers. Obviously, one of the most important future challenges is to determine the nature of the auto-sensitizing antigens (Hohlfeld *et al.*, 2016). Are these myelin autoantigens as might be predicted by many animal models? Are they viral antigens that might stimulate cross-reactive autoimmune responses by molecular mimicry? Or might they belong to a novel category of autoantigens, e.g. intracellular proteins released during cellular damage or decay (Brändle *et al.*, 2016; Winger and Zamvil, 2016; Planas *et al.*, 2018)? All these possibilities are completely open at the moment, suggesting an important and challenging direction for future research.

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doi:10.1093/brain/awz008

Competing interests

The author reports no competing interests.

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How to help cerebellar patients make the most of their remaining learning capacities

This scientific commentary refers to 'Can patients with cerebellar disease switch learning mechanisms to reduce their adaptation deficits?', by Wong *et al.* (doi:10.1093/brain/awy334).

Cerebellar disease results in well known motor deficits. Balance problems and poor limb coordination limit activities of daily living, sharply reducing quality of life. Although

certain genetic cerebellar disorders may soon benefit from genetic treatments, as yet there is no causal treatment for degenerative cerebellar disease. Furthermore, no currently

available anti-ataxic drug has had confirmed effects in cerebellar ataxia. There is some hope that non-invasive brain stimulation might be beneficial. For instance, benefits have been claimed for cerebellar transcranial direct current stimulation, although the reproducibility and reliability of these benefits still needs testing. Lacking any treatment that addresses the underlying causes, the mainstay of treatment is rehabilitative therapy focused on physical therapy.

But despite the widespread use of physical therapy in cerebellar disease, surprisingly little is known about what constitutes the best approach. Indeed, the efficacy of physical therapy in cerebellar disease has been challenged on theoretical grounds. Certainly, there is some experimental evidence that physical therapy improves motor function of patients with cerebellar degeneration (Ilg *et al.*, 2009). Intensive motor training also improves motor performance in mouse models of cerebellar degeneration (e.g. Fucà *et al.*, 2017). Nevertheless, the way physiotherapy is performed is based largely on the empirical knowledge and individual experience of the physical therapist. In order to optimize training programmes, therapists need a mechanistic understanding of how training affects motor control and what drives the beneficial

effects. Knowledge about the underlying functional and structural mechanisms, however, is largely lacking. For instance, training benefits may not be the result of improvement in the primary cerebellar deficit and may instead occur through compensatory mechanisms. Alternatively, the effects may be a combination of improving cerebellar function and strengthening compensatory mechanisms. Motor control theory with its concepts of different types of motor learning offers a promising framework with which to address these questions. In this issue of *Brain*, Wong and co-workers take an important step in that direction (Wong *et al.*, 2019).

Specific learning mechanisms appear to map onto specific brain areas (Mazzoni and Krakauer, 2006; Taylor *et al.*, 2010). In a seminal paper, Doya (1999) proposed that the cerebellum is specialized for supervised learning, the basal ganglia for reinforcement learning and the cerebral cortex for unsupervised learning. In addition, a differentiation between implicit and explicit components of the various learning processes has been proposed. A key challenge now is to resolve the interactions of the explicit and implicit systems with the different learning mechanisms, and map these to brain areas. The use of strategies is often

equated with explicit learning (Taylor *et al.*, 2014). In a clever reach adaptation experiment, Mazzoni and Krakauer (2006) showed that implicit learning and explicit learning strategies operate independently. Because the cerebellum is associated with implicit error-based learning, this would suggest that some form of explicit learning is preserved in patients with cerebellar disease. And indeed, using the same paradigm as in Mazzoni and Krakauer, Taylor *et al.* (2010) showed that the use of explicit strategies was preserved in cerebellar patients whereas implicit learning was impaired. By contrast, a more recent study by the same group indicated that the use of strategies was impaired (Butcher *et al.*, 2017). In a variant of the visuomotor rotation task, participants had to verbally report the location at which they were aiming before performing each movement. Spinocerebellar patients were impaired in both implicit learning and aiming.

Wong *et al.* (2019) have now taken this a step further. They asked why cerebellar patients were able to use strategic information in the 2010 study but not the 2017 study. They challenge the hypothesis that patients do not develop an appropriate strategy because of cognitive problems. Instead, they suggest that errors in

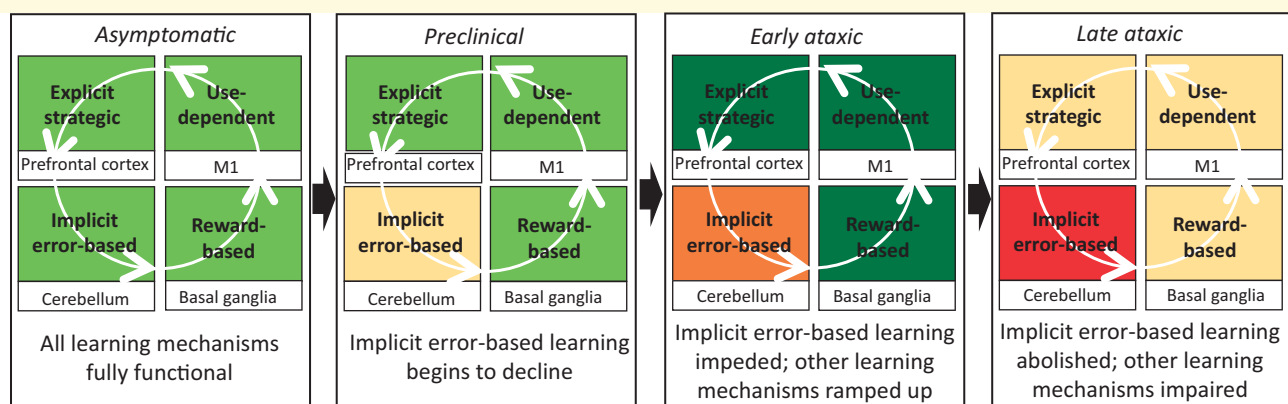


Figure 1 Proposed model of disease stage-dependent interactions between different learning mechanisms in degenerative cerebellar disease. Disease stages of spinocerebellar ataxias. Asymptomatic: proven SCA mutation, no symptoms; Preclinical: proven SCA mutation and unspecific neurological symptoms (e.g. muscle cramps) and/or mild coordination deficits (SARA < 3) and/or abnormal paraclinical test results; Early and late ataxic: proven SCA mutation and manifest ataxia (SARA ≥ 3) (Maas *et al.*, 2015). SARA = Scale for the Assessment and Rating of Ataxia (Schmitz-Hübsch *et al.*, 2006).

Glossary

Error-based learning: A form of supervised learning. Involves the updating of forward models in response to changes in the environment by means of the difference between the predicted and actual sensory outcome (i.e. the sensory prediction error).

Reward (and failure)-based or reinforcement learning: Information about success or failure of a movement is used to guide learning. This error signal does not carry information about the direction of change that will improve performance.

Strategic learning: Learning based on a cognitive plan. Often used synonymously with explicit learning.

Use-dependent learning: A form of unsupervised learning. Does not depend on error signals, but on mere repetition of the movement.

sensory prediction drive adaptation by default, even when cerebellar pathology disrupts this learning. In this view, cerebellar patients in the 2017 study seemingly show impaired strategic learning because their intact strategic learning is being suppressed by impaired error-based learning. Wong *et al.* tested this hypothesis by comparing adaptation when subjects saw a rotated cursor to adaptation when subjects could see their own arm in addition to the rotated cursor. The logic was that seeing the arm would eliminate the illusion that the rotated cursor reflects a change in arm position. Since the position of the arm is no longer perceived as having been perturbed, there is no sensory prediction error. This should suppress the error-driven learning system and release the strategic learning system. As predicted, cerebellar patients learned as well as age-matched controls in this condition, supporting the original hypothesis of Wang *et al.*: when sensory prediction errors are absent, cerebellar patients are able to find and apply strategies. This is good news. Even better, the strategic learning was retained for almost a year. On the other hand, the strategy did not generalize in either patients or age-matched controls. Since both groups comprised middle-aged and elderly individuals, Wong *et al.* propose the existence of an age effect that interferes with strategic generalization. This may be part of the larger phenomenon of cognitive decline in the elderly. Thus, the results have important clinical implications both in releasing strategic learning and in understanding its limitations in specific patient populations.

While Wong *et al.* are the first to advance the theory that eliminating sensory prediction error may release suppressed latent learning mechanisms in cerebellar patients, there are corroborating findings in the literature. For instance, Therrien *et al.* (2016) reported that cerebellar patients learned in a reach adaptation paradigm when they did not receive visual feedback about the movement. Wong *et al.* suggest ways of using this phenomenon to drive clinical recovery, such as distracting patients from the movement itself and refocusing them on its outcome. This could allow patients to acquire more successful movement strategies without interference from the error-driven system.

However, there is still much to clarify before we know whether this approach has any real clinical merit. A more thorough understanding is required of the manipulations that do and do not eliminate sensory prediction (or at least, do and do not induce the effect seen by Wong *et al.*), along with replication in a larger sample with full documentation of cerebellar and extra-cerebellar pathology. These issues will need to be addressed in the experiments that follow-up on the current work.

Another key point is that the approach in this paper addresses rehabilitation and compensation, but it does not address the underlying motor deficit. There is some evidence from the animal literature that in initial stages of cerebellar degeneration, cerebellar-dependent learning systems continue to function (Fryer *et al.*, 2011; Fucà *et al.*, 2017). There would be value in developing a training approach complementary

to that of Wong *et al.* that specifically enhances the residual implicit error-based learning abilities of early phase cerebellar patients. One idea is to apply a perturbation that, based on modelling data, matches the expectation of an upcoming perturbation in individual patients in order to increase consistency. Error-based learning may be enhanced when the sensory prediction signal is more stable.

Different learning mechanisms can interact in complex ways in disease and a well thought-out clinical approach must keep these interactions in mind. We propose a model of these interactions that sees progressive deficits in the error learning system being accompanied by a dynamic response from other learning systems, including implicit reward-based and use-dependent systems as well as an explicit strategic system (Fig. 1). There is also initial evidence that other systems increase their sensitivity to compensate for increasing cerebellar dysfunction (Burciu *et al.*, 2013). However, we also believe that there is a threshold of pathology in the error-driven system for which the other systems cannot effectively compensate. In this situation, performance of all systems may decline. There is ample evidence to support complex interactions between the different learning systems. Learning in the Therrien *et al.* (2016) study was less successful in cerebellar patients than in controls. They concluded that reinforcement learning was present but degraded because of increased levels of movement variability. The link between error-driven learning and reward learning may be mediated through behaviour, as suggested by Therrien

et al., but it may also be direct. The cerebellum and the basal ganglia are directly connected anatomically (Bostan *et al.*, 2010). Furthermore, Wagner *et al.* (2017) showed that granule cells encode not only movement but also the expectation of reward. Thus, cerebellar and basal ganglia dependent learning may interact. A fuller understanding of these complexities may provide a fuller guide for therapy. When is it appropriate to use therapy that seeks to restore underlying function and when does it make more sense to drive compensatory mechanisms? When has the progressive pathology degraded compensatory learning mechanisms to the point where alternative approaches need to be used to maintain quality of life?

In summary, the Wong *et al.* (2019) study is an important step forward in determining the contribution made by the cerebellum to motor learning, but we are far from having attained a comprehensive understanding. The key advance is in isolating different forms of learning and showing how they might be independently manipulated. There is much work still to be done. Future work should aim to isolate the different mechanisms of motor learning further, and to understand how they are separately affected in cerebellar ataxia. We need to understand which aspects of motor learning are preserved in cerebellar patients, at which disease stage and depending on the location of the lesion, and also how the spared mechanisms may be leveraged to help drive effective learning in patients with cerebellar ataxia. Finally, whatever understanding we obtain must also be extended to the role of the cerebellum in the cognitive domain.

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doi:10.1093/brain/awz020

Funding

Funded by the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) DFG Ti 239/16-1 awarded to D.T. and O.D.

Competing interests

The authors report no competing interests.

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