



Published in final edited form as:

Nat Rev Neurosci. 2018 June ; 19(6): 338–350. doi:10.1038/s41583-018-0002-7.

The basal ganglia and the cerebellum: nodes in an integrated network

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Abstract

The basal ganglia and the cerebellum are considered to be distinct subcortical systems that perform unique functional operations. The outputs of the basal ganglia and the cerebellum influence many of the same cortical areas but do so by projecting to distinct thalamic nuclei. As a consequence, the two subcortical systems were thought to be independent and to communicate only at the level of the cerebral cortex. Here, we review recent data showing that the basal ganglia and the cerebellum are interconnected at the subcortical level. The subthalamic nucleus in the basal ganglia is the source of a dense disynaptic projection to the cerebellar cortex. Similarly, the dentate nucleus in the cerebellum is the source of a dense disynaptic projection to the striatum. These observations lead to a new functional perspective that the basal ganglia, the cerebellum and the cerebral cortex form an integrated network. This network is topographically organized so that the motor, cognitive and affective territories of each node in the network are interconnected. This perspective explains how synaptic modifications or abnormal activity at one node can have network-wide effects. A future challenge is to define how the unique learning mechanisms at each network node interact to improve performance.

The essential functional architectures of basal ganglia and cerebellar circuits with the cerebral cortex have several elements in common. The input stages of these circuits are targets of extensive projections from widespread regions of the cerebral cortex^{1,2}, and the output stages send efferents to regions of the thalamus that innervate multiple motor and non-motor areas of the cerebral cortex^{3–5}. An important element of cortico-basal ganglia and cortico-cerebellar circuits is their ‘closed-loop’ architecture: the regions of the cerebral cortex that are the major sources of input to a circuit are also major targets of output from the circuit^{6,7}. Although the thalamic targets of basal ganglia output are different from those of cerebellar output⁸, the two systems influence many of the same areas of the cerebral

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Author contributions

Both authors researched data for the article, made a substantial contribution to the discussion of content and contributed to the writing, reviewing and editing of the manuscript before submission.

Competing interests

The authors declare no competing interests.

cortex (FIG. 1). This structural arrangement has led to proposals that these subcortical circuits with the cerebral cortex have independent but complementary functions⁹.

Interactions between basal ganglia and cerebellar circuits were thought to occur mainly at the level of the cerebral cortex. Over the past decade, results from neuroanatomical studies in nonhuman primates have inspired a dramatic shift in this perspective. These results have provided evidence that the basal ganglia and the cerebellum are not independent subcortical systems but, instead, form a densely interconnected network¹⁰. Thus, changes at one node can percolate throughout the entire network to influence operations at other nodes. This integrated network perspective provides a new way of conceptualizing the functional organization of basal ganglia and cerebellar circuits with the cerebral cortex.

In this Review, we first present the evidence from studies in non-human primates that output from motor and non-motor regions of the cerebellum can influence the input stage of basal ganglia processing through a disynaptic subcortical pathway¹¹. Second, we present the evidence that output from motor and non-motor regions of a nucleus in the basal ganglia, the subthalamic nucleus (STN), can influence the input stage of cerebellar processing through a disynaptic subcortical pathway¹². For each of these connections, we discuss the presence of corresponding pathways in rodents. Last, we highlight evidence, largely from human neuroimaging studies, that these pathways may mediate meaningful interactions between cortico-basal ganglia and cortico-cerebellar circuits in health and disease. These observations provide support for the concept that the basal ganglia, the cerebellum and the cerebral cortex are nodes in an interconnected network that operates over multiple functional domains.

Anatomical evidence

Cerebellar output to the basal ganglia

It is now clear that neurons in the cerebellar output nuclei, especially in the dentate nucleus, are the origin of a disynaptic pathway to an input stage of basal ganglia processing, the striatum (FIG. 2a). Specifically, rabies virus injections into the sensorimotor territory of the putamen of macaque monkeys labelled substantial numbers of neurons in the cerebellar nuclei¹¹. In these experiments, rabies virus underwent retrograde transport to first-order neurons that project to the striatum (for example, neurons in the cerebral cortex and thalamus) and then retrograde transneuronal transport to second-order neurons that innervate the first-order neurons. Second-order neurons in the cerebellum were labelled primarily in the dentate nucleus. A few second-order neurons were labelled in the interposed and fastigial nuclei, suggesting that these nuclei are an additional source of cerebellar influence over basal ganglia function.

At survival times that enabled transneuronal transport of rabies virus to third-order neurons, injections into the external segment of the globus pallidus (GPe) led to the labelling of large numbers of neurons in the dentate nucleus¹¹. Different regions of the dentate contained labelled neurons after injections into spatially separate regions of GPe. This finding suggests that the projection from the cerebellum to the basal ganglia is topographically organized. Furthermore, labelled neurons were located in both the motor and non-motor domains of the

dentate nucleus⁵. Thus, both motor and non-motor outputs from the cerebellum may affect the motor and non-motor functions of the basal ganglia.

The basal ganglia include at least two internal routes of information processing: the ‘direct’ and ‘indirect’ path-ways (reviewed in REF.¹³). The direct pathway refers to the monosynaptic projection from specific medium spiny neurons (MSNs) in the striatum, which express substance P and dopamine D1 receptors, to neurons in the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). The indirect pathway refers to the projection from a different set of MSNs in the striatum, which express enkephalin and dopamine D2 receptors, to neurons in the GPe. Neurons in the GPe then project to the GPi and SNpr monosynaptically, as well as disynaptically via the STN. As noted above, at survival times long enough to allow transport across three synapses, rabies virus injections into the GPe resulted in transneuronal transport to the cerebellar nuclei of non-human primates¹¹. Thus, cerebellar output targets MSNs in the indirect pathway. By contrast, at the same survival time, rabies virus injections into the GPi did not lead to substantial transneuronal labelling of neurons in the cerebellar nuclei¹¹. Thus, cerebellar output may not target MSNs in the direct pathway in non-human primates. This negative result needs further exploration, but it suggests that cerebellar output preferentially influences the indirect pathway through the basal ganglia.

Studies in rodents have also provided support for the notion that cerebellar output may be biased towards the indirect pathway. The presence of the disynaptic projection from the cerebellar nuclei to the striatum in rodents was first confirmed in a study that used a combination of double labelling with conventional tracers and electron microscopy¹⁴. This study demonstrated that the circuit from the cerebellar nuclei to the striatum is mediated by several thalamic nuclei, in particular the intralaminar nuclei¹⁴. A recent study in awake, freely moving mice explored the physiology of the disynaptic pathway from the cerebellar nuclei to the striatum via the central lateral nucleus¹⁵. In this study, cerebellar stimulation elicited short-latency (9 ms) changes in the activity of about half of the examined striatal cells and could modulate cortico–striatal plasticity. Specifically, high-frequency stimulation of the motor cortex induced depression of the cortico–striatal response; however, concurrent stimulation of the motor cortex and the cerebellar nuclei potentiated the cortico–striatal response¹⁵. This study did not specifically explore whether stimulation of the cerebellar nuclei had differential effects on direct-pathway and indirect-pathway MSNs. However, stimulation of the cerebellar nuclei altered activity of striatal neurons that also received cortico–striatal inputs from the motor cortex. In both rodents and non-human primates, there is evidence that the motor cortex primarily targets indirect-pathway MSNs^{16,17}. Thus, cerebellar output in both rodents and non-human primates may preferentially target the indirect pathway through the basal ganglia and influence the plasticity of the cortico–striatal synapse.

As mentioned above, the cerebellar influence over the basal ganglia is primarily mediated through the intralaminar thalamic nuclei^{11,14,15}. In non-human primates, the intralaminar nuclei send topographically organized projections to the entire striatum^{18–20}. Thus, the potential exists for cerebellar output to influence all the functional territories of the striatum.

Basal ganglia output to the cerebellum

The presence of substantial outputs from the cerebellum to the basal ganglia raised the question of whether a reciprocal pathway from the basal ganglia to the cerebellum exists. Early studies provided suggestive evidence for such a connection on the basis of the observation that electrical stimulation in basal ganglia nuclei evoked activity in the cerebellum (reviewed in REF.²¹). However, the origin and efficacy of any basal ganglia outputs to the cerebellum were unclear. To address this issue, we injected rabies virus into different regions of the cerebellar cortex in monkeys. We set the survival time to allow for retro-grade transport of rabies virus to first-order neurons that project to the injection sites in the cerebellar cortex (for example, neurons in the pontine nuclei) and then retrograde transneuronal transport to second-order neurons that innervate the first-order neurons¹². Using this approach, we showed that neurons in the STN are the origin of a disynaptic pathway to the cerebellar cortex (FIG. 2b). Rabies virus injections into a motor region (lobule HVIIB) and into a non-motor region (crus II) of the lateral cerebellar cortex labelled substantial numbers of second-order neurons in motor and non-motor (associative) regions of STN, respectively¹². These findings indicate that the disynaptic pathway from the STN to the cerebellar cortex in non-human primates is topographically organized and influences both motor and non-motor aspects of cerebellar function.

The STN is the only excitatory nucleus in the basal ganglia and has been considered to be a driver of basal ganglia output²². Tracing studies in non-human primates have provided evidence that the STN also targets regions outside the basal ganglia, including the pontine nuclei and the pedunculopontine tegmental nucleus (PPTg)^{23,24}. As the pontine nuclei are the main source of projections to the cerebellar cortex²⁵, we proposed that these nuclei mediate the STN projection to the cerebellar cortex¹² (BOX 1).

A recent study using the transneuronal transport of rabies virus in rats confirmed the presence of a disynaptic projection from the STN to the cerebellar cortex²⁶. However, the authors concluded that the disynaptic pathway from the STN to the cerebellum in this species is largely limited to a portion of the cerebellar vermis. In fact, unlike the results in non-human primates, injections into the lateral cerebellar cortex of rats did not label substantial numbers of second-order neurons in the STN. The authors also noted that they did not observe a clear topographical organization of STN inputs to different sites within the cerebellar cortex. These findings suggest that, although a disynaptic pathway from the STN to the cerebellar cortex exists in rats, this pathway is less prominent than it is in non-human primates.

Although the extent of the disynaptic projection from the STN to the cerebellar cortex in rats remains to be determined, there is evidence for the physiological relevance of this connection in this species. Specifically, two studies examined the effects of STN deep brain stimulation (DBS) on cerebellar activity in rats^{27,28}. One study observed an increase in cFOS expression in the cerebellar nuclei following STN-DBS²⁷. This finding is consistent with the notion that DBS reduces STN activity (reviewed in REF.²⁹): reduced STN activity may lead to a reduction in the activity of cerebellar Purkinje cells and, as a consequence, disinhibition of cerebellar nuclei neurons and increased cFOS expression. This perspective was confirmed in another study that used STN-DBS in rats that had been rendered hemi-

parkinsonian by unilateral injection of 6-hydroxydopamine into the median fore-brain bundle²⁸. In these animals, STN-DBS decreased the activity of STN neurons (by 55%) and Purkinje cells (by 28%) and increased the activity of cerebellar nuclei neurons (by 45%). Additional studies are needed to test whether the effects of STN-DBS on cerebellar activity are mediated in whole, or in part, by the disynaptic pathway from the STN to the cerebellar cortex.

Evidence from disease states

The evidence we have just reviewed provides a framework for a new perspective about interactions between basal ganglia and cerebellar circuits. Specifically, basal ganglia and cerebellar circuits are densely interconnected and form an integrated network. A major prediction of this perspective is that in disease states, abnormalities at one node in the network could percolate throughout the entire system and alter activity at other nodes in the network. Such changes in activity could be compensatory or could exacerbate dysfunction. Thus, symptoms of a ‘basal ganglia disorder’ may be the consequence of abnormal activity in cerebellar circuits that are remote from the initial site of the disorder. Likewise, symptoms of a ‘cerebellar disorder’ may be the consequence of abnormal activity in basal ganglia circuits. In the following sections, we present some of the critical evidence supporting this perspective for two disorders generally considered to originate in the basal ganglia — namely, Parkinson disease (PD) and dystonia. This subject has been comprehensively reviewed in several recent publications (see REFS^{30–34}); thus, we summarize only the major findings here. In addition, we present similar supporting evidence from observations in other disorders, including Tourette syndrome (TS), obsessive–compulsive disorder (OCD) and Huntington disease (HD).

Parkinson disease

PD provides a prime example of how abnormal activity in basal ganglia circuits may propagate to cerebellar circuits and cause dysfunction. From studies of individuals with PD and animal models of the disease, it is well known that the initial relevant insult is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resultant depletion of dopamine from the sensorimotor territory of the striatum leads to changes in basal ganglia activity and the characteristic motor deficits of PD (reviewed in REF³⁵). Numerous findings suggest that the changes in basal ganglia activity are accompanied by striking changes in cerebellar activity. For example, an analysis of ¹⁸F-fluorodeoxyglucose (FDG) using positron emission tomography (PET) indicated that metabolic brain activity in individuals with PD, relative to age-matched controls, is characterized by co-varying increases in the basal ganglia (putamen-GP) and the cerebellar cortex³⁶ (FIG. 3a). The increased metabolic activity in the cerebellum may reflect a pathological drive from the STN, although other pathways may also contribute to the observed changes in the cerebellum (see also REF³⁰). In essence, the disynaptic pathway from the STN to the cerebellar cortex may enable the abnormally high STN activity, which is observed in individuals with PD and in animal models of the disorder^{37,38}, to drive the hyperactivity in the cerebellar cortex^{39–47}. This mechanism is further supported by the

finding that STN-DBS — which disrupts abnormal output from this nucleus — reduces cerebellar hyperactivity and improves motor function in individuals with PD^{48–50}.

Some of the changes in cerebellar activity in individuals with PD are thought to reflect a compensatory mechanism whereas others have been associated with dysfunction^{51,52}. In fact, resting tremor, one of the cardinal symptoms of PD, is optimally treated with surgical interventions (lesions or DBS) in the thalamic region that receives inputs from the cerebellum (that is, the ventral intermediate nucleus (VIM) of the thalamus), whereas interventions in the thalamic region that receives input from the basal ganglia are not as effective^{53–55}. This result suggests that the cerebellum is a key source of the abnormal signals that contribute to the generation of resting tremor in PD. The beneficial effects of surgical STN interventions on resting tremor⁵⁶ may be mediated, in part, through the connection between the STN and the cerebellum³⁰. Indeed, alleviation of resting tremor in individuals with PD following both STN-DBS and VIM-DBS is associated with normalization of cerebellar metabolism⁵⁷.

Tourette syndrome and obsessive–compulsive disorder

Several neuropsychiatric disorders, including TS and OCD, have been associated with dysfunction in cortico–basal ganglia circuits. For example, although the precise origin of tics in individuals with TS remains unclear, reduced GABA function in the striatum has been considered a primary cause of tic production (reviewed in REFS^{58,59}). In line with this perspective, microinjections of the GABA antagonist bicuculline into the striatum^{60,61} or into the GPe⁶² of non-human primates can result in tics and stereotyped behaviours. Furthermore, there is evidence that abnormal basal ganglia activity drives activity changes in both the cerebellum and the primary motor cortex (M1) that predict the onset of tics⁶³. Additional evidence for cerebellar involvement in TS comes from imaging studies in humans, which revealed tic-related activation not only in the basal ganglia but also in the cerebellum^{64,65}. In fact, some of these studies report that tic severity correlated with cerebellar activity⁶⁶.

Alterations in cerebellar activity have been observed in imaging studies of both TS and OCD (reviewed in REFS^{67,68}). For example, a study using resting-state functional MRI (fMRI) demonstrated that individuals with OCD, relative to healthy controls, exhibit increased whole-brain connectivity in regions of both the putamen and the cerebellar cortex⁶⁹ (FIG. 3b). Brain metabolism in individuals with TS, relative to healthy controls, is characterized by hypometabolism in the striatum covarying with hypermetabolism in the cerebellar cortex⁷⁰ (FIG. 3c). A similar metabolic pattern has also been observed in carriers of genetic mutations associated with HD, another prototypical basal ganglia disorder⁷¹ (FIG. 3d). Thus, there is growing evidence that alterations in the function of the basal ganglia are associated with changes in cerebellar activity and metabolism. We propose that the disynaptic pathway from the STN to the cerebellar cortex provides a key link for such effects, although other pathways or independent structural changes in the cerebellum may also be involved^{72,73}. In line with our proposal, a recent computational model of basal ganglia–cerebellar–cerebral cortical network function in TS indicated that hyperactivity in the STN may propagate to the cerebellar cortex and contribute to tic generation⁷⁴. Thus,

similar to observations in PD, the reduction in OCD and TS symptoms^{75,76} in patients undergoing STN-DBS may be mediated, in part, through the STN influence on the cerebellar cortex.

Dystonia

Although it is traditionally considered to be a disorder of the basal ganglia (reviewed in REF.⁷⁷), dystonia provides a compelling example of how abnormal activity in the cerebellum may propagate to the basal ganglia and cause dysfunction. Abnormalities in the cerebello–thalamo–cortical tracts^{78,79}, cerebellar activity and functional connectivity have been observed in many forms of dystonia (reviewed in REF.³¹). For example, manifesting and non-manifesting carriers of genetic mutations that are associated with dystonia show co-varying increases in metabolic activity in the putamen–GP and in the cerebellar cortex. This pattern of metabolic activity is not present in controls⁸⁰ (FIG. 3e).

Mouse models of dystonia also display structural and functional abnormalities in cerebello–thalamo–cortical pathways^{81,82}. In such models, abnormal (for example, bursting) cerebellar output evoked dystonic postures^{15,83–85}. Silencing, lesioning or normalizing cerebellar output in these animal models abolished the dystonic postures^{86,87}. In line with these data, bursting cerebellar output has been recorded during surgery in a patient with dystonia⁸⁸. Currently, DBS and transcranial magnetic stimulation of the cerebellum are being explored as potential treatments for some forms of dystonia^{89–91}.

Overall, these observations suggest that there is a need to re-conceptualize the pathophysiology of several debilitating disorders. What were formerly considered to be basal ganglia or cerebellar disorders may be better understood as network disorders. Even if the initial damage is confined to one node in the basal ganglia or cerebellar circuits, some aspects of the symptoms may be caused by abnormal signals transmitted through the interconnecting pathways.

Evidence from normal function

Given current concepts about basal ganglia and cerebellar function (detailed below), it is commonly considered that specific behavioural tasks rely exclusively on the operations of one of these subcortical structures. However, the integrated network perspective implies that, in many instances, the two structures are likely to cooperate in generating normal behaviours. In support of this perspective, we provide several striking examples of co-activation of the basal ganglia and the cerebellum from imaging studies in humans (FIG. 4). These examples include evidence that the cerebellum is involved in functions that are usually associated with the basal ganglia. We also provide an example of basal ganglia activation in a task that is often considered to rely exclusively on the cerebellum.

Reward and motivation

The basal ganglia are considered to be essential for reward-based (reinforcement) learning, which is guided by reward prediction errors (reviewed in REF.⁹²). Midbrain dopamine neurons in rodents, non-human primates and humans have been associated with reward processing and coding of reward prediction errors (reviewed in REF.⁹³). Recently, a study

using two-photon calcium imaging in behaving mice provided evidence for reward-related activity in granule cells of the cerebellar cortex⁹⁴. In this study, some granule cells responded preferentially to reward or reward omission whereas others selectively encoded reward anticipation. In line with these findings, a recent overview of imaging studies in humans indicated that brain regions outside the basal ganglia, including the cerebellum, are associated with rewards and reward prediction errors⁹⁵. For example, imaging studies in humans have shown that activation in the anterior cerebellar cortex correlates with reward and reward prediction error in studies of both appetitive and aversive conditioning^{96–101} (FIG. 4a,b). Furthermore, humans with cerebellar lesions showed impairments in reward-based reversal learning¹⁰². These observations suggest that the cerebellum functions along with the basal ganglia to provide the neural substrate for reward coding and reward-based learning.

The cerebellum has also been involved in motivation-based adjustment of motor output, a behaviour that is usually associated with the basal ganglia. Basal ganglia activity and reward-based learning mechanisms have been used to explain how individuals adjust action choices and modulate the kinematic parameters of movement on the basis of motivation^{103,104}. Even so, the results of imaging studies in humans demonstrated that cerebellar activation also correlates with movement parameters (such as movement extent and speed¹⁰⁵) that are modulated with changes in motivation (FIG. 4c). The integrated network perspective suggests that motivation-related signals from the basal ganglia drive the cerebellum to optimize movement parameters. This perspective may help explain how interactions between the basal ganglia and the cerebellum mediate the motivational effects of verbal encouragement on movement force¹⁰⁶.

Sensorimotor adaptation

The cerebellum is considered to be a major component of the neural substrate for adapting motor output on the basis of sensory feedback from movement (reviewed in REF.¹⁰⁷). Even so, a recent imaging study in human subjects also provided evidence for striatal activation in a task involving (error-based) sensorimotor adaptation¹⁰⁸ (FIG. 4d). The disynaptic pathway from the cerebellar nuclei to the input stage of basal ganglia processing may underlie this activation, although alternative pathways could also be involved.

Overall, communication between the cerebellum and basal ganglia could be essential to linking sensorimotor adaptation to reinforcement mechanisms for motor learning. Human behavioural studies have shown that combining error-based and reward-based feedback accelerates sensorimotor adaptation¹⁰⁹ and that reward and punishment have differential effects on sensorimotor adaptation¹¹⁰. Thus, motor learning in any number of specific situations can be a complex interplay between the learning mechanisms supported by the basal ganglia and the cerebellum¹¹¹.

Integrated networks for learning

Computationally, the cerebral cortex, the basal ganglia and the cerebellum have been hypothesized to implement distinct learning processes^{9,112–115}. Learning within the cerebral cortex is considered to be primarily unsupervised and driven by Hebbian processes (use-

dependent; synaptic efficacy strengthens with co-activation). As mentioned above, the basal ganglia are usually associated with reward-based (reinforcement) learning, and the cerebellum is associated with error-based learning. However, in light of the anatomical and functional data reviewed here, the view that basal ganglia and cerebellar circuits with the cerebral cortex are independent needs to be modified (FIG. 5). This perspective is in line with previous proposals that use-dependent, reward-based and error-based learning require operation of an integrated mechanism that gradually guides performance¹¹⁶.

More specifically, a number of observations suggest that learning is implemented gradually at the level of topographically organized circuits that link the basal ganglia, the cerebellum and the cerebral cortex. Support for this proposal comes from several imaging studies of skill learning in humans. These studies have revealed the engagement of a distributed network involving topographically organized sites in the basal ganglia, the cerebellum and the cerebral cortex that display linked changes in activation over the course of learning^{108,114}.

For example, in the early stages of sequence learning, activations have been observed in the associative territory of the striatum, the STN, as well as in the cerebellar hemispheres^{112,117–119} (FIG. 4e). The sites of activation in the basal ganglia and in the cerebellum are likely to be anatomically interconnected, and these interconnections probably provide the substrate for the observation that the ‘functional connectivity’ between the basal ganglia and the cerebellum is enhanced early in learning¹²⁰. Additionally, transcranial magnetic stimulation over the cerebellar cortex during early stages of sequence learning causes complex changes in basal ganglia activity and can alter the speed of sequence acquisition¹²¹. Later in the learning process, activity in associative basal ganglia and cerebellar regions declines and the foci of activation shift to the sensorimotor regions within these structures¹¹⁹. Moreover, enhanced effective connectivity from the cerebellum to the sensorimotor putamen is associated with improved learning in the late-stage phase of motor sequence acquisition¹²². These data suggest that improvements in cognitive and motor performance during different stages of sequence acquisition are implemented in distinct networks of functionally related regions of the basal ganglia, the cerebellum and the cerebral cortex.

In support of this view, a recent imaging study in humans provided evidence that distinct basal ganglia–cerebellar–cerebral cortical networks implement different strategies to improve performance on an action selection task¹²³ (FIG. 6). Performance during initial stages of the task was primarily based on trial and error-type exploration (described by model-free reinforcement learning) and involved a limbic network, including the ventromedial prefrontal cortex (PFC), ventral striatum and posterior cerebellum. As learning progressed and subjects acquired a model of the environment (described by model-based reinforcement learning), the site of activation shifted to an associative (cognitive) network, including the dorsolateral PFC, dorsomedial striatum and lateral posterior cerebellum. Finally, with extensive experience, performance relied on motor memory, and the site of activation shifted to a motor network, including the supplementary motor area, putamen and anterior cerebellum. Overall, these data indicate that different learning strategies recruit distinct and topographically organized nodes within an interconnected network that includes

the basal ganglia, the cerebellum and the cerebral cortex. This perspective predicts that shifts in learning strategy, skill level or context will be associated with topographic shifts in the sites of activation within the interconnected network.

Future directions

Functions of the basal ganglia–cerebellar–cerebral cortical network

The anatomical findings reviewed here have provided compelling evidence in non-human primates that the sensorimotor and the associative domains of the basal ganglia are interconnected with functionally related regions of both the cerebellum and the cerebral cortex. One important issue that remains to be investigated is whether the limbic domain of the basal ganglia is also interconnected with the cerebellum. Specifically, do regions of the ventral striatum (including the nucleus accumbens) receive disynaptic projections from the cerebellar nuclei? If so, it would be important to determine which regions of the cerebellar nuclei are involved. Furthermore, do limbic regions of the basal ganglia (for example, the limbic domain of the STN) send disynaptic projections to the cerebellar cortex? If so, it would be important to determine the regions of basal ganglia at the origin of this output and the regions of the cerebellar cortex that are its target. In short, basal ganglia–cerebellar–cerebral cortical networks that operate in the limbic domain remain to be identified using anatomical and physiological techniques in non-human primates. However, neuroimaging studies in humans support the idea that there exist functional interactions between limbic regions of the basal ganglia, the cerebellum and the cerebral cortex^{124–126}.

Basal ganglia–cerebellar–cerebral cortical networks could provide an important component of the substrate for multiple intrinsic resting-state networks¹²⁴. For example, interconnections between cognitive regions of the basal ganglia, the cerebellum and the cerebral cortex could provide part of the foundation for the executive control network. This network includes specific regions of the caudate (associative territory of the striatum), lateral cerebellum (hemispheric crus I and II) and the dorsolateral prefrontal cortex and has been associated with executive function, working memory and verbal fluency¹²⁴. Abnormal activity in this network has been associated with cognitive dysfunction in Alzheimer disease¹²⁷, anxiety¹²⁸, Friedreich ataxia¹²⁹ and spinocerebellar ataxia type 6 (REF.¹³⁰). Similarly, interconnections between limbic regions of the basal ganglia, the cerebellum and the cerebral cortex could provide part of the foundation for the salience network. This network includes specific regions of the striatum, cerebellum (hemispheric lobule VI and crus I) and the dorsal anterior cingulate cortex and has been associated with processing of interoceptive, autonomic and emotional information¹²⁴. Abnormal activity in this network has been associated with symptoms in major depression, schizophrenia, substance use, anxiety and eating disorders (reviewed in REF.¹³¹). Thus, further studies of basal ganglia–cerebellar–cerebral cortical networks may suggest new approaches for intervening in a wide range of neuropsychiatric disorders.

Other interconnections between the basal ganglia and cerebellum

An additional pathway for interactions between the basal ganglia and the cerebellum has been proposed in rodents^{132–134}. Specifically, early studies suggested that dentate output

influences the substantia nigra (SN) and other catecholamine centres^{132,134,135}. A recent study confirmed the presence of a direct pathway from the dentate nucleus to dopaminergic and GABAergic neurons in the mouse SN and ventral tegmental area¹³³. There currently is no compelling evidence that this pathway exists in monkeys, although diffusion tensor imaging studies provide some support for the pathway in humans^{136–139}. If this connection exists, it will be important to define the specific cells of origin in the dentate and the physiological consequences of this input on target neurons in the SN and the ventral tegmental area.

Computational roles

To date, there have been limited proposals regarding the computational roles of interconnections between the basal ganglia and the cerebellum¹⁴⁰. According to one computational framework¹⁴¹, cortico-cerebellar processing provides a means to evaluate the sensory consequences of an action whereas cortico-basal ganglia processing provides a means to evaluate the value of outcomes from an action. As discussed above, optogenetic stimulation of the pathway from the cerebellum to the striatum alters cortico-striatal plasticity¹⁵. Further studies are needed to confirm the evidence that cerebellar output primarily influences the indirect pathway. However, if this finding proves to be correct, then cerebellar output could influence the balance of activity in the direct versus indirect pathways through the basal ganglia. In doing so, cerebellar outputs may provide the basal ganglia with information that is necessary to evaluate competing action candidates¹⁴⁰. However, it is noteworthy that cerebellar activation has been associated with action timing as opposed to action selection^{142,143}. Thus, an alternative contribution of cerebellar outputs may be to control the timing of actions selected by basal ganglia processing.

The computational role of the disynaptic pathway from the STN to the cerebellar cortex is also unclear. Some have viewed the role of the STN as mediating a ‘stop signal’ to inhibit action^{144–146}. Thus, one potential role for STN projections to the cerebellar cortex is to convey information relevant to the suppression or termination of action¹⁴⁰. However, a recent study in non-human primates found that STN neurons capable of providing a signal for action stopping or switching are restricted to a small, ventromedial portion of the nucleus. Neurons in other regions of the STN encoded other task dimensions¹⁴⁷. Our data indicate that the STN projection to the cerebellar cortex originates from a broad region of the nucleus¹². Thus, any further speculation about the computational role of STN output to the cerebellum must await a firmer understanding of the signals encoded by the activity of STN neurons.

Another source of insight about the computational role of the interconnections between the basal ganglia and the cerebellum may come from a comparative approach. The basal ganglia and cerebellum are phylogenetically old structures that have undergone extensive expansion with the evolution of the cerebral cortex. This expansion is especially striking in primates and it appears to support the increased complexity of the motor, cognitive and affective functions in these animals^{148,149}. However, it is possible that the subcortical connections between the basal ganglia and the cerebellum precede the appearance of cortico-basal ganglia and cortico-cerebellar connections. Clearly, there are animals that lack a cerebral

cortex but have a well-developed cerebellum and basal ganglia (for example, song birds). We speculate that the two subcortical systems may be linked to form an integrated network even in these animals. These interconnections would enable each system to utilize the learning mechanisms implemented by the other. If this is the case, then studies in animals that lack a cerebral cortex might provide some unique insights into the role of the connections that link the basal ganglia and the cerebellum.

Summary

In summary, further experimental and modelling studies are needed to determine the full extent of the interconnections between the basal ganglia and the cerebellum as well as their computational role. However, the evidence reviewed here makes it clear that the basal ganglia and the cerebellum are densely interconnected to form an integrated network with the cerebral cortex. We discussed evidence that the interconnections between the basal ganglia, the cerebellum and the cerebral cortex are topographically organized and create functional distinct networks that operate over the domains of movement, cognition and perhaps affect. We illustrated results showing that abnormal activity at one node can percolate throughout the entire network to cause dysfunction at other nodes in the network. We also showed evidence that during a task, linked nodes are activated and there is an orderly shift in activation as performance changes. Ultimately, we think that these observations suggest that questions about basal ganglia or cerebellar function should be reframed to consider the entire basal ganglia–cerebellar–cerebral cortical network.

Acknowledgements

The preparation of this manuscript was supported in part by US National Institutes of Health grants R01 NS24328, P40 OD010996 and P30 NS076405 (all to P.L.S.).

Glossary

Rabies virus

An RNA virus that is highly neurotropic and can be used as a retrograde transneuronal tracer. Rabies virus is transported retrogradely to neurons that project to an injection site (that is, first-order neurons). The virus replicates in the first-order neurons and is transmitted transneuronally to neurons that project to the first-order neurons. The virus continues to replicate and move transneuronally through chains of synaptically connected neurons in a time-dependent fashion.

Direct pathway

A monosynaptic pathway that connects one type of MSN in the striatum with neurons in the CPi and the SNpr.

Indirect pathway

A polysynaptic pathway that connects another type of MSN in the striatum to neurons in the CPi and the SNpr.

Reward-based (reinforcement) learning

Learning process (algorithm) that allows reward signals to optimize performance.

Error-based learning

Learning process (algorithm) that allows error signals to improve performance in a gradual manner.

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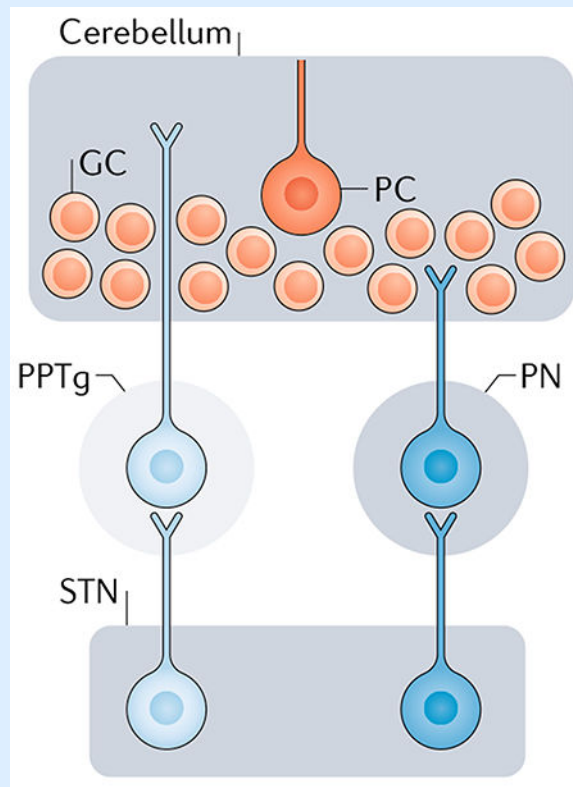
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Box 1 |**Potential routes from the subthalamic nucleus to the cerebellum**

There are two potential mediators of the subthalamic nucleus (STN) input to the cerebellar cortex — namely, the pontine nuclei (PN) and the pedunculopontine nucleus (PPTg). In non-human primates, the STN sends projections to the PN²⁴ (see the figure), and these nuclei are a key source of mossy fibre input to the cerebellar cortex and to the cerebellar nuclei²⁵. By contrast, tracing studies in rats have shown that the STN projects to the PPTg¹⁵⁰. The rat PPTg is a source of cholinergic inputs to the cerebellar nuclei and, possibly, to the cerebellar cortex^{151–153}. In a recent study in rats, PPTg microstimulation resulted in short-latency activation of the cerebellar nuclei¹⁵³. This activation was reduced in the presence of cholinergic antagonists, indicating that cholinergic fibres from the PPTg to the cerebellum are responsible for this activation¹⁵³. A recent report²⁶ raised the possibility that the PPTg may mediate STN input to the cerebellar cortex (see the figure). However, conventional tracer injections into the cerebellar cortex of rats result in limited retrograde labelling of PPTg cells^{26,151}. Thus, the extent to which the PPTg may mediate STN input to the cerebellar cortex remains to be determined in both rats and monkeys. GC, granule cell; PC, Purkinje cell.



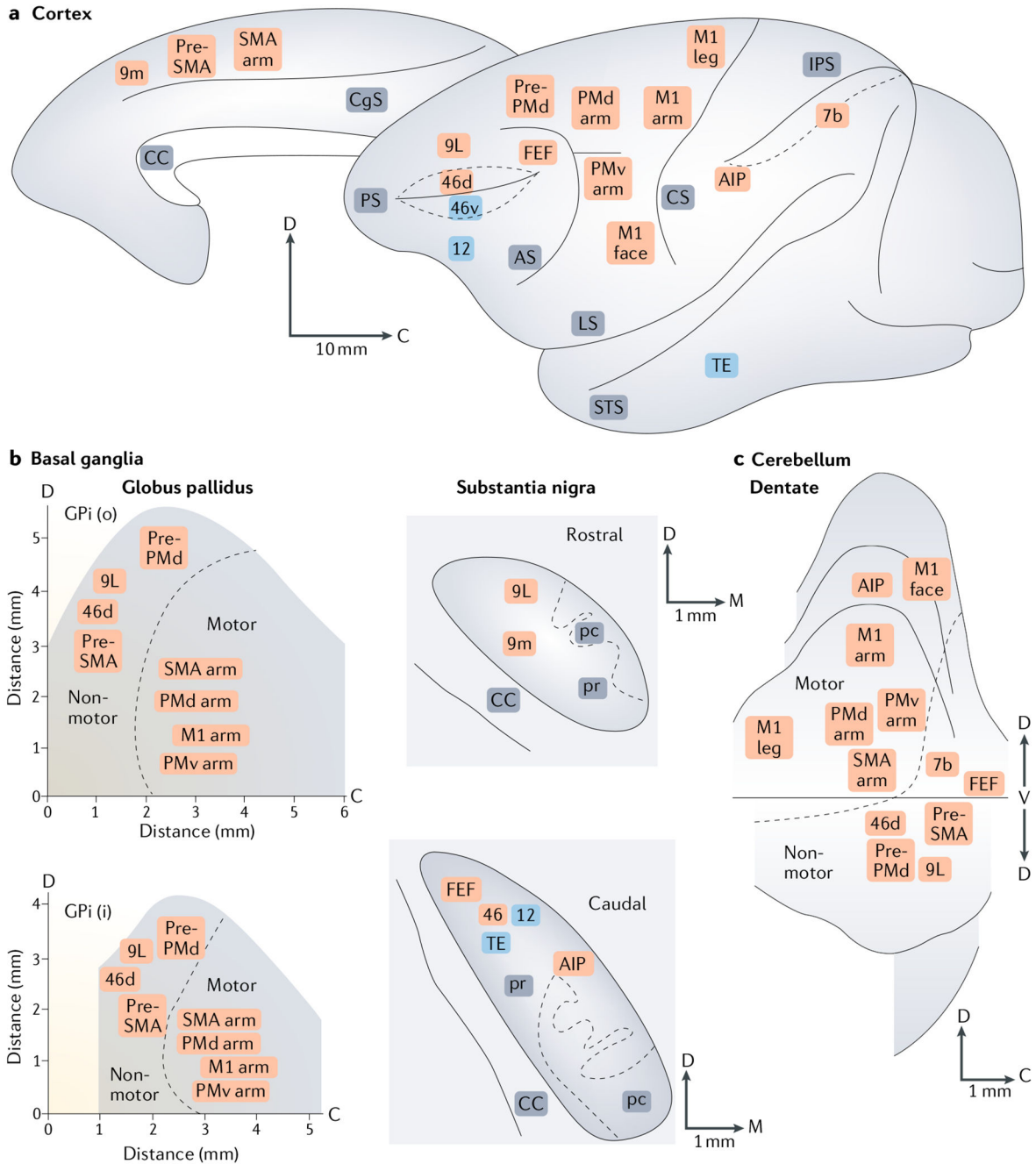


Fig. 1 | Organization of basal ganglia and cerebellar outputs to the cerebral cortex.

a | The cortical targets of basal ganglia and cerebellar outputs are indicated on medial and lateral views of the *Cebus* monkey brain. **b,c** | These panels show summary maps of topography in the basal ganglia (part **b**) and cerebellar (part **c**) output nuclei on the basis of their cortical targets. The division between motor and non-motor areas of the internal segment of the globus pallidus (GPI) and the dentate nucleus is indicated by the dashed lines. In all panels, orange labels indicate areas of the cerebral cortex that are the targets of both basal ganglia and cerebellar outputs, whereas blue labels indicate areas of the cerebral

cortex that are the targets of basal ganglia, but not cerebellar, output. The numbers refer to cytoarchitectonic areas. AIP, anterior intraparietal area; AS, arcuate sulcus; C, caudal; CC, corpus callosum; CgS, cingulate sulcus; CS, central sulcus; D and d, dorsal; FEF, frontal eye field; i, the inner portion of the internal segment of the globus pallidus; IPS, intraparietal sulcus; LS, lateral sulcus; M and m, medial; M1, primary motor cortex; M1 arm, arm area of M1; M1 face, face area of M1; M1 leg; leg area of M1; o, the outer portion of the internal segment of the globus pallidus; pc, pars compacta; PMd arm, arm area of the dorsal premotor area; PMv arm, arm area of the ventral premotor area; pr, pars reticulata; Pre-PMd, predorsal premotor area; Pre-SMA, presupplementary motor area; PS, principal sulcus; SMA arm, arm area of the supplementary motor area; STS, superior temporal sulcus; TE, area of inferotemporal cortex. Based on data from REFS^{4,5,154–156}.

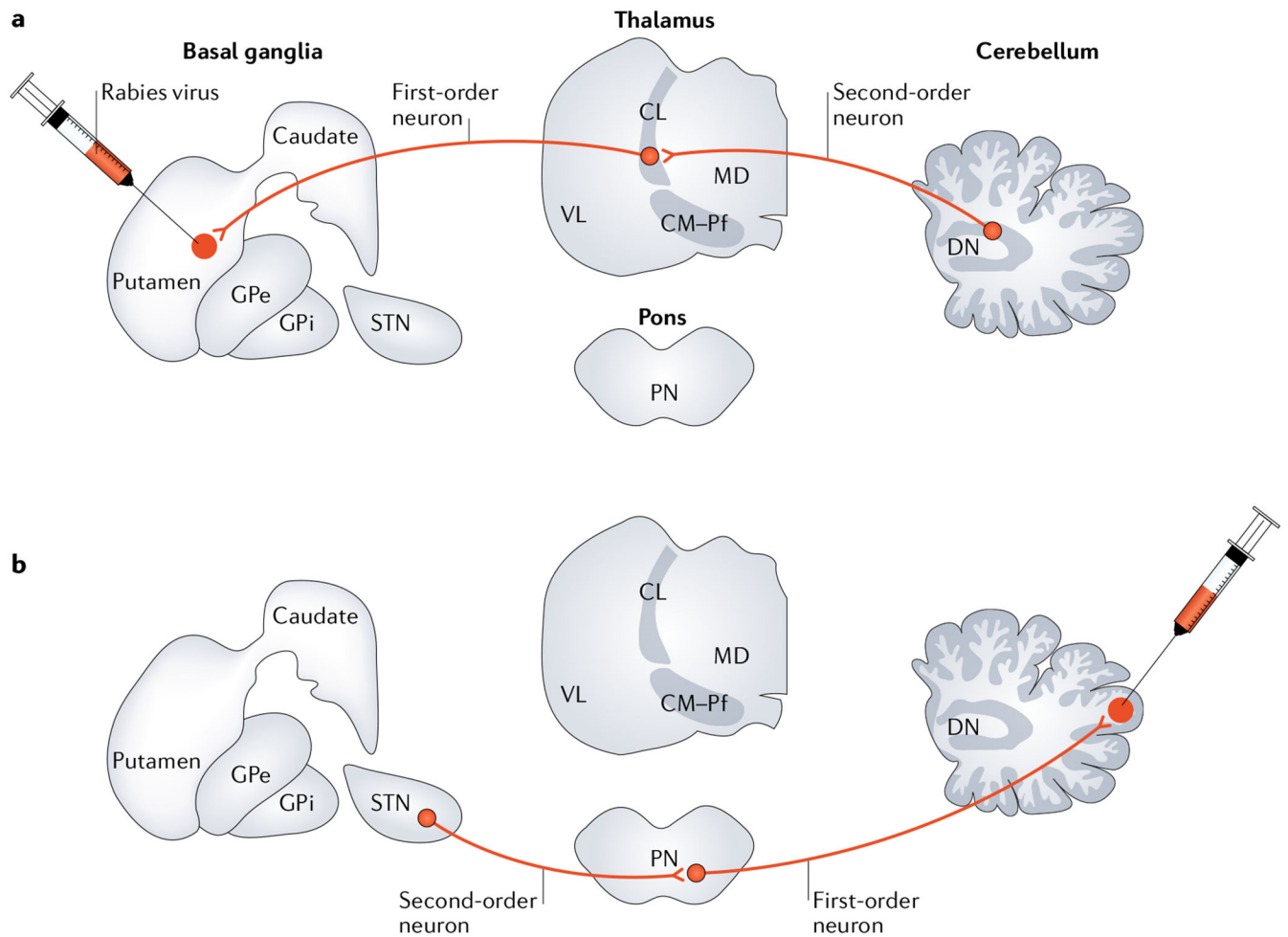


Fig. 2 | Anatomical connections.

a | A study using retrograde transneuronal transport of rabies virus in monkeys revealed a disynaptic pathway from the dentate nucleus (DN) to the putamen¹¹. Rabies virus was injected into the putamen and underwent retrograde transport to first-order neurons that project to the striatum (for example, neurons in the intralaminar thalamic nuclei) and then retrograde transneuronal transport to second-order neurons that innervate the first-order neurons. The second-order neurons in the cerebellum were located primarily in the DN. **b** | A study using retrograde transneuronal transport of rabies virus in monkeys revealed a disynaptic pathway from the subthalamic nucleus (STN) to the cerebellar cortex¹². Rabies virus was injected into the lateral cerebellar cortex and underwent retrograde transport to first-order neurons that project to the cerebellar cortex (for example, neurons in the pontine nuclei (PN)) and then retrograde transneuronal transport to second-order neurons that innervate the first-order neurons. The study revealed second-order neurons labelled in the basal ganglia, primarily in the STN. CL, central lateral thalamic nucleus; CM, central medial thalamic nucleus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MD, medial dorsal thalamic nucleus; Pf, parafascicular thalamic nucleus; VL, ventral lateral thalamic nucleus.

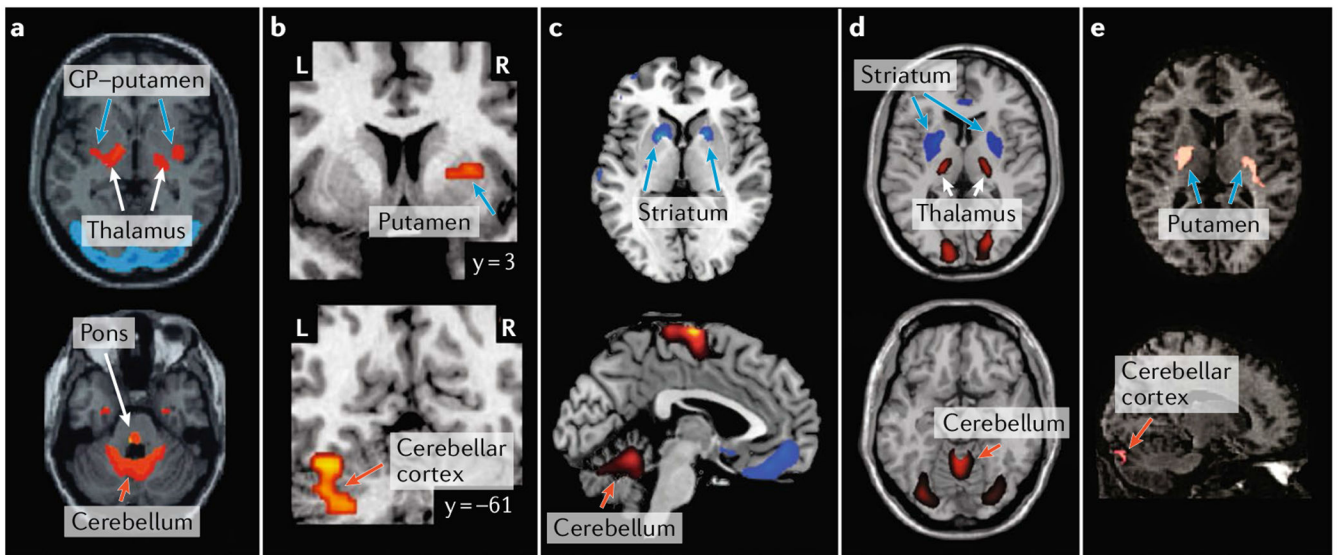


Fig. 3 | Neuroimaging evidence for basal ganglia and cerebellar interactions in disease. Findings from neuroimaging studies of several disorders provide evidence for interactions between the basal ganglia and cerebellum. Indeed, abnormal structure, connectivity and activity in both the basal ganglia and the cerebellum have been reported in several debilitating disorders. Note that in this figure, orange arrows point to sites in the cerebellum, blue arrows point to sites in the basal ganglia and white arrows point to sites in the thalamus and/or the cerebral cortex. **a** | Analysis of ^{18}F -fluorodeoxyglucose (FDC) positron emission tomography (PET) scans indicated that brain metabolism in individuals with Parkinson disease (PD), relative to age-matched controls, is characterized by co-varying pallido-thalamic, pontine and cerebellar hypermetabolism³⁶. The metabolic pattern associated with PD is illustrated on two axial sections in which marked metabolic increases and decreases are shown on red to yellow and blue to purple colour scales, respectively. **b** | In individuals with obsessive-compulsive disorder (OCD), relative to healthy control subjects, regions within both the basal ganglia and the cerebellum demonstrated increased whole-brain connectivity⁶⁹. Clusters in which individuals with OCD showed markedly increased whole-brain connectivity in the putamen and cerebellar cortex are illustrated on two coronal sections on a red to yellow colour scale. **c** | Analysis of FDC-PET scans indicated that brain metabolism in individuals with Tourette syndrome (TS), relative to healthy controls, is characterized by hypometabolism in the striatum that co-varies with hypermetabolism in the cerebellum⁷⁰. The metabolic pattern associated with TS is illustrated on axial and sagittal sections in which notable metabolic increases and decreases are shown in red and blue, respectively. **d** | A similar metabolic pattern was identified in Huntington disease (HD) gene carriers, relative to healthy controls⁷¹. The metabolic pattern associated with HD is illustrated on axial sections, and marked metabolic increases and decreases are shown on red to yellow and blue to purple colour scales, respectively. **e** | Finally, analysis of FDC-PET scans in non-manifesting carriers of dystonia-associated mutations in torsin 1A (*TOR1A*; also known as *DYT1*), relative to healthy controls, revealed co-varying hypermetabolism (red) in the striatum and the cerebellar cortex⁸⁰. GP, globus pallidus; L, left; R, right. Part **a** is adapted with permission from REF³⁶, John Wiley and Sons. Part **b** is adapted with

permission from REF.⁶⁹, Elsevier. Part **c** is adapted with permission from REF.⁷⁰, American Academy of Neurology. Part **d** is adapted from Feigin, A et al. Thalamic metabolism and symptom onset in preclinical Huntington's disease. *Brain* (2007) **130**, 2858–2867, by permission of Oxford University Press, REF.⁷¹. Part **e** is adapted with permission from REF.⁸⁰, John Wiley and Sons.

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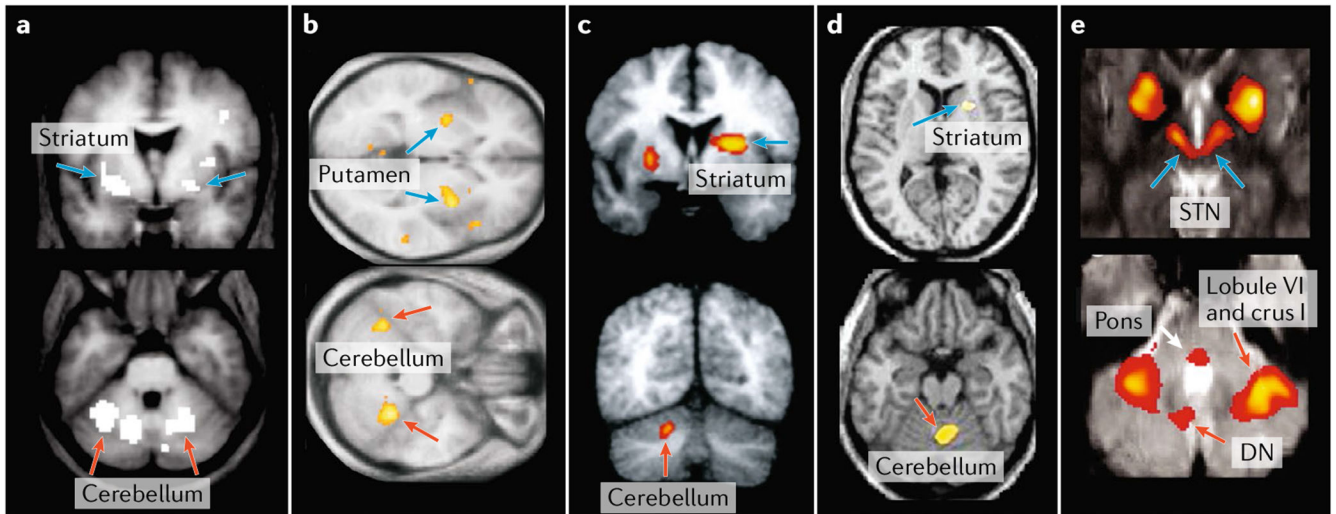


Fig. 4 | Neuroimaging evidence for basal ganglia and cerebellar interactions in normal function. Findings from neuroimaging studies in healthy individuals have shown co-activations in the basal ganglia and cerebellum in various tasks. Event-related functional MRI (fMRI) studies revealed that activity in both regions of the basal ganglia and the cerebellum is correlated with temporal difference prediction error during appetitive conditioning with a pleasant taste reward⁹⁷ (part **a**) and during higher-order aversive conditioning⁹⁸ (part **b**). A positron emission tomography (PET) study demonstrated that movement vigour (that is, extent and speed) is associated with regional cerebral blood flow increases in regions of both the basal ganglia (putamen and globus pallidus) and the cerebellum¹⁰⁵ (part **c**). An fMRI study of healthy subjects adapting to visuomotor rotations, in the context of a joystick aiming task, indicated that sensorimotor adaptation is associated with increased activity in both the basal ganglia and the cerebellum¹⁰⁸ (part **d**). Finally, early stages of sequence learning are associated with activation of both the subthalamic nucleus (STN) and the cerebellum¹¹⁹ (part **e**). Note that orange arrows in this figure point to activation sites in the cerebellum and blue arrows point to activation sites in the basal ganglia. DN, dentate nucleus. Part **a** is adapted with permission from REF.⁹⁷, Elsevier. Part **b** is adapted from REF.⁹⁸, Macmillan Publishers Limited. Part **c** is adapted with permission from REF.¹⁰⁵, American Physiological Society. Part **d** is adapted from REF.¹⁰⁸, Macmillan Publishers Limited. Part **e** is adapted with permission from REF.¹¹⁹, Proceedings of the National Academy of Sciences.

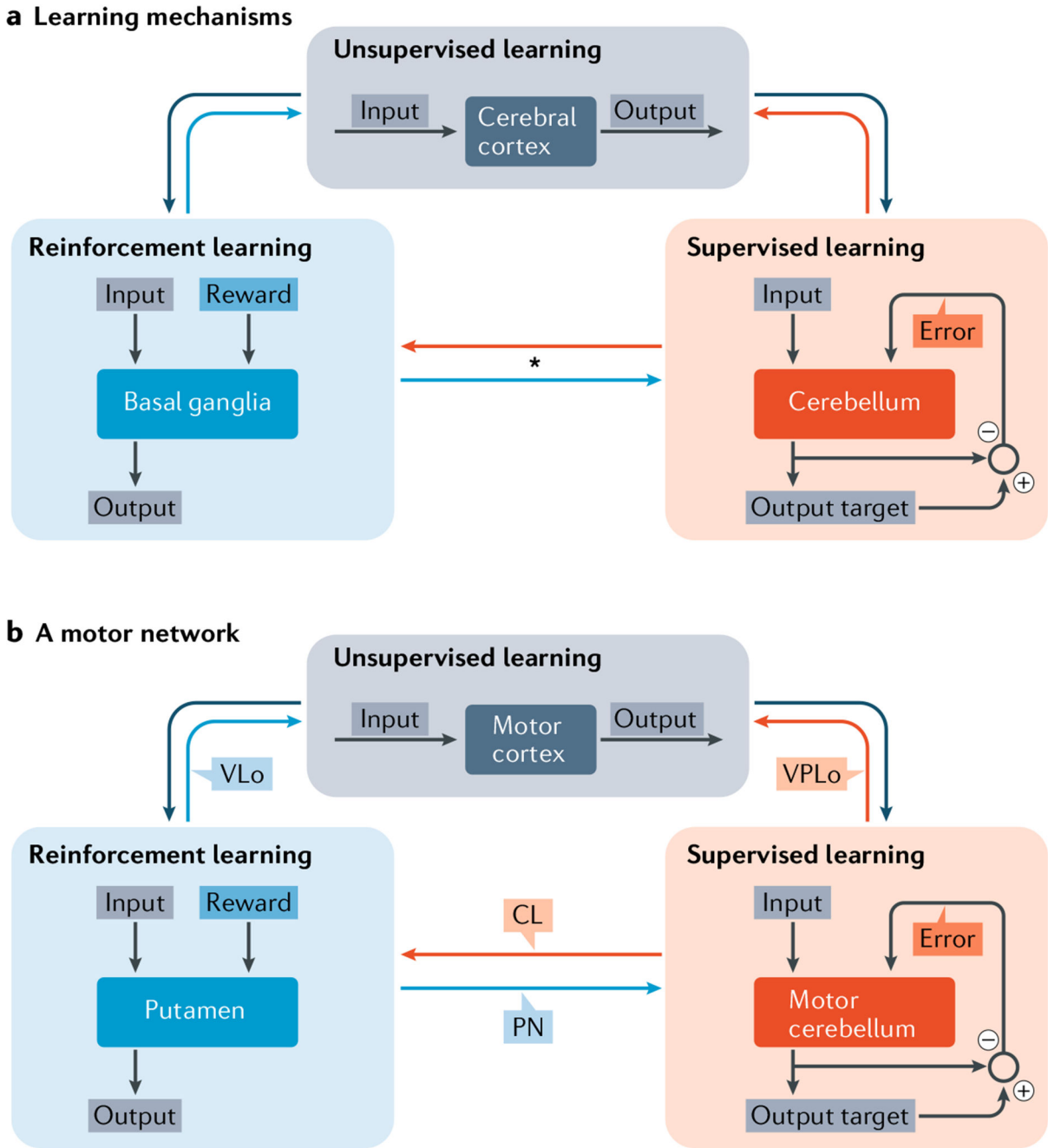


Fig. 5 | Learning specializations of cortico–basal ganglia and cortico–cerebellar loops.
a | The cerebral cortex, basal ganglia and cerebellum are thought to implement distinct learning algorithms⁹. According to this view, the cerebral cortex is specialized for unsupervised learning based on Hebbian plasticity. The basal ganglia are specialized for reinforcement (reward-based) learning, guided by the reward signals from midbrain dopaminergic neurons. The cerebellum is specialized for supervised (error-based) learning, guided by error signals from the inferior olive. The interconnections between these structures are illustrated by large arrows. Outputs from the cerebral cortex are depicted as

large dark grey arrows. Outputs from the basal ganglia are depicted as large blue arrows. Outputs from the cerebellum are depicted as large orange arrows. The asterisk emphasizes the newly discovered connections between the basal ganglia and cerebellum that are the subject of this Review^{11,12}. **b** | An example of learning in the motor domain. Within the basal ganglia, only the input stage of basal ganglia processing (putamen) is included for simplicity. Labelling next to the interconnection arrows identifies the intermediary structure for the connection. CL, central lateral nucleus; PN, pontine nuclei; VLo, ventral lateral nucleus, pars oralis; VPLo, ventral posterior lateral nucleus, pars oralis. Part **a** is adapted with permission from REF⁹, Elsevier.

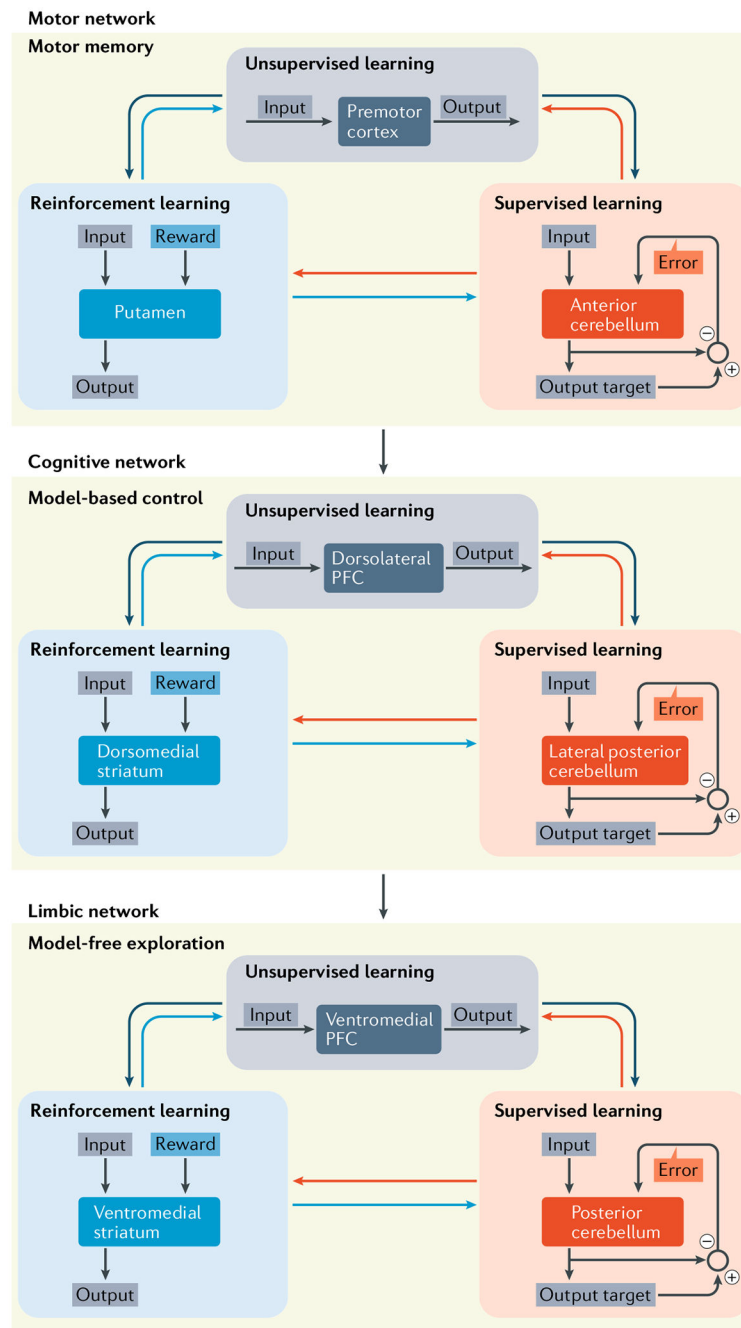


Fig. 6 |. Action planning.

Functionally related cortical, basal ganglia and cerebellar sites within interconnected networks participate in progressive stages of action planning¹²³. On the basis of these results, learning through exploration involves a limbic network, including the ventromedial prefrontal cortex (PFC), ventromedial striatum and posterior cerebellum. Model-based learning involves an associative (cognitive) network, including the dorsolateral PFC, dorsomedial striatum and lateral posterior cerebellum. Performance based on motor memory involves a motor network, including the supplementary motor area, putamen and anterior

cerebellum. The authors' imaging data suggest that as learning progresses, the sites of activation shift in a topographically organized fashion. Our interpretation of these data is that each stage of the learning progress involves a different set of interconnected basal ganglia, cerebellar and cerebral cortical regions.

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