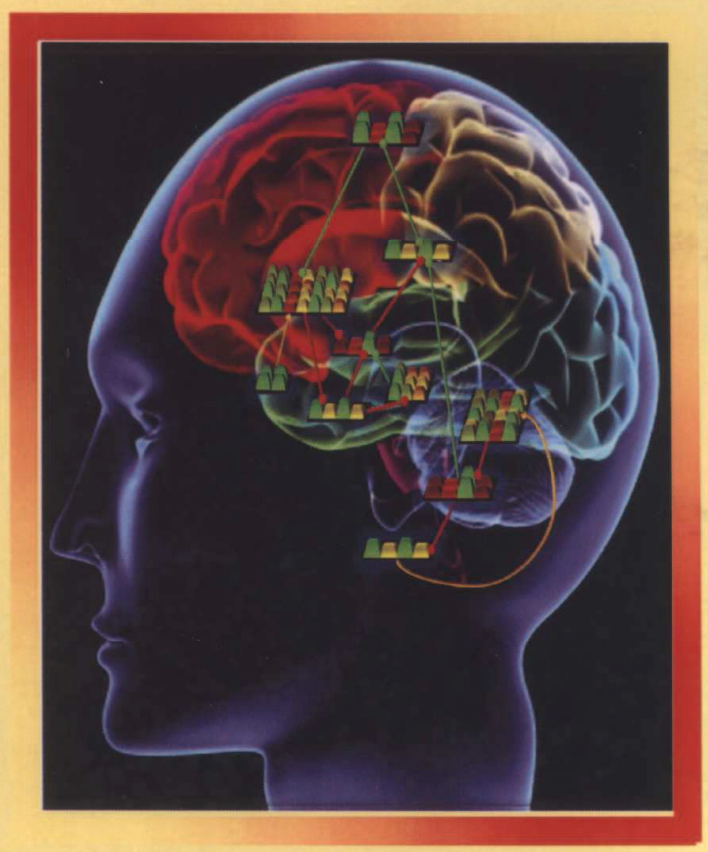
UNIVERSITÀ DEGLI STUDI DI SALERNO

Dipartimento di Ingegneria Elettronica ed Ingegneria Informatica

Dottorato di Ricerca in Ingegneria dell'Informazione

The role of Basal Ganglia and Cerebellum in Motor Learning: A Computational Model

Rosa Senatore



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TESI DI DOTTORATO

The Role of Basal Ganglia and Cerebellum in Motor Learning: A Computational Model

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Anno Accademico 2010 – 2011

To my mother Luisa
and my father Sabato

Acknowledgments

For me there is only the traveling on paths that have heart,
on any that may have heart,
and the only worthwhile challenge is to travel its full length.
And there I travel looking, looking breathlessly
...
The teaching of Don Juan: A Yaqui Way of Knowledge
Carlos Castaneda (1968)

By traveling along this path I understood that *"paths that have heart"* are not always easy to travel. Sometime these paths are full of pitfalls, leaving you to deal with decisions that are hard to make, to ask yourself questions to which you don't know when, or if you ever will find an answer.
But these paths could bring you to places where you have never been before, enrich your mind with knowledge, and make you breathless...
It is there that I have traveled, enjoying my voyage, with so many people at my side that love me and believe in me; without which I would not have been able to deal with difficulties I had encountered and would not be where I am now.
First, I want to thank my family, who was there for me even though a thousand miles separated us.
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Dulcis in fundo, I thank Prof. Angelo Marcelli, my mentor, who followed and wisely advised me; but mainly because he showed me that "only the travel along the paths that have a heart exists," and that "the only worthwhile challenge is to travel its full length".

Contents

Introduction

In everyday life people satisfy most of their exigencies by performing movements, which need to be executed in a timed and coordinated fashion in order to perform the motor behavior properly and achieve the desired goal.

Many research areas, from neuroscience to engineering, investigate, from different perspectives and for diverse purposes, the processes that allow humans to efficiently perform skilled movements.

From a biological point of view, the execution of voluntary movements requires the interaction between nervous and musculoskeletal systems, involving several areas, from the higher cortical centers to motor circuits in the spinal cord.

Understanding these interactions could provide important insights for many research fields, such as robotics and machine learning, and is essential for finding new treatments for movement disorders that affect the neural systems involved in controlling motor behaviors. Indeed, depending on the brain areas affected by the disease, movements become uncoordinated, slower or faster than normal, the ability to learn a novel motor task or to perform a well-known motor skill becomes impaired.

Therefore, it is important to understand the neural processes involved in generating a complex sequence of movements, and how different levels of the nervous system interact and contribute to the gradual improvement of motor performance during learning.

This goal could be achieved by finding an answer to the following questions:

- How does the central nervous system control and coordinate natural voluntary movements?
- Which brain areas are involved in learning a new motor skill? What are the changes that happen in these neural structures? What are the aspects of the movement memorized?
- Which is the process that allows people to perform a skilled task, such as playing an instrument, being apparently unaware of the movements they are performing?
- What happen when a neurodegenerative disease affects the brain areas involved in executing movements?

These questions have been addressed from different perspectives and levels of analysis, from the exploration of the anatomical structure of the neural systems thought to be involved in motor learning (such as the basal ganglia, cerebellum and hippocampus) to the investigation of their neural interaction; from the analysis of the activation of these systems in executing a motor task to the specific activation of a single or a small group of neurons within them. In seeking to understand all the breadth and facets of motor learning, many researchers have used different approaches and methods, such as genetic analysis, neuroimaging techniques, animal models and clinical treatments.

These studies have provided a large body of knowledge that has led to several theories related to the role of the central nervous system in controlling and learning simple and complex movements. These theories envisage the interaction among multiple brain regions, whose cooperation leads to the execution of skilled movements.
How can we test these interactions for the purpose of evaluating a theory?

One answer to this question is investigating these interactions through computational models, which provide a valuable complement to the experimental brain research, especially in evaluating the interactions within and among multiple neural systems.

Based on these concepts arises the research presented in this thesis, which addresses the questions previously pointed out and aims at understanding the computational processes performed by two neural circuits, the **Basal Ganglia** and **Cerebellum**, in motor learning.

We suggest a new hypothesis about the neural processes occurring during acquisition and retention of novel motor skills, and propose a neural scheme for procedural motor learning, comprising the Basal Ganglia, Cerebellum and Cortex, which envisages that the cortex-basal ganglia interaction plays a key role during learning, whereas the cortex-cerebellar interaction is crucial for motor skill retention.

The neural scheme (and the hypothesis behind it) is evaluated through a computational model that incorporates the key anatomical, physiological and biological features of these brain areas in an integrated functional network, that allows to test experimentally the potential role of the basal ganglia and cerebellum in motor function. Exploring these interactions gains further understanding of the functional dynamics of information processing within the basal ganglia and cerebellum in normal as well as in diseased brains. Therefore, it might give some insights in developing more efficacious therapies for many diseases in which these subcortical structures are involved.

The thesis is organized as follows:

Chapter 1 reviews the anatomical and physiological features of the basal ganglia and cerebellum and briefly describes their involvement in motor diseases.

Chapter 2 analyzes the results of several studies in the field of

motor control and learning and illustrates the proposed hypothesis about the processes occurring in the brain during acquisition and retention of novel motor skills.

Chapter 3 describes the proposed neural scheme for motor learning, highlighting similarities and differences with those already presented in the literature. This chapter also provides a detailed explanation of the neural networks that simulate the Basal Ganglia and Cerebellum.

Finally, *Chapter 4* reports the validation of the model. The behavior of the network, in terms of the neural activations and motor responses (provided in learning a novel motor task), is compared to the results of experimental studies on motor learning. This chapter also reports the results of further experiments, in which neurodegenerative diseases (such as Parkinson's and Huntington disease) or brain lesions (such as cerebellar strokes) are simulated in the model. The behavior shown by the damaged networks (in terms of the motor response provided) is compared to that exhibited by patients affected by the motor disorders.

Chapter 1

Functional Neuroanatomy of the Basal Ganglia and Cerebellum

What are the brain areas involved in the formation of a motor plan? How do the interactions among cortical and subcortical regions allow humans to acquire a novel motor skill?

According to the current knowledge, a motor plan is executed through interactions between parietal and premotor areas. Depending on the sensory and proprioceptive information received from the posterior parietal cortex, the premotor cortex specifies the characteristics of a motor plan and sends this information to the motor circuits in the spinal cord, which control the movements of the limbs [70].

A primary role in modulating the information that the premotor cortex sends to the spinal cord is played by two supraspinal structures, the **Basal Ganglia** and the **Cerebellum**. These two groups of nuclei are the key structures of a group of pathways, which form distinct parallel loops between the spinal cord and the higher motor centers.

In order to outline the principal characteristics of the basal ganglia and cerebellum, whose role in motor learning is investigated in this work, this chapter reviews the anatomical

and physiological features of these neural structures and their involvement in motor diseases.

1.1 The Basal Ganglia

The Basal Ganglia (BG) are a group of closely interconnected gray matter nuclei located deep within the white matter of the brain [24]. This group of nuclei is now viewed as component of complex functional/anatomical loops, involving the cerebral cortex and thalamus [2, 3, 4].

This section reviews the anatomical structure of the BG, including their important subdivisions and the neuronal relations in the principal BG circuit. Last part of this section briefly describes BG functions and the diseases commonly associated with BG dysfunctions.

1.1.1 The anatomical structure of the Basal Ganglia

The BG comprise four structures: the striatum, the globus pallidus, the substantia nigra, and the subthalamic nucleus (as shown in Figure 1.1).

The *striatum* is the major recipient of inputs to the basal ganglia from the cerebral cortex, thalamus and brain stem nuclei. The striatum can be broken down into two primary subdivisions, the dorsal striatum and the ventral striatum. The dorsal striatum consists of the *caudate nucleus* and the *putamen*, whereas the ventral striatum (not shown in Figure 1.1) comprises the *nucleus accumbens*, the *septum*, and the *olfactory tubercle*.

Although the striatum contains several distinct cell types, the majority (90-95%) of the medium-sized neurons belongs in the category of medium spiny projection neurons (MSNs), which are all inhibitory and use gamma-aminobutyric acid (GABA) as their principal neurotransmitter [24]. These cells are both major targets of cortical input and the sole source of the striatal output. The

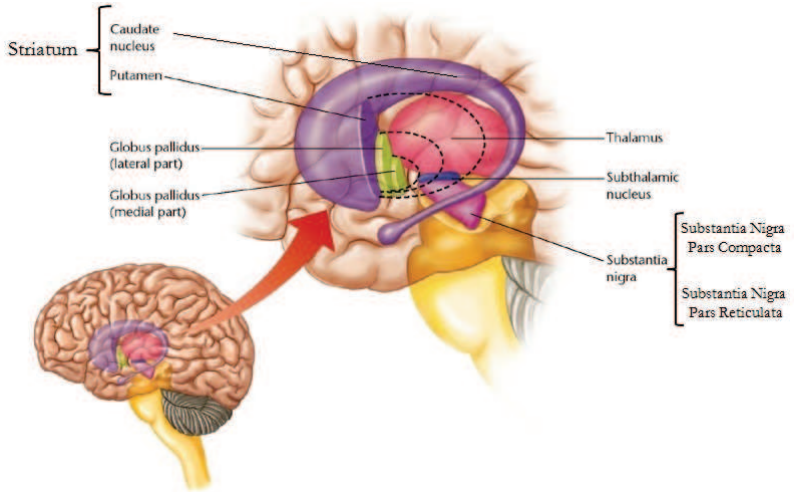


Figure 1.1 The basal ganglia comprise several nuclei. The striatum (that is composed primarily of the caudate nucleus and putamen) is the input nucleus of the basal ganglia. The globus pallidus can be divided into a lateral and medial part. The medial part of the globus pallidus is the output nucleus of the basal ganglia. The substantia nigra supplies the basal ganglia with the neurotransmitter dopamine, which is fundamental for learning. The subthalamic nucleus modulates the basal ganglia output.

MSNs have a very low spontaneous firing rate, fire very rarely, and in episodes that only last for about 0.1-3 s. In order to fire, they must be stimulated by the cortex [89]. Moreover, the axons of the MSNs issue numerous collateral branches within the striatum, which contact other neurons of the same type and provide for lateral or surround inhibition [109, 105]. In primates, the striatal MSNs can be subdivided into two populations, according to their neuroactive peptide content, kind of dopamine receptors expressed on their surfaces (D1 or D2 receptors), and their site of termination [24]. The striatum also contains two types of local inhibitory interneurons that have extensive axon collaterals that reduce the activity of the striatal MSNs neurons.

The *globus pallidus* (or *pallidum*) can be subdivided into a lateral (external) and a medial (internal) component, called external segment of the globus pallidus (GPe) and internal

segment of the globus pallidus (GPi), respectively. All the large neurons within both pallidal segments are GABAergic, inhibitory projection neurons. Neurons in the GPi fire tonically at very high rates. In doing so, they keep the thalamic neurons in a permanent state of inhibition.

The *Substantia Nigra*, according to cytoarchitectonic criteria, can be subdivided into two parts, the Substantia Nigra pars compacta (SNpc) and the Substantia Nigra pars reticulata (SNpr). The SNpc is mainly composed of darkly pigmented cells, which are an important source of dopamine synthesis. These cells project to most other regions of the BG, supplying them with the neurotransmitter dopamine. The cells in the pars reticulata are somewhat smaller than those in the pars compacta and most of them are GABAergic.

The *subthalamic nucleus* (STN) is composed of fairly large, triangular and polygonal cells. The subthalamic neurons are excitatory and use glutamate as their neurotransmitter. In animal models of Parkinson's disease this nucleus may be dysfunctional and neurons may fire in oscillatory patterns that can be closely related to tremor. It has been found that deep brain stimulation of the STN significantly improves motor function in patients with severe Parkinson's disease, but impairs cognitive functions [46, 132]. These results have confirmed its crucial role in motor functions and raised the possibility that it also participates in cognitive processes. Indeed, it has been suggested that the STN normally reduces the excitability of the BG and cortical circuitry involved in decision making, thus allowing extra time to consider the best option when confronted with conflicting choices [38].

Basal Ganglia circuitry: Direct, Indirect and Hyperdirect pathways

The BG are major components of large cortical-subcortical reentrant circuits linking cortex and thalamus [4]. These loops project from all cortical areas to striatum, from striatum to pallidum, from pallidum to thalamus, and from thalamus back

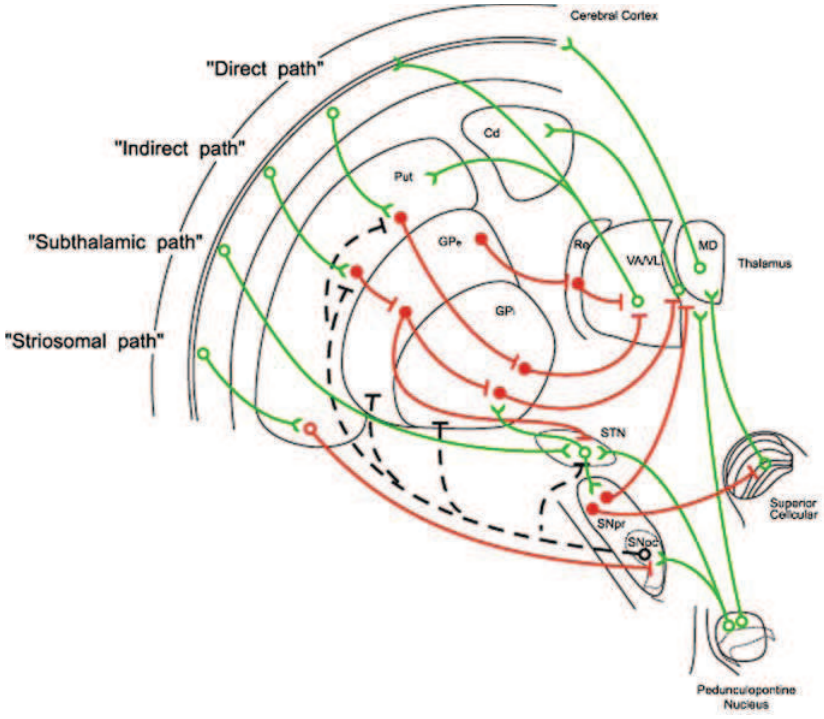


Figure 1.2 Parallel loops among the basal ganglia, thalamus and cortex. Excitatory connections are shown in green. Inhibitory connections are shown in red. The broken line illustrates the dopaminergic modulatory inputs from the substantia nigra pars compacta (SNpc) to the striatum (Put: putamen, Cd: caudate nucleus, GPe: external segment of globus pallidus, GPi: internal segment of globus pallidus, STN: subthalamic nucleus, SNpr: substantia nigra pars reticulata, VA/VL: ventral anterior/ventral lateral thalamic nuclei, MD: medial dorsal thalamic nucleus). Reproduced from [88].

to cortex (see Figure 1.2). Therefore, the BG potentially influence a wide range of behaviors.

The input anatomy of the BG provides a substrate for a wide variety of contextual information to be made available to the striatum. The major inputs to the BG are the topographically arranged glutamatergic corticostriatal and thalamostriatal fibers [2, 100]. Output from BG is composed largely of GABAergic pathways projecting from the GPi to the ventrolateral and

ventroanterior nuclei of the thalamus. In turn, the thalamus sends excitatory projections to the cortex. These thalamocortical projections are reciprocated by strongly developed corticothalamic projections [87].

Within the overall sequence of cortico-subcortico-cortical connections, three different circuits can be distinguished: the direct, indirect and hyperdirect pathways [2] (Figure 1.3).

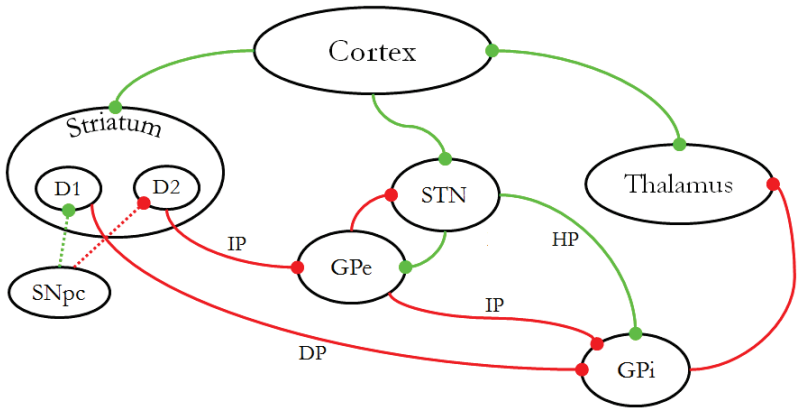


Figure 1.3 Direct(DP), indirect(IP) and hyperdirect (HP) pathways. Excitatory connections are shown in green. Inhibitory connections are shown in red. The broken line illustrates the dopaminergic modulatory inputs from the substantia nigra pars compacta (SNpc) to the striatum. Within the basal ganglia circuitry, the direct pathway (striatum-GPi) starts from the striatal neurons expressing D1 dopamine receptors, whereas the indirect pathway (striatum-GPe-GPi) starts from the striatal neurons expressing D2 dopamine receptors.The hyperdirect pathway comprises the excitatory projections from the STN to the GPi.

The *direct pathway* goes from the cortex to the striatum, from the striatal neurons to the GPi, from GPi to thalamus and from thalamic nuclei back to the cortex. Therefore it is composed of the excitatory corticostriatal, the inhibitory striatopallidal, the inhibitory pallidothalamic and the excitatory thalamocortical projections. The fibers of the corticostriatal projection exert an excitatory influence on the MSNs expressing D1 dopamine receptors that, in turn, project to the GPi, where they exert an

inhibitory influence on the constituent neurons. The efferents of the GPi, which are also inhibitory, project to the thalamus. The final link in the direct striatal circuits is formed by the excitatory projections from the thalamus to the cerebral cortex.

Therefore, when phasic excitatory inputs from the cortex transiently activate the direct pathway, the tonically active pallidal neurons are briefly suppressed, thus permitting the thalamus and cortex to become active [24]. Consequently, this produces a disinhibition (and hence an activation) of a particular behavior. In other words, the direct circuit supports thalamocortical interactions by positive feedback.

According to the classical BG model, the *indirect pathway* consists of projections from the cortex to the striatum, from striatum to GPe, from GPe to the STN, and from STN to GPi. In addition to the classical indirect pathway through the GPe and STN, it has been found that GPe sends focused projections directly to the GPi [120, 101], so that the indirect pathway consists of striatum-GPe-GPi and the STN is part of the hyperdirect pathway (described later), but also interacts with the indirect pathway at the level of the GPe. Within the pathway the fibers of the corticostriatal projection exert an excitatory influence on the MSNs expressing D2 dopamine receptors. The increased activity in these GABAergic elements leads to decreased activity of the GPe neurons. Since the efferents of the GPe are inhibitory and project to the GPi, increased activity in the indirect pathway leads to increased activity of the GPi neurons. The activation of the inhibitory neurons of the GPi reduces the thalamic activation of cortical neurons, thus providing to the thalamocortical interactions a negative feedback, which suppresses the behavior.

The most common explanation of this circuitry is that the direct and the indirect pathways operate in opposite directions and in balance. Activity in the direct pathway causes the GPi to release inhibition on the thalamus, therefore causing behavioral release. On the contrary, activity in the indirect pathway enhances GPi activity, therefore inhibiting the thalamus and

causing behavioral suppression. Consequently, the direct pathway is believed to be important for releasing wanted movements, while the indirect pathway for inhibiting closely related unwanted movements.

The interaction between direct and indirect pathways provides the basal ganglia with a function that can be referred to as action selection. Since the GPi is tonically active, it exerts a tonic inhibition on the thalamus, thus keeping all potential behaviors suppressed. When an appropriate behavior is identified within the striatum through cortical activation, tonic inhibition is reduced (through the direct pathway), but only for that selected action, which is then executed. At the same time, tonic inhibition is enhanced for the unwanted competing actions (through the indirect pathway), which are then suppressed. It has also been suggested that lateral inhibition within the striatum enhances response selection. Indeed, MSNs send inhibitory collaterals to the nearby neurons, so that strongly activated neurons inhibit those weakly activated, therefore reducing potential competitions for response selection [105, 109].

The *hyperdirect pathway* is so named because cortical activity targets the STN, which directly excites the GPi, bypassing the striatum altogether. The STN receives an excitatory, glutamatergic input from the cortex. These cortical afferents arise mainly, but not exclusively, from the primary motor, premotor and supplementary motor cortices [92]. Thus activation of the STN by the cortex leads to an increased activity of the already tonically active GPi, effectively making this last structure more inhibitory on the thalamus, and therefore less likely to facilitate a response. Indeed, when this pathway is active, it suppresses all behaviors. An important feature of this pathway is that it functions faster than the indirect pathway, because it has fewer synapses than the indirect pathway. Therefore, it is the quickest way to terminate a behavior in process of execution. In addition, this pathway is important for preventing premature responding [38] and impulse control. Indeed, stimulation of the STN pathway applies the "brake", allowing the individual to think before responding.

Basal Ganglia synaptic plasticity

The flow of information from the cerebral cortex to the striatum is modulated by dopaminergic fibres originating from the SNpc. Dopaminergic fibres are critically involved in learning, because they provide rewarding signals related to environmental and internal cues in response to a particular behavior selected through the BG. In humans, phasic bursts and dips of dopamine (DA) have been inferred to occur during positive and negative feedback of trial-and-error tasks, respectively [52]. Several lines of evidence support the notion that these changes in extracellular levels of DA during feedback are critical for learning.

Direct and indirect pathways within the basal ganglia are affected differently by the dopaminergic projections, because changes of extracellular levels of DA modify synaptic plasticity via D1 and D2 receptors [37, 45]. A well-established principle is that the synapses between two neurons that are activated simultaneously are long-term strengthened. This phenomenon is called Long-Term Potentiation (LTP). Because dopamine enhances activity in the direct pathway, dopamine bursts may induce LTP in the direct pathway cells [76]. On the contrary, since DA has an inhibitory effect on the indirect pathway, it may induce Long-Term Depression (LTD) [20, 95].

1.1.2 Cortico-Basal Ganglia loops

Information from several cortical areas is processed by the basal ganglia and sent back to the same areas. Anatomical and functional studies suggested that BG participate in five functionally segregated loops: motor, premotor, oculomotor, dorsolateral prefrontal and limbic [3, 4] (see Figure 1.4).

Since motor and premotor loops are more related to motor behavior, this section is focused primarily on the functions of these two BG subcircuits.

The *motor loop* originates from the primary motor cortex, whose projections terminate in the lateral part of the putamen [86, 125]. The lateral putamen projects to the posterolateral part

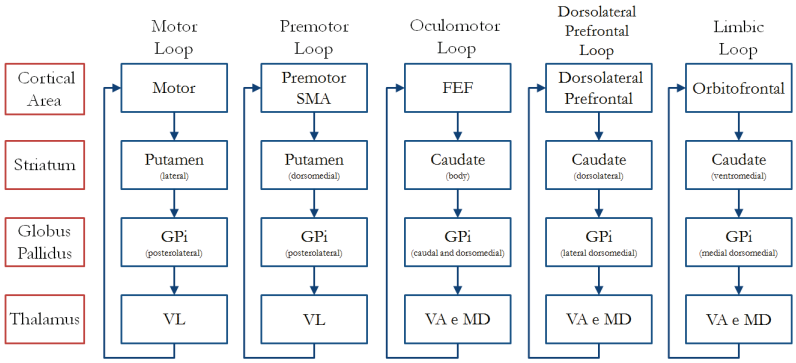


Figure 1.4 Basal ganglia loops: motor, premotor, oculomotor, dorsolateral prefrontal and limbic (FEF: frontal eye field, SMA: supplementary motor area, VL: ventrolateral, VA: ventroanterior, MD: mediodorsal).

of the GPi, which in turn projects to the anterior part of the ventral lateral thalamic nucleus [74]. Finally, this thalamic nucleus projects back to the motor cortex, completing the loop.

The *premotor loop* originates from the area 6 of Brodmann, which comprises the dorsolateral premotor, supplementary motor and presupplementary motor areas. Projections from these areas terminate in the dorsomedial zone of the putamen and the most lateral zone of the caudate nucleus [125]. The dorsolateral zone of the striatum also receives overlapping projections from parietal areas associated with somatosensory function (areas 1, 2 and 3 of Broadmann) and these projections follow the same somatotopic organization as those from the motor and premotor areas [32].

These anatomical connections suggest that motor and premotor loops mediate different aspects of motor behavior, including planning, learning, and execution [24]. It has been suggested that neuronal activity within these loops underlies procedural learning and development of "habits", in which a sequence of behaviors can be triggered by particular sets of stimuli [50, 68, 75].

The *oculomotor loop* originates from the frontal eye field and from the supplementary eye field. This loop is thought to be

involved in the control of saccadic eye movements [51].

The *dorsolateral prefrontal loop* originates principally in Brodmann's areas 9 and 46. According to the current knowledge, this loop regulates cognitive functions, such as working memory and planning the order and timing of future behaviors [99].

Finally, the *limbic loop* originates from medial and orbitofrontal cortical regions. It has been suggested that this loop is involved in mood, emotions and reward-guided choice of behaviors [31, 116].

1.1.3 Basal Ganglia function and dysfunction

The BG have been considered to be involved in motor functions for a very long time, although during the past few decades it has become increasingly clear that these group of subcortical nuclei is also involved in cognitive functions such as procedural learning and working memory. Moreover, it has been suggested that BG are involved in the pathology of a variety of psychiatric disorders [16].

One of the roles of the BG within the frontostriatal system lies in gating or selecting behaviors already processed by the cortex so that the appropriate behavior becomes active and can be expressed [37, 56, 109]. This function, referred as *action selection*, is performed through the direct and indirect pathways that, operating in concert, release the desired response and inhibit the unwanted ones.

However, pathologic lesions of specific BG nuclei impair the ability to control and initiate voluntary movements. A classic example is *Parkinson's disease* (PD), a neurodegenerative disorder characterized by difficulties in initiating and executing movements, muscular rigidity, tremor and disturbances in posture and gait. PD patients loss the dopaminergic neurons in the SNpc, which leads to a reduction in the DA content within the striatum. Loss of dopaminergic inputs to the striatum decreases activity in the direct circuit and increases activity in the indirect circuit, due to the different influence of DA on the two circuits, via

the D1-type and the D2-type receptors, respectively. Since the two circuits converge on the inhibitory BG output neurons in the GPi, lack of DA in the direct circuit leads to a decrease in the inhibition of the GPi, while lack of DA in the indirect circuit ultimately leads to an increase in the excitation of the GPi neurons. Therefore DA deficiency increases the activity of the GPi output neurons and increases the inhibition of the thalamocortical neurons on which they impinge. The resultant reduced cortical motor output explains the hypokinetic features of PD. Because of the feedback effects of DA on the synaptic plasticity in the direct and indirect pathways, PD patients are more sensitive to negative reinforcement than they are to positive rewards.

Another disorder associated with a dysfunction of the BG (particularly, with a severe atrophy of the striatum) is the *Huntington's disease* (HD). This disease is characterized by rapid, involuntary movements of the face, arms and legs and by progressive mental deterioration. It has been reported that HD first affects the indirect pathway and later the direct pathway [24].

Hemibalism is a disorder known to be caused by lesions of the STN and is characterized by vigorous involuntary movements of the extremities [44].

Finally, the BG (particularly the limbic loop) have also been associated with several mental disorders [16], in particular schizophrenia, obsessive-compulsive disorder and drug addiction, albeit this association is less compelling than in PD and HD.

1.2 The Cerebellum

The Cerebellum (Latin, "little brain") lies outside of the cerebral cortex and occupies most of the posterior cranial fossa. The cerebellum contains more neurons than the remainder of the human brain, even though it constitutes only about ten percent of its total volume [70].

The cerebellum (CB) processes information from many sources, including the spinal cord, the brain stem and the cerebral cortex,

and projects to many different centers in the brain involved in postural adaptation and movements generation. Despite its structural regularity, the CB can be divided into several distinct regions, whose function depends on the brain areas from which it receives and sends connections.

This section describes the essential features of the CB circuitry, from the main neurons composing the cerebellar cortex and deep cerebellar nuclei to the most significant connections among them. The CB functional organization and the main cerebellar afferent (mossy and climbing fibers) is also reviewed in this section, which ends with a brief description of the disorders that result from damage to particular cerebellar areas.

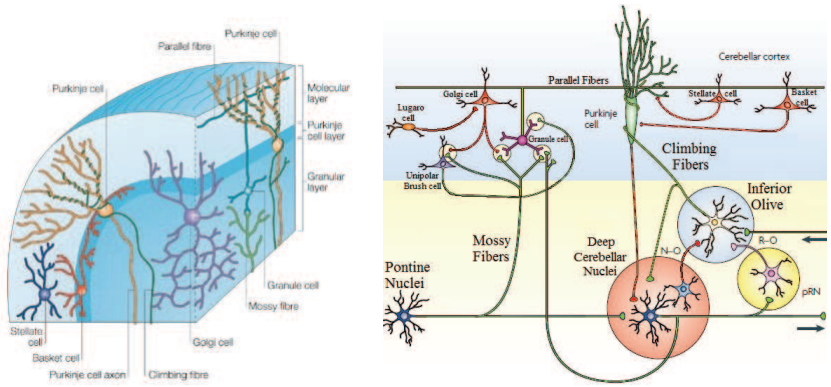
1.2.1 The anatomical structure of the Cerebellum

The CB is covered with an outer mantle of gray matter, the *cerebellar cortex*. Its internal white matter contains three pairs of deep nuclei: the *fastigial*, the *interposed* (itself composed of two nuclei, the *globose* and the *emboliform*), and the *dentate*. The CB receives two types of excitatory afferents, the *mossy fiber* (MF) and the *climbing fiber* (CF) and sends its efferents to several brain areas, from the cerebral cortex to the brain stem.

Figure 1.5 illustrates the main cerebellar circuit (composed of the cerebellar cortex and deep cerebellar nuclei), the neural connections among the neurons composing the cerebellar regions, and the main cerebellar afferent and efferent.

While the cerebral cortex is composed of six layers of specialized neurons, and the BG comprise a single layer group of nuclei, the cerebellar cortex is a three-layered structure, composed of the *molecular layer*, the *Purkinje cell layer*, and the *granular layer* (Figure 1.5(a)). These layers are composed of three types of neurons: afferent (input) neurons (*granule cells*), interneurons (*Golgi cells*, *basket cells*, *stellate cells*, *unipolar brush cells*, and *Lugaro cells*), and efferent (output) neurons (*Purkinje cells*) [15].

The *molecular layer*, the most superficial layer of the cerebellar



(a) (b)

Figure 1.5 Cerebellar Circuitry. (a) The cerebellar cortex consists of three layers: molecular, Purkinje cell and granular layer. Reproduced from [7]. (b) The cerebellar cortex receives two excitatory afferents: the mossy fibers from the precerebellar nuclei and and the climbing fibers from the inferior olive. Mossy fibers synapse to the granule cells, whose axons give rise to the parallel fibers that, in turn, excite Purkinje cells. Purkinje cells modulate the activity of the deep cerebellar nuclei, which also receive excitatory collaterals from climbing and mossy fibers. Cerebellar nuclei send back excitatory connections to the cerebellar cortex and inhibitory connections to the inferior olive. Excitatory connections are shown in green. Inhibitory connections are shown in red. Adapted from [65] (pRN: parvocellular red nucleus; N-C: nucleo-cortical projections; R-O: rubro-olivary projections).

cortex, contains the cell bodies of two types of inhibitory interneurons, the stellate and basket cells, dispersed among the excitatory axons of granule cells and the dendrites of inhibitory Purkinje cells.

Beneath the molecular layer is the *Purkinje cell layer*, consisting of a single layer of Purkinje cell bodies.

The innermost *granular layer* contains the cell bodies of Golgi cells together with a large number of the small granule cells.

The *granule cells* are the input neurons of the cerebellar cortex and their dendrites receive inputs from the mossy fibers. The total number of granule cells has been estimated to be of the order of 10^{10}-10^{11}, more than any other type of neurons. Granule cell

axons ascend toward the molecular layer, where they split into two branches that run parallel to the transverse fissures and, therefore, are called *parallel fibers* (PFs). Parallel fibers pass through the dendrites of the Purkinje cells, which in turn project to the deep cerebellar nuclei. The ratio of granule cells to Purkinje cells is of the order of $5,000$ to 1, but estimates vary appreciably.

The *Purkinje cells* (PCs), which integrate information from both the mossy fiber and climbing fiber inputs, are the sole output element of the cerebellar cortex and represent the fundamental information-processing units of the CB. These neurons are approximately $1,500,000$ in cats and $15,000,000$ in humans. PCs are inhibitory and use GABA as their neurotransmitter [66], have large cell bodies and their dendritic arborization extends upward into the molecular layer. The distal dendritic branches are covered with spines, with which excitatory parallel fibers make contact. PCs activity is also influenced by the feed-forward inhibition of the basket and stellate interneurons, which terminates around proximal and distal portion of PCs dentritic tree, respectively. PCs axons traverse the white matter and terminate on neurons of the deep cerebellar nuclei, therefore modulating their activity. A single PC may contact approximately 35 nuclear cells.

The *basket cells* (BCs) and *stellate cells* (SCs), which lie in the molecular layer and inhibit the activity of the PCs, are GABAergic interneurons. The SCs have a cell body and a dendritic arborization that is smaller than those of the BCs. These interneurons receive synapses mainly from PFs, even though the PFs that synapse with basket and stellate cells may not necessarily be the same ones that synapse with PCs. Basket and stellate cell axons synapse principally with PCs in its immediate vicinity. The SC axons form synapses only on dendritic shafts of PCs, whereas BCs synapse primarily around the proximal dendrite and cell body of PCs, but they also synapses with terminal brush around the initial segment of the PCs axon. BCs axons make synaptic contact with an average (in the cat) of about 30 PCs, whereas the ratio of stellate to Purkinje cells is estimated to be about 1:17.

The *Golgi cells* represent another type of inhibitory

interneurons located in the granular layer. Their number approximates that of the PCs. The Golgi cells have elaborate dendritic trees that extend in all directions into the molecular layer (about three times as far as the Purkinje dendritic trees) rather than being confined to the transverse plane of the folium, as is the case for the Purkinje, stellate, and basket cells. PFs form excitatory synapses with the Golgi cells dendrites, which are also contacted by other afferent (e.g., Golgi cell dendrites that remain in the granular layer may be contacted by mossy fibers directly). Moreover, recurrent Purkinje axons synapse onto Golgi somata. The GABAergic terminals of Golgi cells make synaptic contacts with dendrites of granule cells at the glomeruli. Golgi cell firing, initiated by firing in the parallel fibers, suppresses mossy fiber excitation of the granule cells and thus tends to shorten the duration of bursts in the parallel fibers, providing feedback inhibition to the granule cells. The granule cell to Golgi cell ratio is of the order of $5,000$ to 1.

Unipolar brush cells (UBs), which have recently been identified, are located in the granular layer of certain lobules. These neurons emit a single dendrite that ends in a brush, which forms a large glutaminergic (excitatory) synapse with an afferent mossy fiber terminal [96]. A single mossy fiber stimulus evokes a prolonged train of action potentials in the UB, which is presumably distributed to the postsynaptic targets [96]. Inhibitory input to the UBs originates from inhibitory Golgi cell axons. UBs axons terminate on granule cell dendrites, similar to the mossy fiber afferent.

Another important region of the cerebellum, which constitutes the only cerebellar output, is composed of the *cerebellar nuclei*. The cerebellar nuclei are embedded deep within the white matter of the cerebellum. There are four pairs of deep cerebellar nuclei, represented bilaterally on each side of the CB midline: the fastigial, the interpositus (composed of the globose and emboliform nuclei), and the dentate nuclei.

The fastigial nucleus receives input from the vermis, whereas the interpositus nucleus receives input from the intermediate zones

of the cerebellum. Finally the dentate, which is the largest of the cerebellar nuclei, is located laterally and receives input from the lateral cerebellar hemispheres.

The cerebellar nuclei contain three types of neurons. Excitatory (glutamatergic) neurons of different size give rise to axons that terminate in widely different regions, extending from the spinal cord to the thalamus. Some of their collaterals feed back into the cerebellar cortex as mossy fibers. Small GABAergic neurons give rise to the nucleo-olivary pathway [93, 111]. Interneurons have been identified as mainly small GABAergic and glycinergic neurons [21].

Cerebellar afferent systems: Mossy and Climbing fibers

As already mentioned, there are primarily two kinds of afferent fibers to the cerebellar cortex: the mossy fibers (that give rise, through the granule cells, to the parallel fibers) and the climbing fibers. Both groups of fibers form excitatory synapses with cerebellar neurons, but terminate differently in the cerebellar cortex and produce different patterns of firing in the Purkinje neurons. The primary and secondary dendritic branches of Purkinje cells receive climbing fibers, whereas the tertiary "spiny branchlets" are the site of parallel fiber synapses [62]. Mossy and climbing fibers also give off collaterals to the cerebellar nuclei. The geometry of these principal connections - the mossy, parallel and climbing fiber systems - is shown in Figure 1.5 and 1.6.

Mossy fibers are thick and heavily myelinated fibers that mostly originate outside the cerebellum, from the spinal cord, brain stem and pons, as shown in Figure 1.6. Consequently, mossy fibers carry sensory information from the periphery as well as from the cerebral cortex. Mossy fibers enter the cerebellum through the middle cerebellar peduncle and terminate as excitatory glutaminergic synapses onto the somata of Golgi cells and on the dendrites of granule cells in the granular layer (Figure 1.5). One mossy fiber has been estimated to make contact with some 450 granule cells.

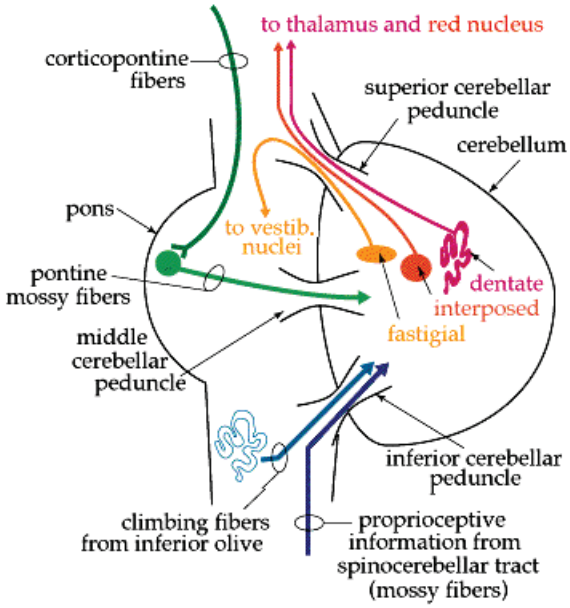


Figure 1.6 Cerebellar afferent and efferent fibers. Input to and output from the cerebellum pass through the cerebellar peduncles (inferior, middle and superior). The inferior cerebellar peduncle contains the spinocerebellar (mossy fibers) and olivocerebellar (climbing fibers) tracts. The middle cerebellar peduncle contains the pontocerebellar (mossy fibers) tracts. The superior cerebellar peduncle contains the efferent projections of the cerebellar nuclei.

The mossy fibers indirectly excite the dendritic trees of Purkinje cells via the dendritic glomeruli of the granule cells and their axonal branches in the form of the *parallel fibers*. Indeed, the unmyelinated (or thinly myelinated) axons of granule cells ascend into the molecular layer and terminate with excitatory (glutamatergic) synapses on the spiny branchlets of Purkinje cell dendrites and on the dendrites of cortical interneurons (stellate, basket, and Golgi cells) they meet on their way. A given Purkinje cell is under the influence of a large number of granule cells, each collecting input from many mossy fibers. In humans each Purkinje cell receives inputs from as many as 200,000 parallel fibers [36]. Purkinje cells are, therefore, in a position to integrate very

considerable information from a wide range of sources. Conversely, a given parallel fiber has been estimated to pass through from 450 to 1,100 Purkinje cells along a folium, but if synapses are made with only one in three to five Purkinje cells, the number could decrease to about 100 or even less.

The parallel fibers are the main determinant of the firing rate of the Purkinje cells. Parallel fibers produce a brief excitatory postsynaptic potential on the Purkinje cells that generates a single action potential or *simple spike*. Consequently, spatial and temporal summation of inputs from several parallel fibers is necessary before the Purkinje cell will fire. Somatosensory, vestibular, and other input stimuli change the frequency of the simple spikes, which may reach several hundred spikes per second. Since voluntary movements are associated with a marked change in frequency, the frequency of simple spikes can readily encode the magnitude and duration of peripheral stimuli or centrally generated behaviors.

The climbing fibers constitute the second, main afferent system of the cerebellar cortex. Moderately thin and myelinated, climbing fibers originate from the inferior olivary nuclei and convey somatosensory, visual, and other cortical information. The terminals of the climbing fibers in the cerebellar cortex are arranged topographically. Each subnucleus of the inferior olive innervates one to three Purkinje cell zones and provides their cerebellar target nucleus with a collateral projection [17, 103, 124]. The climbing fibers are so named because they wrap around the cell bodies and proximal dendrites of Purkinje neurons like a vine on a tree, making numerous synaptic contacts. Indeed, each adult Purkinje cell receives input from only one climbing fiber, which terminates with multiple, excitatory (glutamatergic) synapses on the proximal branches of its dendritic tree, thus forming the basis of an extensive and powerful excitatory synaptic action. Each climbing fiber contacts as many as 10 Purkinje neurons [123]. In humans there is a total of about 1 million neurons for both inferior olives, as compared with about 15 million Purkinje cells, for a ratio of 1 to 15.

Climbing fibers have unusually powerful synaptic effect on Purkinje neurons. Each action potential in a climbing fiber evokes a strong depolarization of Purkinje cells, resulting in an initial large-amplitude spike followed by a high-frequency burst of one to five smaller-amplitude action potentials, called *complex spike*. However, olivocerebellar fibers only conduct impulses at a very slow rate (less than 10 Hz) and the overall contribution of the climbing fibers to the firing rate of the Purkinje cells is small.

Cerebellar synaptic plasticity

Within the cerebellar cortex, the synaptic connections between the parallel fibers and dendrites of the Purkinje cells show a remarkable plasticity. According to the theories of Marr [83] and Albus [1], altering the strength of certain parallel fiber-Purkinje cell synapses would select specific Purkinje cells to program or correct eye or limb movements. Different types of synaptic plasticity within the cerebellum were reviewed by Hansel [47], albeit LTD mechanism in the parallel fiber-Purkinje cell synapses has been studied most extensively. It has been shown [64] that during the execution of movements the climbing fibers would provide an error signal that would depress parallel fibers that are active concurrently, inducing selective LTD in the synaptic strength of parallel fiber-Purkinje cell. However, for this depression to occur, the parallel fiber's simple spike must occur within some 100-200 ms of the climbing fiber's complex spike. Therefore, as learning occurs, the effects of parallel fiber inputs associated with a wrong central command would increasingly be suppressed and a more appropriate pattern of activity would emerge over time, allowing "correct" movements to emerge. The long-term effect of the climbing fiber on the transmission of signals from parallel fibers to Purkinje cells sculpts the cerebellar cortical network according to previous experience and, most likely, forms the basis for one of the main function of the cerebellum, the optimization of movements.

1.2.2 Cortico-Cerebellar loops

The cerebellum is characterized by two features, its uniformity and simplicity (only five basic types of neurons and only two major input channels: mossy and climbing fibers). Cerebellar neurons are arranged in a highly regular manner as repeating units, each of which is a basic circuit module. The cerebellar cortex is uniform throughout the cerebellum, therefore it can be divided into a number of independent zones, termed *microzones*, consisting of a certain number of Purkinje cells. Each microzone projects to a distinct group of nuclear neurons, forming a *microcomplex*, the operational unit of the cerebellum [62]. Each microzone receives inputs from mossy and climbing fibers, which also supply collaterals to the corresponding nuclear cell group. Within the projections of a microzone to a cerebellar nucleus there is a strong convergence of a large number of Purkinje cells to a much smaller number of nuclear cells. The output of each microcomplex is provided by the deep nuclear cells.

Since the cerebellar circuitry is remarkably uniform, it can be hypothesized that the cerebellum performs the same operation on whatever afferent information it receives. Therefore, functional differentiation depends largely or exclusively on the diverse nature and origin of inputs. The cerebellum has widespread reciprocal connections to most regions of the cerebral cortex [115]. These reciprocal or reentrant connections, or "loops" of interaction place the cerebellum in an anatomic position to modulate or regulate neural activity in most other parts of the brain [56]. The routes of all nerve fibers to and from the cerebellum pass through the cerebellar peduncles: the inferior cerebellar peduncle, the middle cerebellar peduncle, and the superior cerebellar peduncle.

The *inferior cerebellar peduncle* contains the spinocerebellar and olivocerebellar tracts.

The *middle cerebellar peduncle* is the largest afferent system of the cerebellum and contains the mossy fibers arising from the pontine nuclei.

The *superior cerebellar peduncle* contains most of the efferent

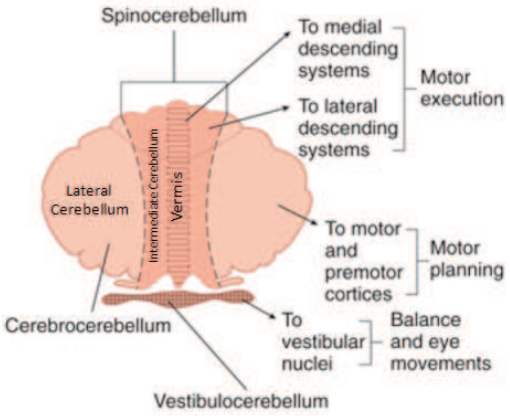


Figure 1.7 Functional divisions of the cerebellum. The vestibulocerebellum receives reentrant connections from the vestibular nuclei and coordinates movements of the head and eyes in relation to body position. The spinocerebellum (comprising the vermis and intermediate part of the cerebellar hemispheres) receives reentrant connections from the cortex and the spinal cord. The spinocerebellum is involved in motor execution. The cerebrocerebellum comprises the lateral part of the cerebellar hemispheres and receives inputs from the pontine nuclei. The cerebrocerebellum is concerned with planning, initiation, and timing of movements.

projections of the cerebellum, which arise from the cerebellar nuclei.

Different, functional regions have been recognized in the cerebellum, each having its distinctive connections with the cortex and spinal cord: the vestibulocerebellum, the spinocerebellum and the cerebrocerebellum [70] (Figure 1.7).

The *vestibulocerebellum* receives information via the mossy fibers arising from neurons in the vestibular nuclei. The vestibulocerebellar cortex also receives visual input from the superior colliculi and from the striate cortex. Purkinje neurons in the vestibulocerebellum project back directly to the vestibular nuclei. In conjunction with the vestibular nuclei, the vestibulocerebellum coordinates movements of the head and eyes in relation to body position and controls axial muscles and limb extensors, controlling balance during gait.

The *spinocerebellum*, so named because much of its input originates from the spinal cord, comprises the medial (vermis) and intermediate parts of the cerebellar hemispheres. The spinocerebellum receives inputs from the sensorimotor cortex and information from the periphery though the spinal cord. Purkinje neurons in the spinocerebellum project somatotopically to the fastigial and interposed nuclei, which control various components of the descending motor pathways. Indeed, both nuclei project to the limb control areas of the primary motor cortex through the ventrolateral nucleus of the thalamus. Some axons of the interposed nucleus also terminate in the magnocellular portion of the red nucleus, whose axons descend to the spinal cord. The spinocerebellum controls the more distal muscles of the limbs and fingers, but it also governs posture, locomotion and gaze.

The *cerebrocerebellum* comprises the lateral part of the cerebellar hemispheres and is the largest part of the cerebellar cortex. The cerebrocerebellum receives inputs from the pontine nuclei, which relay information from several cortical areas, such as sensory, motor and premotor, and posterior parietal cortex. Cortical inputs terminate as mossy fibers in the lateral cerebellar cortex (and also give off collaterals to the contralateral dentate nucleus). Purkinje cells in the lateral cerebellar cortex, in turn, inhibit the dentate nucleus. Most dentate axons exit the cerebellum via the superior cerebellar peduncle and project primarily via the contralateral ventrolateral thalamus to primary motor, premotor and supplementary motor areas of the cerebral cortex. Visual and visuomotor areas also contribute substantially to the corticopontine projections [18, 42, 114]. Frontal areas that give rise to corticopontine projections receive projections from the contralateral cerebellar nuclei. Extensive areas in the parietal and occipital lobes, which project to the pontine nuclei, seem to lack cerebellar nuclear afferents. Dentate neurons also form inhibitory synapses with olivary neurons. The distribution of these dentato-olivary fibers reciprocates the collateral projections of the subnuclei of the inferior olive to the dentate [23, 93, 111, 112]. The inferior olivary nucleus, which also receives excitatory afferents

that convey somatosensory, vestibular, visual and optokinetic information [110], projects back to the contralateral cerebellum through the climbing fibers, thus forming a feedback loop. In relation to motor control, the cerebrocerebellum is considered to be concerned with planning, initiation, and timing of movements. Recent imaging data indicate that the cerebrocerebellum is intimately involved in planning and mental rehearsal of complex motor actions and in the conscious assessment of movement errors.

1.2.3 Cerebellar function and dysfunction

Marr [83] and Albus [1] were the first to independently suggest that cerebellar cortical circuits might be used in learning motor skills. It is agreed that the neuroanatomical infrastructure of the cerebellum suggests that it controls the quality of behavioral output, modulating the cortical signals and sending them back to the cortex. In other words, the cerebellum does not function as a primary sensory processor or generator of behavior, but rather it functions as a modulator of behavior. Indeed, the organization of cerebellar afferents and efferents indicates that the cerebellum evaluates the discrepancy between the intended and actual movement. This comparison allows the cerebellum to adjust a movement in progress modulating the activation of motor centers in the cortex and brain stem. This function is accomplished through the mechanism of synaptic plasticity within the cerebellar cortex. In this way, during repetitions of the same movement, the cerebellum generates feed-forward corrective signals. In accordance with this idea, climbing fibers detect differences between expected and actual sensory inputs rather than simply monitoring afferent information.

Several authors [27] have also suggested that the cerebellum is involved in motor adaptation. It has been shown that patients affected by cerebellar degeneration are severely impaired or unable to adapt at all [119]. Moreover, it has been shown [61] that the vestibulocerebellum plays an important role in the vestibulo-ocular reflex (a coordinated response that maintains the eyes on a

fixed target when the head is rotated). Indeed, disruption of this area through lesions or disease impairs this adaptation.

The cerebellum's contribution to motor adaptation may occur also in certain forms of associative learning. Indeed, lesions of the cerebellum in rabbits disrupt the acquisition and retention of a classically conditioned eyeblink reflex [134].

Moreover, lesions of the cerebellum impair motor learning and certain cognitive functions, resulting in distinctive symptoms and signs [41, 81]. Damage to the cerebellum usually results in a disruption of the spatial accuracy and temporal coordination of movements, known as *cerebellar ataxia*. Cerebellar dysfunction also results in variable delays in initiating movements, loss of precision in muscle contraction, movement overshoot or undershoot (*dysmetria*), intention tremors (irregular oscillations at the end of a movement, in the proximity of the target) and errors in the rate and regularity of movements. Another category of symptoms associated to cerebellar disfunctions is the *hypotonia*, a diminished resistance to passive limb displacements.

The laterality and localization of symptoms are usually in accordance with the known anatomy of the input and output channels of the cerebellum. Indeed, the nature of any observed deficit depends on the specific focal region of the cerebellum that is affected.

Focusing on the lateral cerebellar hemispheres, lesions of these areas result in variable delays in initiating movement and disrupt the timing of movement components, which appear to take place sequentially rather than being coordinated smoothly (this defect is called *decomposition of movement*). Patients affected by cerebrocerebellum damages are impaired in decomposition of multi-joint movements, in which the motions of each joint are coordinated precisely one with another. These patients cannot move all limb segments together in a coordinated fashion, but instead move one joint at a time [81]. The same defect is seen in primates with lesions of the dentate nucleus, which receives afferent from the lateral cerebellar cortex [22, 130].

1.3 Anatomical connections and functional interactions between the Basal Ganglia and Cerebellum

The basal ganglia and cerebellum are densely interconnected with the cerebral cortex. Indeed, the basal ganglia receive a large number of reentrant connections from the cerebral cortex. Cortical projections terminates in the striatum and the basal ganglia project back to the same cortical regions through the internal segment of the globus pallidus and the ventroanterior and ventrolateral thalamic regions. Similarly, the cerebellar cortex receives cortical projections and projects back, via the deep cerebellar nuclei and the thalamus, to the same cortical regions.

Until recently, basal ganglia and cerebellar loops have been assumed to be anatomically separated and perform distinct functional operations [26]. In this way, specific behaviors or functions would be realized by a combination of multiple distributed modules (cortical-basal ganglionic modules, cortical-cerebellar modules and cortical-cortical and their associated cortical-thalamic modules) that interact at the cortical level [58].

Many brain-imaging experiments have revealed that different parts of the cerebellum, basal ganglia and cerebral cortex are activated simultaneously. These results led to investigate the existence of directs routes between the basal ganglia and cerebellum that are independent of the cerebral cortex. In their experiments, Strick and colleagues [14, 54] injected the rabies virus into selected regions of the brain in cebus and macaque monkeys and used transneuronal transport of the virus to determine the origin of multisynaptic inputs to the injection sites. Using this approach they reached two important results. In the former work [54] they found a disynaptic pathway, linking an output stage of cerebellar processing, the dentate nucleus, with an input stage of basal ganglia processing, the striatum. Particularly, they found a projection from the dentate nucleus to the striatal MSNs that innervate GPe (i.e. a projection from an output nucleus of the

cerebellum to the "indirect" pathway of the basal ganglia). In the latter [14] they found a disynaptic pathway from the subthalamic nucleus (in the basal ganglia) to the cerebellar cortex. They also observed that this connection was topographically organized.

These results provide the anatomical substrate for a substantial two-way communication between the basal ganglia and cerebellum and lead to the possibility that cerebellum adaptively adjusts the basal ganglia activity on the basis of some error signals, in a manner similar to the cerebellar mechanisms for adjusting voluntary movements.

Chapter 2

The role of the Basal Ganglia and Cerebellum in motor learning: a new hypothesis

According to the daily experience, a coordinated sequence of "elementary" movements is acquired and executed faster and more accurately the more it is practiced. However, early in learning actions are attentionally demanding, slower and less accurate. After long-term practice of the motor sequence, the performance becomes quick, movements are smooth, automatic, and can be performed effortlessly, using minimal cognitive resources. Consequently, when a behavior becomes automatic, it can be executed successfully while performing a secondary task.

What are the brain areas involved in this process? At what stage of motor learning a particular cortical or subcortical region plays a key role?

In order to address these questions, we suggest a new hypothesis about the processes occurring during the acquisition of novel motor skills.

The process that allows humans to acquire a novel motor skill can

be divided into two distinct phases:

- During the early, fast learning stage, humans learn the spatial sequence associated to the motor task in visual coordinates, i.e. the sequence of points to reach in order to realize the task.

- During the late, automatic phase, the sequence of motor commands in motor coordinates is acquired and comes to be executed as a single behavior.

Based on this hypothesis, we propose a neural scheme for the acquisition and retention of motor behaviors. In this chapter we describe the hypothesis behind the neural scheme for procedural learning here proposed and analyze the results provided by studies on motor learning and motor adaptation.

2.1 How do humans learn a novel motor skill?

Studies on motor control have shown that selection, execution and learning of movements needed to perform a skilled task involve several brain areas and motor subsystems, but their activation and cooperation depend on the kind of movements that are being made and on the effector that is being used [71]. For instance, a highly trained motor skill, such as handwriting, is produced through a perception/action cycle, involving brain areas implicated in attentive vision, learning, control and coordination of several motor subsystems [43].

According to these studies, a motor skill is acquired after repeated practice and can be seen as a sequence of elementary actions, combined in the appropriate order to achieve a particular goal. For example, writing a cursive word is a complex sequential procedure and, on the basis of studies in handwriting generation, the complex movement needed to generate handwriting results from concatenation of elementary movements [104].

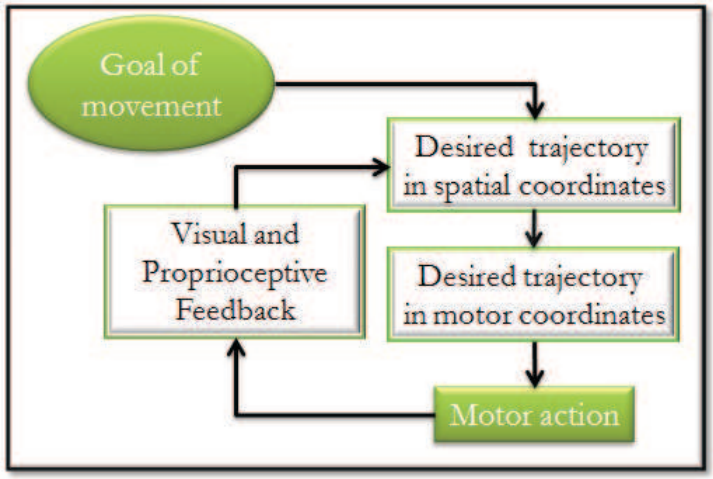


Figure 2.1 Execution of an elementary motor action, as proposed by Kawato [71]. An elementary motor action is performed following a sensorimotor transformation process in which the location of the target, encoded in trajectory coordinates, is converted into a motor command. Information provided by the visuo-proprioceptive feedback guides learning.

Kawato suggested that each elementary motor action is performed following a sensorimotor transformation process in which the location of the target, encoded in trajectory coordinates, is converted into information suitable for the motor system [71] (see Figure 2.1). However, this process involves a large amount of computation, especially for more complex actions, so it is extremely demanding for the brain to carry out the serial sensorimotor process precisely. Accordingly, the first phase of learning is characterized by slower and attention demanding actions that rely on visual and proprioceptive feedback. Indeed, even a simple task such as reaching for a glass of water requires visual and proprioceptive information to establish an internal representation of the location of the glass and arm, respectively. This process allows humans to select the appropriate motor commands. In more complex tasks the feedback information allows humans to correct, trial by trial, the trajectory and motor plans, in order to perform the task more efficiently, adopting a

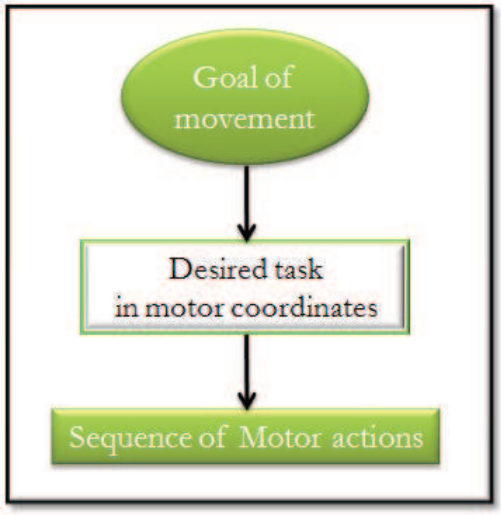


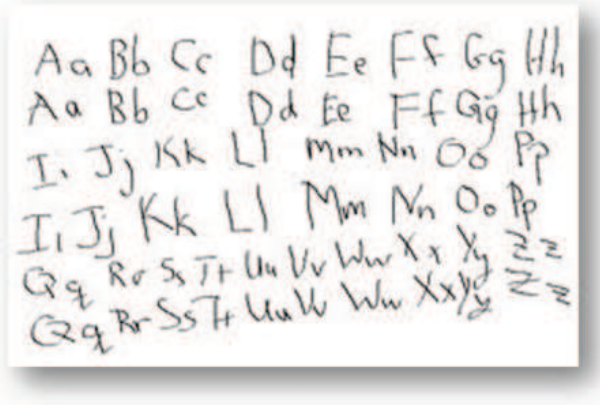
Figure 2.2 Execution of a well-learned sequence of motor actions. After long-term practice of the motor task, the sequence of motor commands comes to be executed as a single behavior.

coordination and control solution more accurate in terms of the motor production and more economical in terms of the metabolic energy expenditure. In their study, Sparrow and Newell [122] explored the hypothesis that adaptive movement patterns emerged as a function of the organism's propensity to conserve metabolic energy. Their study showed that metabolic energy regulation is a fundamental principle underlying learning and control of motor skills.

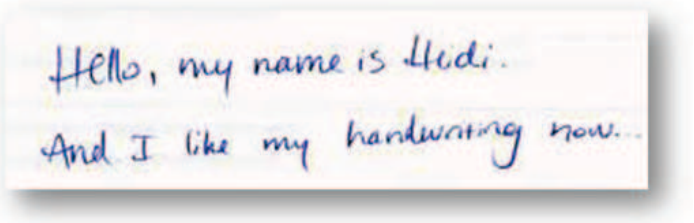
However, after long-term practice, performance becomes quick, less metabolic energy is consumed, and the sequence becomes automatic, with anticipatory movements, and with little or no thought needed to complete it.

Following these considerations, it can be suggested that when a skill is acquired, the sequence of movements is learned as a single behavior and there is no more need for the visuo-proprioceptive feedback and the sensorimotor transformation (Figure 2.2).

Indeed, when a child starts learning handwriting by copying letters or words, he attempts several trajectory patterns in order



(a)



(b)

Figure 2.3 Handwriting samples. (a) Sample of handwriting written by a child; movements are quite straight and aimed to reach a sequence of points. (b) Sample of handwriting written by a skilled writer; movements are continuous, curved and smoother.

to replicate the same shape of the letters, selecting the points to reach through the visual system, and performing the appropriate sequence of movements through the motor system. During the initial phase of learning movements are quite straight and aimed to reach a sequence of points (as in Figure 2.3(a)). In addition, the action plan is corrected according to the information provided by visual and proprioceptive feedback so that the actual trajectory corresponds to the desired one, and the lowest energy is spent by the muscular subsystem involved [122]. As learning proceed, simple point-to-point movements become continuous, curved and

smoother, the motor sequence comes to be executed as a single behavior and is performed automatically, using minimal cognitive resources (as in Figure 2.3(b)).

These results give rise to the hypothesis that learning novel motor skills requires two phases, in which two different processes occur.

There is also strong evidence, supported by the results of several experimental studies on motor learning, that a given sequence of actions is learned from different perspectives: as a sequence in visual coordinates (the spatial sequence of points to reach) and as a sequence in motor coordinates (the sequence of motor commands to perform). Indeed, it has been observed, first by Lashley [78] and then by Hebb [48], that a generic movement, learned with one extremity, can be executed by different effectors.

Furthermore, studies on motor control and learning showed that writing movements learned through the dominant hand could be repeated using different body parts, such as non-dominant hand, the mouth (with the pen gripped by teeth) and foot (with the pen attached to it), even if the subject had essentially no previous experience writing with any of this body parts [106, 131]. Despite the different muscle and skeletal systems used and, even though the movements are not smooth, in the results reported by Raibert [106] it can be observed that the writing production follows the same trajectory in all conditions (see Figure 2.4).

The ability to perform the same movement pattern by different muscular systems is called *"motor equivalence"*. It suggests that movements directed to perform a task are stored in the brain in two ways: in an abstract form (effector-independent) related to the spatial sequence of points representing the trajectory plan, and as a sequence of motor commands (effector-dependent) directed to obtain particular muscular contractions and articulatory movements.

Other studies on motor learning showed that when the untrained hand is used to perform a given sequence, learned with long-term practice with the other hand, performances are poor, but this is not true for a newly learned sequence [108], supporting

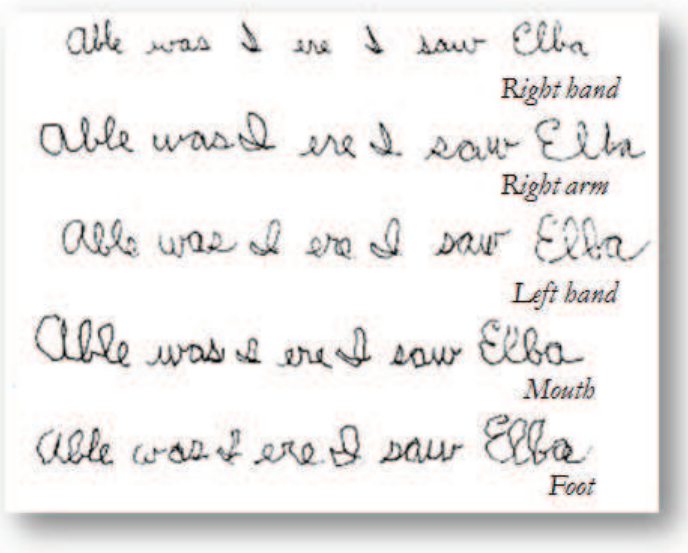


Figure 2.4 Writing samples written by the same subject. Each row shows a sentence written by using different body parts: dominant (right) hand, right arm, non-dominant hand, the mouth (with the pen gripped by teeth) and foot (with the pen attached to it). Reproduced from [106].

the hypothesis that early in learning the execution of a motor task is more based upon the trajectory plan, whereas late in learning upon the sequence of motor commands.

This hypothesis is incorporated in the neural scheme for learning sequential procedures proposed by Hikosaka and colleagues [49].

Other studies have suggested that motor sequence learning is characterized as having an explicit component (acquisition of the order of the elements in the sequence) as well as an implicit mechanism for learning how to produce the movement fast and accurately and combine them into a single behavior [39].

These results give rise to the hypothesis that, in the first stage of learning, a motor skill is acquired as a sequence of spatial coordinates converted into motor commands and, as learning proceeds, the sequence of motor commands is acquired and it

comes to be executed as a single behavior.

2.2 Analysis of experimental studies on motor learning

Experimental studies on motor learning showed that several cortical and subcortical structures, including the basal ganglia, cerebellum, and motor cortical regions, play a crucial role in different stages and aspects of the acquisition and/or retention of skilled motor behaviors.

Using different approaches, several authors investigated the functional anatomy and the cerebral plasticity associated with motor skill learning. These studies used brain imaging techniques (such as fMRI, PET, and EEG) in healthy subjects to track the time course of cerebral activation during extended practice of a motor sequence. With the same aim, other studies analyzed motor performances of patients affected by cerebral damage during the execution and acquisition of a motor task. The analysis of the results obtained from these studies gives some clues to understand the role of different brain areas in distinct phases of motor learning.

Evidence supporting the involvement of basal ganglia and cerebellum in motor learning comes from the results of neuroimaging studies, which reported the activation of these subcortical structures during execution and learning of motor tasks. Further evidence comes from impairments found in patients with BG dysfunctions (e.g. Parkinson's disease and Huntington disease), with cerebellar damage and from lesion experiments in primates.

On the basis of the training paradigm employed and form of learning used, the studies here analyzed can be classified as follows:

1. Explicit learning of a sequence of finger movements (keypress sequence). In these studies subjects have to learn a sequence of movements through extended practice, having complete declarative knowledge of the sequence [27, 28, 79, 102];

2. Implicit learning of a sequence of finger movements (keypress sequence) by trial and error. In these studies subjects have to acquire a sequence of movements through practice without prior knowledge of the sequence [67, 68, 69, 127];

3. Learning to track a sequence demanding variable isometric force development between the finger and thumb [34, 35];

4. Learning and retention of visuomotor sequences after deep cerebellar nuclei lesions [80] and after striatal inactivation [90].

5. Motor adaptation task. In these studies participants have to:

   - reach target points on a screen moving a cursor through a joystick. They have to adapt their movements when changes in the relation between the movements of the joystick and cursor are imposed by the experimenter [33, 59];
   - point visual targets through a robotic arm. They have to adapt their movements when a force field is applied to the robotic arm. These studies involve healthy subjects [94, 117] as well as HD patients and patients with cerebellar degeneration [119].

In order to outline an hypothetical neural scheme for the acquisition and retention of motor skills, next subsections analyze the results of these studies, with a particular attention paid to the basal ganglia and cerebellum.

2.2.1 Procedural motor learning

On the basis of the motor performance, results obtained from the studies in procedural motor learning (mentioned under points 1 to 4 above) showed that the learning process can be divided into distinct phases: an early, fast learning stage, in which there is a considerable improvement in performance that occurs

within a single training session; a later, slow stage, in which further gain can be seen across several session of practice; and an automatic phase, during which the skilled behavior requires minimal cognitive resources and is resistant to interference.

Lehéricy and colleagues [79], using functional magnetic resonance imaging (fMRI) at high field (3T) in humans, tracked the time course of changes in activation of cerebral areas during extended practice (4 weeks) of an explicit known sequence of finger movements. Subjects were scanned three times (on days 1, 14 and 28) and they practiced the sequence 15 minutes daily with the left hand. Performances were evaluated through reaction time and error rate. With regard to the motor performances, reaction times decreased rapidly and significantly over the 10 epochs of the first run (30 min) and remained unchanged afterward, whereas the percentage of errors decreased more slowly and regularly over the 3 fMRI sessions. Their results showed a dynamic shift of activity from the associative striatum (caudate nucleus) to the sensorimotor striatum (putamen). They also found bilateral activation in lobules V and VI of the cerebellar hemisphere, the pons, and in the left dentate nucleus during the first session (90 min). This activation decreased over a month of practice. Their results suggest that the associative cortico-basal ganglia circuit is engaged at the beginning of learning, and contributes to the acquisition of an accurate representation of the sequence, whereas the sensorimotor cortico-basal ganglia circuit is involved in maintaining a speedy representation of the skill after learning, when performance becomes automatic. Furthermore, since the activation in lobule VI is proportional to performance accuracy, it can be suggested that the lateral cerebellar cortex is critical for building up an accurate motor sequence routine. An additional increase in signal was observed in the right dentate nucleus, but this increase is transient (between 10 and 20 minutes of practice).

Doyon and colleagues [28] investigated the time course of changes in activation of human's cerebellar cortex and nuclei during learning of an explicit known sequence of finger movements (all subjects memorized the sequence before scanning), using their

right hand. In their study, subjects performed the task for 9 hours and were scanned using fMRI (1.5T) during three sessions. Each scanning session lasted 2 hours, with a 30 minutes practice session between first and second session, and between second and third session. Performances were evaluated through reaction time, which showed a significant reduction between subsequent sessions, but did not reach a plateau. With regard to the neural activations, they found a significant activation in the cerebellar lobule V and CRUS I, mainly on the right, in session 1 and 2, but with a significant decrease in the activated area. By contrast, they measured increased activity in the right cerebellar dentate nucleus from session 1 to session 2, followed by a decline in session 3, with simultaneous increased activity in the putamen. Their results suggest that in the early phase of learning there is recruitment of the cerebellar cortex, mainly ipsilateral to the hand used, but its contribution declines as proficiency at performing the task improves. By contrast, improved performance is associated with recruitment of the dentate nucleus, suggesting a transfer of plasticity in the neural representation of the motor sequence from the cerebellar cortex to the deep cerebellar nuclei.

Park and colleagues [102] used fMRI (3T) in humans to track the changes in the neural activation during the early motor learning and early automatization period (the scanning session lasted 8 min) of an explicit known sequence of finger movements, using the left hand. Performances were measured in terms of movement time and accuracy (number of correct push-button responses). Early in learning (from block 1 to block 4) they found a significant improvement in performance, whereas in the automatization phase (from block 5 to 8) performance reached a plateau. Their results showed increased cortical activity during the early stage of learning (motor, premotor, supplementary motor and posterior parietal cortices) that decreased late in learning, with concurrent increased activity in the dentato-thalamo-striatal circuit. According to the neural activations reported in this study, it can be suggested that the development of movement automaticity is associated with increased activity in the ipsilateral

cerebellum (with the peak of activation in the dentate nucleus) and in the basal ganglia. Their findings support the notion that the cerebellar cortex is more involved during learning, whereas the dentate nucleus is recruited when automaticity is achieved.

Jenkins and colleagues [67], using Positron Emission Tomography (PET), measured the changes in brain activity occurring during implicit learning of a keypress sequence by trial and error, using auditory feedback. Subjects used their right hand and were scanned in three different conditions: 1) resting condition, 2) while performing a sequence that was practiced 90 minutes before scanning until they could perform it automatically, and 3) during learning of a new sequence by trial and error. Each session lasted 3.5 minutes. Learning performances were evaluated through the error rate. For each subsequent trial of the new sequence, they found a progressively diminishing error rate, even if the lowest mean error rate was still much greater than that found for the prelearned sequence. Their imaging data showed that the cerebellar cortex was active during both new sequence learning and automatic execution, with a more extensive activation during new learning. This pattern of activation was also found in the cerebellar nuclei. These results are in contrast to the known inhibitory connections between cerebellar cortex (Purkinje cells) and cerebellar nuclei. An explanation of this apparent contradiction is that changes in cerebral blood flow are thought to be related to synaptic activity [107] and thus lower activation in the cerebellar nuclei during execution of the prelearned task probably reflects a reduction in activity of the neurons that project to these nuclei, and these include the Purkinje cells of the cerebellar cortex. According to their results, they suggested that the cerebellum is involved in the process by which motor tasks become automatic.

In similar studies, Juepter and colleagues [68, 69] used PET to identify the brain areas involved in learning a new keypress sequence by trial and error (using auditory feedback) and those involved in the execution of a prelearned sequence. Subjects were asked to perform a sequence of movements using their

right hand. In the former study [69] subjects were scanned during three conditions: 1) while learning a new sequence of keypresses by trial and error (NEW), 2) while performing a sequence learned before scanning (PRE) and 3) while making no movements (BASE). In the latter study [68] subjects were scanned: 1) during NEW condition, 2) while pressing any key randomly (FREE) 3) while performing repetitive movements of the right middle finger (REP) and 4) during BASE condition. Comparison of NEW with FREE condition allowed to identify the brain areas involved in motor learning (because in the FREE task no learning occurs) and comparison of FREE with REP condition allowed them to identify the brain areas involved in the selection of movements. Performance evaluation was obtained measuring error rate and response time. Imaging results showed increased activity in prefrontal, anterior cingulated, premotor and parietal cortices during the early phase of learning. With regard to the basal ganglia and cerebellum, they found increased activity in the caudate nucleus and cerebellar cortex during initial learning, although activity in the cerebellar cortex decreased linearly with time and no activity in the caudate nucleus was measured after the subjects overlearned the task. Comparing NEW and FREE condition they found that the cerebellar nuclei (bilaterally) and vermis were more active during NEW condition, suggesting their involvement in motor learning.

Toni and colleagues [127] used fMRI (2T) to investigated the time course of changes in cortical and subcortical activation throughout the course of learning of a keypress sequence by trial and error, using visual feedback. Subjects performed the same sequence, using their right hand, for 40 minutes until it became relatively automatic. This experiment used as control condition a baseline condition in which the subjects made no movements. Performance were evaluated through the error rate and response time. They reported that the sequence was performed without errors after 9 blocks of learning (in each block the subject had to complete one sequence correctly). Response time did not show any consistent tendency over time. With regard to the neural activity,

their results showed that the controlateral caudate nucleus was active early in learning, but the signal reduced sharply to the baseline level after 10 blocks. The controlateral anterior putamen showed similar decreased activity at first, but then remained active above the baseline level. With regard to the cerebellum, they found a large activation in the ipsilateral cerebellar vermis that decreased during the second half of learning. They also observed linear increased activity in the ipsilateral anterior cerebellar cortex that decreased at the end of the session. No significant activation was found in the cerebellar nuclei.

In their studies, Floyer-Lea and Matthews [34, 35] used fMRI (3T) to characterize the dynamic changes in brain activation associated with learning of a visually guided motor tracking task. Subjects held a pressure sensor in their right hand between thumb and fingers. Two vertical bars were shown on a screen during the experiment, a target bar on the left-hand side of the screen and a response bar on the right-hand side of the screen (whose height depended upon the pressure applied by the subject). Each subject was instructed to apply the appropriate pressure on the sensor in order to maintain the two bars at equal heights on the screen all the times. In each tracking block the target bar performed four repeats of a 8s tracking pattern. Task performance was measured through the tracking error (difference between the target and response forces). In the former study [34] they evaluated dynamic changes in brain activation associated with improved performance and greater automaticity during fast (short-term) learning of the visuomotor task. After initial rapid reductions in tracking errors, stable, improved performance was achieved by the subjects in five blocks. Automaticity was evaluated using a dual-task experiment (in which subjects also counted backward, in step of 3, as quickly as possible). They reported that counting task did not affect tracking performance after it had reached a plateau. Imaging results showed different patterns of functional changes in the brain activity associated with behavioral changes. The early, more attentionally demanding, stage of learning was associated with the greatest relative activity in widely distributed cortical

regions, including prefrontal, bilateral sensorimotor and parietal cortices. The caudate nucleus and the ipsilateral cerebellar hemisphere (CRUS I and CRUS II) also showed significant activity. Over time, as performance improved, activity in these regions progressively decreased. They measured increased activity in subcortical motor regions including the ipsilateral dentate nucleus, the controlateral thalamus and putamen. Their results suggest that early performance gains relay strongly on prefrontal-caudate interactions, whereas automatic performance involves the subcortical circuit comprising the dentate and the putamen. In the latter study [35] they investigated long-term learning phase, after a period of three weeks of training. Also in this study, the results showed an increased activation of the motor cortical-basal ganglia loop, encompassing the putamen, during late phase of learning.

Other studies employing cerebral lesions have been carried out in order to understand the role of the basal ganglia and cerebellar nuclei in learning and memory of visuomotor sequence.

Lu and colleagues [80] trained monkeys on a sequential button press task with both hands and inactivated different portions of the deep cerebellar nuclei in different stages of learning. Before the injection experiments started, the monkeys had learned a set of sequences extensively. After each injection, the monkeys performed the learned sequences and, in addition, learned novel sequences. Performance were evaluated by error rate and movement time (time between button release and next button press). Experimental results reported a deficit in learning/memory due to injections into the dorsal and central parts of the dentate nucleus. Error rate increased significantly for learned sequences but not for novel sequences. This effect was present only when the hand ipsilateral to the injection was used. Injections in the lateral and ventral parts of the dentate nucleus and interpositus and fastigial nuclei led to no change in the error rate. Moreover, they found that after the injections, the movement time increased significantly for learned as well as for novel sequences, especially for the injections into the ventral parts of the dentate nucleus. Their results suggest that, among the cerebellar nuclei, the dentate

nucleus, especially its dorsal and central regions, is related to the storage and/or retrieval of long-term memory for motor skill, whereas movement-related function is distributed more widely in the nucleus. Their results also suggest that, with a long-term practice, the monkey depends less on the explicit knowledge of button order (which is likely to be available to both hands) and more on the implicit motor skill (specific to the hand), in which the dentate nucleus plays a preferential role. However, they reported that after the inactivation of the dentate nucleus, although performance of learned sequences was worse than the control level, it was still better than the performance in executing the novel sequence. This suggests that even if the motor sequence was not available, the button order was still available.

In another study aimed at understanding the role of the basal ganglia in acquiring new motor sequences and executing pre-learned motor sequences, Miyachi and colleagues [90] induced local inactivation of different parts of the striatum in monkeys. Their results showed that monkeys were impaired in learning new motor sequences after inactivation of the associative striatum (caudate and anterior putamen), whereas the execution of well-learned motor sequences was disrupted after inactivation of the sensorimotor striatum (posterior putamen). Therefore, their results suggest that the anterior striatum and posterior striatum are related to the acquisition of new sequences and memory storage, respectively.

2.2.2 Motor adaptation

The studies reported under point 5, at the beginning of this section, investigate the brain areas involved in motor adaptation task, in which the subject has to learn how to adapt his/her movements according to some external changes, artificially imposed by the experimenter.

Flament and colleagues [33] used fMRI (4T) in humans to study the changes in cerebellar activation occurring during the execution of a motor adaptation task. Subjects had to reach one

of eight targets on a screen a cursor through a joystick. The targets were arranged circumferentially at 45° angles and subjects were asked to perform movements with their right hand. The essential feature of the task paradigm used is the change in the visuo-motor relation produced by altering the directional gains of the x and y axis of the joystick. The task involved three different visuo-motor relation: 1) a "standard" gain paradigm, in which the relation between movements of the cursor and joystick was predictable and expected, 2) a "random" gain paradigm, in which the relation between joystick and cursor movements direction was varied randomly from trial to trial among four conditions (therefore subjects were unable to learn the relation between movement of the cursor and joystick), and 3) a "reversed" gain paradigm, in which the relation was different from that in the standard task, but remained constant from trial to trial during the movement period, giving the subjects the opportunity to learn the new relation and to acquire skill at performing it. Motor performance was evaluated by a performance index that combined three parameters: number of successful movements, path length and movement time. Movement-related activity was analyzed in terms of the activation intensity and area. Experimental results reported that in the early stage of learning in the "reversed" conditions, and during the "random" conditions, performance was poor with a decrease in the number of completed movements. They also measured increased movement time and length as compared with the standard conditions. After repeated practice in the "reversed" condition performance improved and reached the same level of proficiency as in the "standard" condition. The area of cerebellar activation reached its peak (with higher intensity on the side ipsilateral to the hand used) during the random task and in the early stage of "reversed" condition, but decreased throughout the subsequent "reversed" gain periods. Activation of both intermediate and lateral cerebellar cortex was measured. Therefore, their results showed an inverse relation between the performance index and cerebellar activation. Furthermore they found that in the "random" gain period there was a greater area

of activation and a higher intensity in the dentate nucleus than the "standard" gain period, but the difference did not reach statistical significance. The only significant change was increased activity in the last period of learning in the left dentate.

In a similar study, Imamitzu and colleagues [59] used fMRI (1.5T) to track the changes in human cerebellar activation during the acquisition of a motor skill. Subjects were asked to manipulate a computer mouse so that the corresponding cursor followed a randomly moving target on a screen. The task involved two different visuo-motor relations: 1) a test condition, in which the cursor appeared in a position rotated 120° around the center of the screen (novel mouse) and the subjects necessitated to learn the new relation and acquire skill at performing it; 2) a baseline condition in which the cursor was not rotated (ordinary mouse). Subjects performed eleven sessions (each lasting 9 min and 23 sec). Performance was measured by the tracking error (i.e. the distance between the cursor and the target). Obtained results showed that in test condition errors decreased significantly as the number of sessions increased with no significant changes in the last three sessions. Instead, in the baseline period the tracking errors were constant. With regard to the neural activation, during the first session a large regions near the posterior superior fissure in the lateral cerebellum were significantly more active during test than baseline period. However, in the last session only restricted subregions were activated. Consequently, activity in the lateral cerebellum became smaller as learning progressed. They also found that within regions that remained activated in the last sessions, activity did not markedly decrease with learning. Based on their results, they suggested that remaining activity in the cerebellar hemisphere reflected the acquired internal models, whereas decreased activity as learning progresses might largely reflect the error signals.

Shadmeher and Holcomb [117] used PET to examine changes in the brain areas as subjects learned to make movements with their right arm while holding the handle of a robot that produced a force field. Subjects had to reach one of eight target arranged

circumferentially at 45° angles. They acquired PET scans during three conditions: 1) null field condition, 2) learning condition in which a stationary force field was applied (they analyzed the early, last and recall phase of learning) and 3) random field condition, in which the robot produced a random, non stationary, velocity-dependent force field, representing an unlearnable mechanical system. Performance was evaluated by the average length of the movements as an indicator of motor output. They observed that rapid improvements occurred when the field was held stationary because, with practice, the movements gradually converged to those recorded in the null field condition. Conversely, in the random field, movements did not significantly improve with practice. They did not observe increased activation in the cerebellum both in the early learning and random condition, but they did not rule out the influence of the cerebellum in initial acquisition of the motor skill, because they sampled only the anterior regions of the cerebellum. However, in the recall phase (after skill acquisition and 5.5 hours of rest), they found a significant activation in the ipsilateral anterior cerebellar cortex with no significant changes in motor performance. Their results led them to the conclusion that the cerebellum is part of a system that maintains long-term motor memories.

In a similar PET experiment, Nezafat and colleagues [94] focused their attention on cerebellar activity changes in adapting to dynamics of reaching movements with the right arm. Subjects had to reach one of eight target arranged circumferentially at 45° angles. The task involved two conditions: a learning condition, in which the forces imposed on the hand of the subjects were described by a constant relation to hand velocity; a random (unlearnable) condition, in which the force field was non-stationary as the velocity coefficient was changed randomly. Brain images were acquired during learning and recall at 2 and 4 weeks. Subjects practiced on both fields but performance improved only in the learnable field. During initial training (day 1), coincident with decrease in movement errors, they measured increased regional cerebral blood flow (rCBF) in the right posterior

cerebellar cortex. Later in training, they measured monotonic decreased activity in the same area, and increased rCBFs in the ipsilateral and controlateral deep cerebellar nuclei. When they looked for neural correlates of recall of the acquired motor skill on days 15 and 29, they found that between day 1 and 29 there was a single region with a significant decreased activation in the right anterior cerebellar cortex, despite the fact that there was little or no difference in task performance during the scan periods.

Smith and Shadmehr [119] used a standard force field adaption paradigm to test the ability to learn internal models of arm dynamics in patients with cerebellar degeneration and Huntington's disease patients. Subjects held the handle of a manipulandum with their predominant hand. A small cursor, indicating hand position, was displayed on a vertically oriented computer monitor in front of the subjects. They had to reach one of eight targets arranged circumferentially at 45° angles. Subjects initially reached in a null field, then in a clockwise curl field and finally in a counter-clockwise curl field. During the field sets, catch trials (null field trials) were inserted at a probability of 1/6. The force field perturbed movements, but control subjects improved reaching with training, and errors in catch trials closely mirrored the errors made on initial exposure to the field. Subjects with HD also appeared to learn the field. After the dynamics of reaching was altered, the authors evaluated the effect of error in one trial on the motor commands that initiated the subsequent trial. Change in motor commands of HD patients was strongly related to the error in the preceding trial and this error-dependent change had a sensitivity that was comparable to that of the controls. Indeed, as for the healthy subjects, initial exposure to the field substantially perturbed movements in HD patients, but their movements in late training trials became straighter and their catch trials closely mirrored the errors recorded in field trials. In contrast, patients with cerebellar degeneration showed sign of impaired adaptation. Moreover, the movements performed by these patients changed from trial-to-trial by an amount that was comparable to that of control subjects, but these

changes were random and uninformed by the error in the preceding trial. Indeed, in catch trials, movement did not have errors that mirrored the errors in field trials, indicating that they did not produce anticipatory compensation for the field. Therefore, their results showed that patients affected by cerebellar damage were profoundly impaired in adapting to altered arm dynamics, whereas HD patients exhibited no significant deficits. In a prior work Smith and colleagues also found that on-line error correction was disturbed in HD patients, whereas it was largely intact in patients with cerebellar degeneration [118].

2.3 A new hypothesis

According to the hypothesis formulated in the first section, derived from the analysis of the experimental results reported by studies on motor generation, and on the base of the neural activity reported by studies on motor learning discussed in the previous section, we propose a neural scheme for the acquisition and memory storage of sequential procedures.

The studies discussed in section 2.2 show that multiple brain areas contribute to different stages and aspects of motor learning. The table reported in Figure 2.5 summarizes these results, reporting the brain areas that show increased activity early in learning and after long practice.

These results support the notion that caudate nucleus (in the basal ganglia) and cerebellar cortical input regions are more active in early stage of learning. As learning proceeds, activity in putamen (basal ganglia) and dentate nucleus increases until automaticity is achieved. Thus, we speculate that the extended area of activation in the cerebellar cortex is mainly due to the activity of climbing fibers that carry the error's information, and that increased activity in the dentate nucleus reflects the acquired internal model of the behavior.

Other authors have suggested that motor skill learning follows a two-stage process and that different neural circuits contribute

	Activated Area		Experimental studies
	Initial Phase	Automatization phase	
Basal Ganglia	Caudate Nucleus	Putamen	Juepter (1997), Floyer-Lea & Matthews(2004), Lehericy(2005), Toni(1997)
Cerebellum	Cerebellar Cortex		Jenkins (1994), Flament(1996), Toni(1997), Lehericy (2005), Floyer-Lea & Matthews(2004), Juepter(1997), Park(2010), Doyon(2002), Nezafat(2001), Imamizu(2000).
		Dentate Nucleus	Floyer-Lea & Matthews(2004), Jenkins(1994), Flament(1996), Park(2010), Doyon(2002), Nezafat (2001).

Figure 2.5 Neural areas within the basal ganglia and cerebellum that show increased activity (as reported by the studies on the right) during early and late phase of learning.

to the two stages [49]. Research on habit learning has shown that learning involves distinct processes during acquisition and after extended training. The former involves the formation of the associations between action and outcome, and the latter between stimulus and action. It has been suggested that learning involves a shift from these processes, i.e. the behavior changes from goal-directed to stimulus-driven after extended training [25]. In other words, during the acquisition of a motor skill, actions are more sensitive to the outcome value, whereas extended training leads to respond according to the environmental stimuli rather than the associated consequences. It has been suggested that the associative striatum is more critical during acquisition, whereas the sensorimotor striatum is more important for habit formation. It has been shown that rats with lesions of the dorsolateral striatum (that corresponds to the sensorimotor striatum in humans) do not change their behavior, i.e. a shift from goal-directed actions to stimulus-response habit does not occur, even with extended training [135]. Indeed, these studies showed that after extended training, if the expected reward is reduced through devaluation, rats with lesions of the dorsolateral striatum

significantly reduce responding, indicating that their actions are still goal-directed. Instead, controls and rats with lesions of the dorsomedial striatum (that corresponds to the associative striatum in humans) do not reduce responding, indicating the habit formation. Similar results were obtained by another study conducted on humans, which compared the behavior of two groups of subjects with different intervals of training (1-day and 3-day training) [128]. The results showed that during training there were no significant differences in response rates between groups, whereas after devaluation, only the less-trained subjects reduced the responding rate. The fMRI data, acquired during training, revealed significant increased activity of the sensorimotor striatum as training progresses, suggesting its involvement in habit formation.

Therefore, it can be supposed that associative and sensorimotor striatum are involved in acquisition and retention of a motor skill, respectively.

Although there is solid evidence that the initial learning of many skills depends on the striatum [29, 99], there are contrasting results in the literature regarding to the role of the sensorimotor striatum in automatic responding. For example, whereas some fMRI studies reported increased activity in the sensorimotor striatum with extended training [34, 79, 128], others reported decreased activity [9, 126]. Moreover, Turner and colleagues [129] reported that temporary inactivations of sensorimotor regions of the internal segment of the globus pallidus (whose activity depends on the sensorimotor striatum) did not impair the ability of monkeys to produce previously learned motor sequences. Other studies showed that dopamine critically mediates the acquisition and expression of a behavior during the initial stage of learning, whereas plays a diminishing role in executing a well-learned behavior [53, 121]. Therefore, these results sustain the hypothesis that the basal ganglia play an important role in the initial stage of learning, whereas it is not well-established their importance in the final stage of learning.

Consequently, we propose a neural scheme based on the

hypothesis that during the learning of a new motor sequence, the cerebral cortex, basal ganglia and cerebellum initially work in parallel. The basal ganglia, through the caudate nucleus, are involved in the acquisition of the order of the elements in the sequence (the spatial sequence) and the cerebellar cortex starts working to acquire the motor skills (as imaging studies suggest). After long practice, when the sequence of motor commands is acquired and stored in the dentate nucleus, there is no more need for the resort of the trajectory plan. Therefore the motor sequence is executed as a single behavior and is performed fast and accurately.

The hypothesis here formulated is consistent with a theory proposed by Mauk [84], which suggested that early stages of motor learning might be associated with experience-induced plasticity at parallel fiber-Purkinje cell synapses with later changes at the mossy fiber synapses within the deep cerebellar nuclei.

Moreover, as reported in [80], the inactivation of the dentate nucleus would not result in a loss of performance in learning a new sequence, whereas after a long-term practice loss of the dentate nucleus function affected the performance. We speculate that dentate inactivation during the early stage of learning does not affect performance because in the early phase of learning the procedural knowledge is maintained by the cortex-basal ganglia mechanism. Instead, when the motor sequence is acquired within the dentate, the execution of the motor sequence is more dependent on the cortex-cerebellar mechanism, therefore dentate inactivation during this stage affects performance.

Other authors [27] suggested that the cortico-cerebellar system was involved in motor adaptation, especially in the late stage of learning and in the retention phase. The study of Smith and Shadmehr [119] on motor adaptation showed that patients affected by cerebellar degeneration were impaired in adapt their movements. On the basis of their results, we speculate that in motor adaptation task, when the relation between movements of the joystick and cursor is altered, knowledge of the sequence of points to reach is not sufficient to efficiently perform the task, but

it is also necessary to acquire the sequence of motor commands.

Furthermore, the anatomical two-way path between basal ganglia and cerebellum, found by Strick and colleagues [14, 54], provides further evidence about the plausibility of this hypothesis. In the former work [54], they found a disynaptic pathway that links the dentate nucleus with the putamen. Particularly, they found that projection from the dentate to the putamen connects with medium spiny neurons that innervate GPe and thus influences the "indirect" pathway of basal ganglia. In the latter work [14] they found a disynaptic pathway that links the subthalamic nucleus with the cerebellar cortex, in the posterior lobe (CRUS II and HVIIB), and that this connection is topographically organized. These connections are consistent with the neural activation paths found by the imaging studies.

Accordingly, we assume that:

- Since the subthalamic nucleus is more active in the early stage of learning, it would provide the cerebellar cortex with further excitatory input that decrease as the spatial sequence is acquired. This, in turn, would provide more inhibitory input to the dentate nucleus.

- In the late stage of learning, when the sequence of movements is acquired as a single behavior and, at the same time, the activity in the dentate nucleus increases, its activation provides an excitatory input to the putamen, and in particular to the indirect pathway. This pathway would exclude the function of basal ganglia in selecting the next spatial target in the ordered sequence, because the sequence of motor commands is already acquired as a single behavior and released by the cerebellum.

We can now reformulate the hypothesis presented at the beginning of the chapter as it follows:

Acquiring a new motor skill requires *two phases*, in which two different processes occur. The early stage of learning is more

related to the acquisition of the order of the movements (or, in other words, the sequence of point to reach), and this process is performed by the basal ganglia (through the caudate nucleus). Simultaneously, the cerebellar cortex starts to acquire an internal model of the skill. As learning proceeds, the activation is confined to a specific area of the cerebellar cortex and increased activity in the dentate nucleus reflects the acquired internal model of the skill. Consequently:

- **Early in learning**, task performance is more dependent on the procedural knowledge maintained by the **cortex-basal ganglia system**.
- **After a long-term practice**, task performance is more dependent on the motor sequence maintained by the **cortex-cerebellar system**.

In the next chapter we will present a neurocomputational model, comprising the interactions among the basal ganglia, cerebellum and cortex, which instantiates key biological properties of these brain areas. This model is used to test the proposed hypothesis.

Chapter 3

A Computational Model for procedural motor learning

It's now well established that learning to perform complex motor behaviors requires multiple brain areas and that basal ganglia and cerebellum are essential in this process.

How do these areas interact in order to acquire a new motor skill?

Many researchers have addressed this question, proposing hypothetical neural schemes for motor learning. This chapter briefly reviews the neural schemes reported in the literature comprising the interaction among the cerebral cortex, basal ganglia and cerebellum and sharing some features with the proposed model. Subsequently, the proposed neural scheme for motor learning is described, highlighting the similarities and differences between the neural model developed here and those already presented in the literature. Following sections analyze the interactions among the brain areas constituting the model and illustrate how this model can be useful to validate the hypothesis formulated in chapter 2. Finally, the networks that simulates the neural circuits of the basal ganglia and cerebellum are described.

3.1 The neural scheme of the model

One of the earliest neural schemes for motor control, envisaging a cooperation among the cerebral cortex, cerebellum and basal ganglia, was proposed by Allen and Tsukahara [5]. The main hypothesis of the model is that the association areas participate in translating the intention to move into a patterned activation of specific motor cortical columns and of the elemental movements associated to them. They suggested that a motor act was performed following two distinct phases: a planning phase and an execution phase. In their neural scheme the movement is programmed within the association cortex through the interaction with the basal ganglia and lateral cerebellum during the planning phase. In the execution phase the motor cortex issues the appropriate motor commands that descends to motor neurons. At the same time, the intermediate cerebellum updates the intended movement according to the motor command issued by the motor cortex and the somatosensory feedback received from the limbs.

Another neural scheme incorporating the interactions among the cortex, basal ganglia and cerebellum was proposed by Hikosaka and colleagues [49]. According to their neural scheme, a motor sequence is learned by two distinct neural systems, comprising cortex-basal ganglia and cortex-cerebellum loop circuits. This sets of loops work independently and allow to acquire a sequential motor procedure in two different coordinates: spatial and motor. The spatial sequence process corresponds to the loop circuit comprising the association cortex and the caudate nucleus, whereas the motor sequence process corresponds to the loop circuit comprising the premotor-motor cortices and the putamen. They also speculated that cerebellum was crucial in organizing the movements with correct timing, and that the anterior cerebellum (including the dorsal dentate nucleus) contributed to the late stage of learning, when movements are performed according to the learned motor sequence.

Kawato and Gomi [73] proposed a computational model of four regions of the cerebellum, in which the parietal cortex would

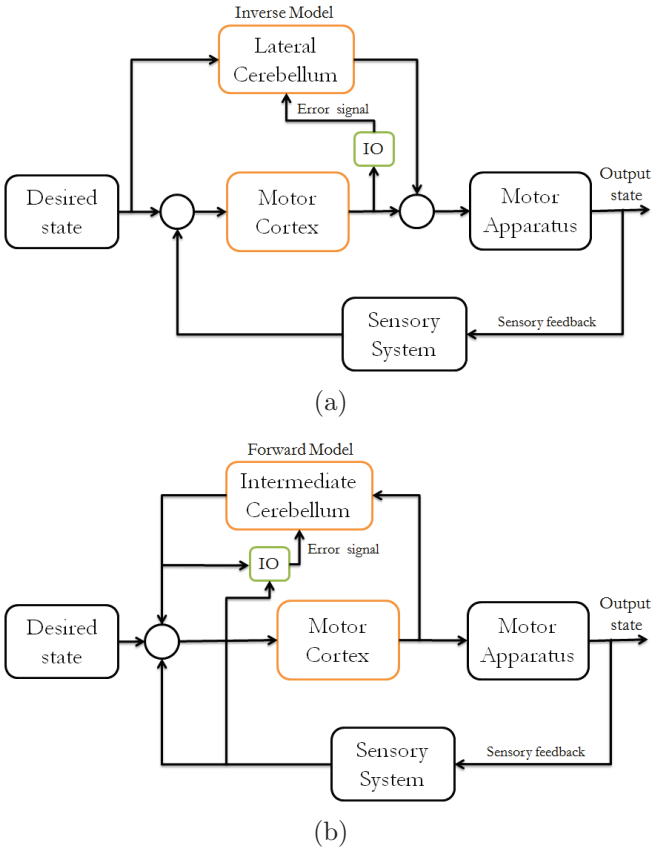


Figure 3.1 Internal models control systems for motor learning (IO: inferior olive). (a) Inverse model control system as proposed by Kawato [73], based on the hypothesis that an inverse model is acquired in the lateral cerebellum and replicates the inverse dynamics of a motor apparatus. (b) Forward model control system as proposed by Ito [62], based on the hypothesis that a forward model is acquired in the intermediate cerebellum and mimics the input-output behavior of a motor apparatus. The description of the control schemes is reported in the text.

provide the motor cortex and cerebellum with the information representing the desired trajectory of a limb movement (Figure 3.1(a)). In their neural model both the output from the motor cortex and cerebellum converge to the motor apparatus, determining its resulting output state, that is sent back to the

motor cortex through the sensory system. The motor cortex compares the actual state with the desired one and sends an error signal to the cerebellar cortex through the inferior olive [72]. This signal sculpts the cerebellar cortex and forms an *inverse model* of the limb, which would predict the most appropriate sequence of movements needed to follow the desired trajectory. Therefore, after extended training, the lateral cerebellum acquires the inverse models that reproduce the inverse dynamics of the limbs and might accurately control movements without referring to the consequences provided by the sensory feedback.

The notion that the cerebellum contains internal models of the motor apparatus was also advanced by Ito [62], who suggested that cerebellar microcomplexes provide *forward models* of the limbs, which capture the causal relationship between the input motor command and the resulting output state of the limb (e.g. in terms of position and velocity). Therefore, a forward model predicts the sensory consequences of a motor command, providing the motor cortex with a feedback information before the biological feedback (that is slower and has a smaller gain) is available. In the model (Figure 3.1(b)) the input signals (provided by the motor cortex) drive both the cerebellar microcomplex and motor apparatus. Their output is compared through the inferior olive, which "computes" the difference between the actual and predicted output of the limb and sends this information to the microcomplex via the climbing fibers. Changes in the synaptic strength within the cerebellar cortex, due to the climbing fibers activity, sculpts the microcomplex, forming a forward model that mimics the input-output behavior of the limb. Therefore, after extended practice, the forward model simulates the motor apparatus closely, and the motor cortex can accurately control the limb by referring only to the prediction given by the forward model. According to Ito, this mechanism would allow humans to perform fast and coordinated movements without the sensory feedback (e.g. with the eyes closed) after extended training. While Kawato [73] suggested that inverse models were formed within the parallel connections between lateral cerebellar hemispheres and motor cortex, Ito

instead suggested that forward models were instantiated within the cerebrocerebellar loop formed between the motor cortex and the intermediate cerebellar hemispheres. Moreover, Kawato [133] have proposed that a system with high learning capability could be obtained by a combination of inverse and forward models, and Ito have recently suggested that the notion of internal models in the cerebellum could be also applied to the mental representations [65].

The proposed neural scheme for motor learning is shown in Figure 3.2 and incorporates parietal and motor cortex, basal ganglia and cerebellum. The cerebellum model comprises only the lateral cerebellum, which consists of the lateral cerebellar cortex and its connections with the dentate nucleus.

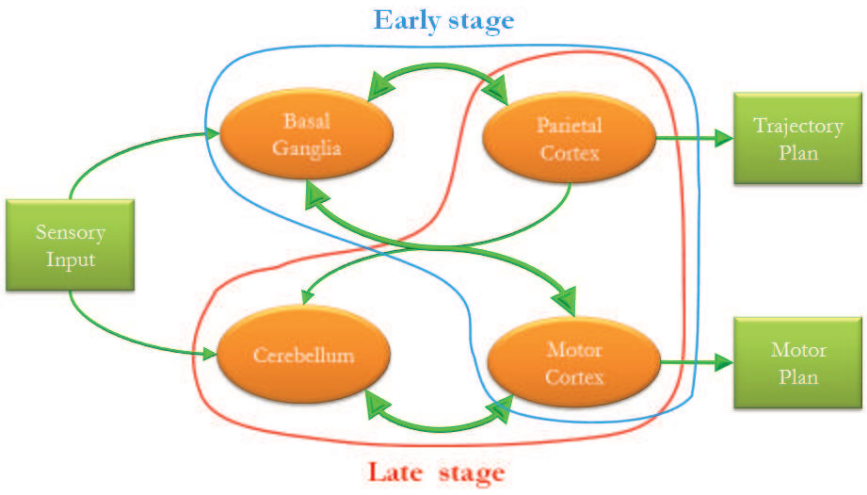


Figure 3.2 Neural scheme of the model for procedural motor learning, comprising the basal ganglia, cerebellum, parietal and motor cortex. Early in learning task performance is more dependent on the procedural knowledge maintained by the parietal cortex-basal ganglia system, while after a long-term practice task performance is more dependent on the motor sequence maintained by the motor cortex-cerebellar system.

Sensory information is provided by an input module (*sensory input* in the figure) to the cerebral cortex, basal ganglia and

cerebellum. The parietal association cortex releases signals that specify the position of targets in extrapersonal space (according to the studies conducted by Andersen and Zipser [6]). Therefore, the basal ganglia, interacting with the parietal cortex, select the next target point in the sequence. In turn, parietal cortex sends this information to the cerebellum that, interacting with the motor cortex, selects the appropriate motor command.

This model fits the hypothesis presented in chapter 2, according to which motor learning follows two distinct phases. During the early phase of learning, the model learns the spatial sequence in visual coordinates (i.e. the sequence of points to reach in order to realize the motor task) through the interactions between the basal ganglia and the parietal cortex. The spatial sequence is then converted into motor commands through the interactions of the cerebellum and the motor cortex. Therefore the cerebral cortex, basal ganglia and cerebellum initially would work in parallel. The basal ganglia, through the caudate nucleus, are involved in the acquisition of the spatial sequence and the cerebellar cortex starts working to acquire the motor sequence. As learning proceeds, the sequence of motor commands in motor coordinates is acquired and stored in the dentate nucleus. Consequently, it would be expected that, early in learning, task performance is more dependent on the procedural knowledge maintained by the cortex-basal ganglia system and, after a long-term practice, task performance is more dependent on the motor sequence maintained by the cortex-cerebellar system.

The neural scheme for procedural motor learning proposed here is based upon the following assumptions:

a) A sequence of movements is stored in the brain as a spatial sequence of target points and as a sequence of motor commands;

b) The parietal cortex participates in the planning stage of the movement, whereas the motor cortex is involved in the execution stage;

c) The cerebellum selects the motor command on the basis of the information provided by the parietal cortex;

d) The cerebellum has a key role in the acquisition of the motor sequence.

The neural scheme for procedural motor learning proposed by Hikosaka and colleagues incorporates the assumption a). However, they suggested that distinct portions of the basal ganglia, interacting with the motor and parietal cortex, were involved in the acquisition of the spatial and motor sequences, whereas the cerebellum just performed a timing role. Moreover, the computational model based on their scheme, developed in a later work [91] comprises only the basal ganglia, whereas the proposed model comprises also the cerebellum, according to the assumption d).

The neural scheme proposed by Allen and Tsukahara incorporates the assumption b). However, they suggested that the lateral cerebellum was not involved in the execution stage (which would involve, according to their scheme, only the intermediate cerebellum) as in the proposed model. Moreover, they did not formulate a computational model to test the validity of their neural scheme.

Finally, the model of Gomi and Kawato incorporates the assumption c). However, although Kawato and Gomi mapped their controller onto the gross anatomy of the brain, no attempt was made to show how the microcircuitry of the cerebellum might be used in implementing an inverse model.

3.2 The Basal Ganglia

Several studies have focused on the functions of the Basal Ganglia, giving rise to several models and theories [40]. According to the results obtained from anatomical, electrophysiological, and neuroimaging data, as well as experimental studies conducted on healthy subjects and patients affected by basal ganglia

degenerations, this group of subcortical nuclei plays a key role in motor learning.

This section briefly describes the neural network that simulates BG circuitry within the proposed neural scheme and illustrates the novel aspects of this model compared to other models presented in the literature.

3.2.1 Basal Ganglia theories

Studies conducted by numerous researchers have shown that the BG facilitate motor learning and that dopamine plays an important role in this process. Recent studies place emphasis on the parallel interactions between corticostriatal and corticosubthalamic afferents on the one hand, and internal feedback circuits modulating basal ganglia output through the GPi on the other hand [97]. There is also solid evidence that the initial learning of many skills depends critically on the BG, especially on the striatum, because striatal plasticity alters the transfer of information throughout basal ganglia circuit and may present a key substrate for adaptive motor control and procedural memory.

Several computational models of the BG have focused on how response selection and reward information may be implemented in biological circuitry (e.g., [10, 19, 45]). In these models DA has a performance effect, by differentially modulating excitability in the direct and indirect pathways. However, most of the BG models reported in the literature relies primarily on the direct pathway, but it is now clear that the indirect pathway plays a crucial role in BG functioning. Furthermore, recent evidence indicates that the subthalamic nucleus should be considered part of a third 'hyperdirect' pathway, rather than just a relay within the indirect pathway. With regards to the role of DA, these models emphasize the tonic effects of DA, without taking into account the phasic effects.

The BG model developed by Frank [37, 38] (shown in Figure 3.3) integrates the basic BG anatomical structure in a

neural network that captures the dynamic of activity in various basal ganglia areas during response selection. This model includes both the direct and indirect pathways, and predicts that the indirect pathway contributes to discrimination learning by developing response-specific NoGo representations that compete with Go representations (related to the direct pathway) to enhance discriminability. This model also includes the computational functions of the STN and provides insight into its role in response selection and decision making [38]. Finally, the model incorporates phasic changes in DA release during positive and negative feedbacks. The model posits that phasic bursts and dips in DA during error-feedback modulate Go/NoGo representations in the BG direct and indirect pathways through modification of synaptic plasticity, thus facilitating or suppressing the execution of a motor command [37]. Due to the synaptic modifications the most reinforcing responses are subsequently facilitated, whereas those more ambiguous are suppressed. One of the network's key emergent properties is that a large dynamic range in DA release is critical for BG-dependent learning.

3.2.2 The Basal Ganglia model

In our neural scheme we incorporate the neural network model developed by Frank that incorporates the principal aspects of the BG anatomy and biology discussed in chapter 1, together with cellular and systems-level effects of DA. This model provides a theoretical basis for procedural learning functions of the BG.

The model is based on the following assumptions:

1. The BG facilitate or suppress stimulus-response associations represented in the cortex.

2. DA has a key role in modulating the activity of the BG.

3. Phasic changes in DA during feedback are critical for learning stimulus-response associations. Indeed, results reported in [37] showed that a reduced dynamic range of

phasic DA signals impaired the ability to learn Go/NoGo associations.

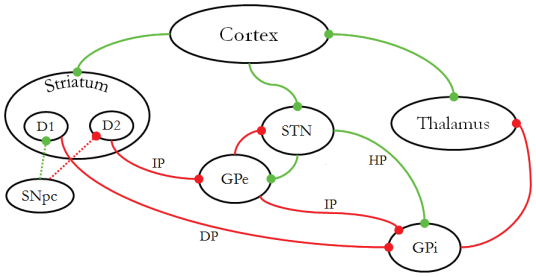
The model comprises the main circuitry of the BG and their anatomical connections with the thalamus and motor cortex (MC). The BG circuitry incorporates the striatum, the globus pallidus (internal and external segments), the subthalamic nucleus and the substantia nigra pars compacta (Figure 3.3).

Depending on the input stimuli and past experience, the model selects a response through the interaction of distinct parallel subloops, each modulating a response. Particularly, each subloop comprises a direct (Go) and an indirect (NoGo) pathway for a given response. As already mentioned in chapter 1, the direct pathway facilitates the response, whereas the indirect pathway suppresses the response. Therefore, competitive dynamics among subloops allow selective facilitation of one response with concurrent suppression of the others.

In the current implementation it is supposed that the model can select a response among four possible alternatives, but the model can be extended to include more responses.

Direct (Go) and indirect (NoGo) pathways start from two distinct populations of MSNs in the striatum, expressing D1 and D2 receptors, respectively. In the model the four leftmost columns of the striatum represent the direct pathways, whereas the four rightmost columns represent the indirect pathways. The Go columns project to the corresponding columns in the GPi, whereas the NoGo columns project to the corresponding column in the GPe. GPe columns inhibit the associated columns in GPi, so that striatal Go and NoGo activity have opposing effects on the GPi. Finally, each column in the GPi tonically inhibits the associated column of the thalamus, which is reciprocally connected to the MC. Thus, if Go activity is stronger than NoGo activity for a response, the corresponding column of the GPi will be inhibited, removing tonic inhibition of the corresponding thalamus unit, and facilitating its execution in the MC.

Projections from the SNpc to the striatum incorporate modulatory effects of DA. In the model, phasic bursts and dips



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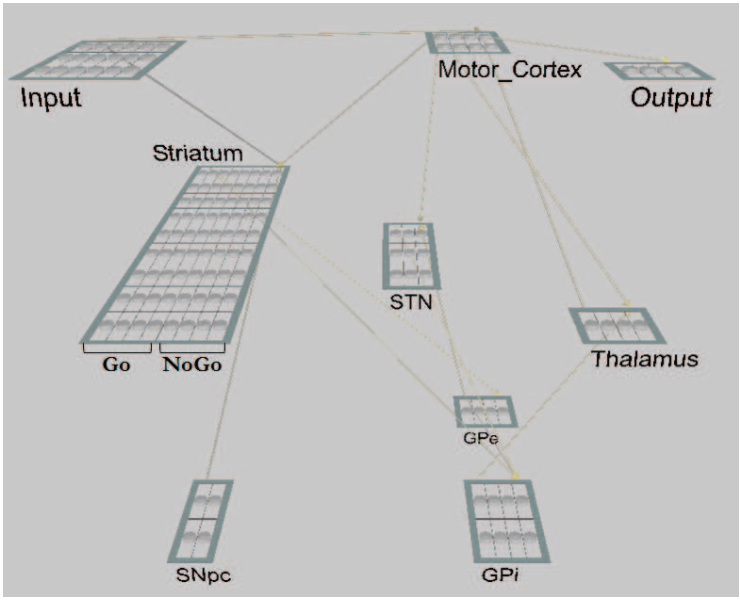


(b)

Figure 3.3 The basal ganglia model. (a) Schematic representation of the basal ganglia circuitry incorporated in the model. (b) The neural network model developed by Frank [38]. The description of the model is provided in the text (GPe: external segment of globus pallidus, GPi: internal segment of globus pallidus, STN: subthalamic nucleus, SNpc: substantia nigra pars compacta).

of DA occur after a correct and an incorrect response is selected, respectively (as shown in Figure 3.4 and 3.5). DA phasic changes differentially modulate the excitability and synaptic plasticity of

direct and indirect pathways. Particularly, DA bursts (due to a positive feedback) activate the direct pathway, reinforcing the selected response, whereas DA dips (due to a negative feedback) activate the indirect pathway, suppressing the selected response. This causes the two groups of striatal cells (forming direct and indirect pathways) to independently learn positive and negative reinforcement values of responses, and ultimately acts to facilitate or suppress the execution of commands in the MC.

At the beginning of each trial, incoming stimuli weakly activate a response in the MC through direct excitatory connections. However, these excitatory connections are not strong enough to select a response, because they also require the excitatory support from the thalamus. Therefore BG integrate stimulus input with the dominant response selected by the MC and facilitate or suppress that response, thereby providing a gating function.

In the initial trials, the network weakly selects a random response, dictated by random initial weights together with a small amount of random noise in MC activity. Depending on the response selected, a transient burst or dip of DA occurs for a correct or an incorrect response, respectively. Therefore, learning of stimulus-response associations is driven by DA transient changes. Indeed, weights from the input layer and the MC to the striatum are adjusted on the basis of the difference between phases of response selection (hypothesized to involve moderate amounts of DA) and error feedback (hypothesized to involve phasic increases/decreases in DA). In this way the striatum learns which responses to facilitate and which to suppress in the context of incoming sensory input. In addition, the MC itself learns to favor a given response for a particular input stimulus, via Hebbian learning from the input layer. Therefore the BG learn which response to gate via phasic changes in DA ensuing from random cortical responses. Learning transfers to the cortex once it starts to select the correct response more often than not.

In the examples shown in the Figures 3.4 and 3.5, the correct response to the input stimuli is represented in the model by the second unit in the output layer.

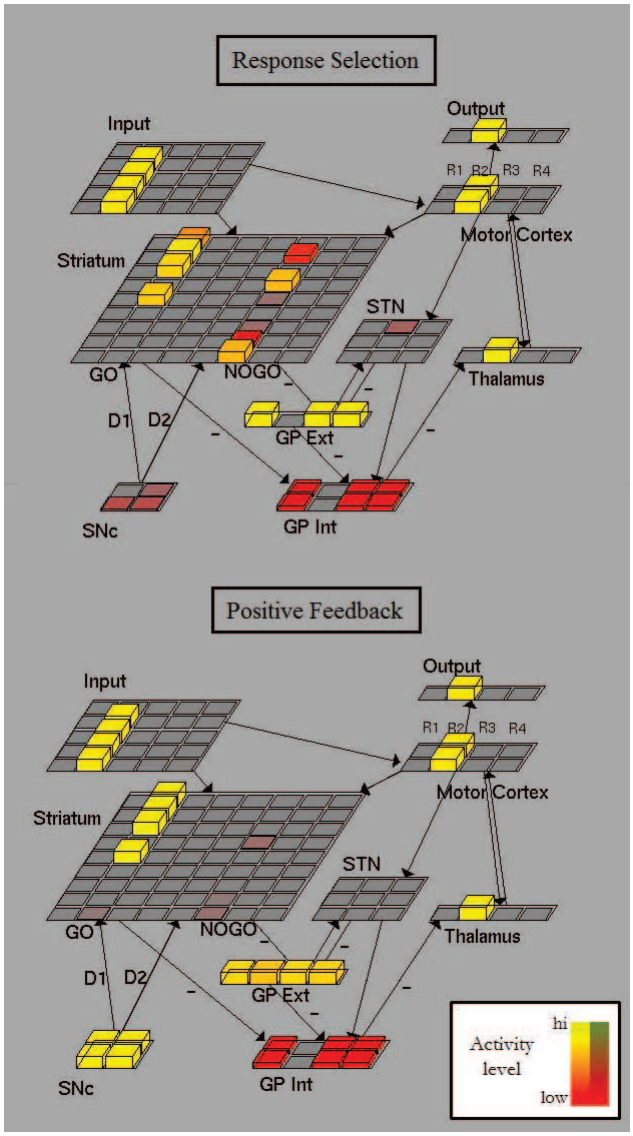


Figure 3.4 A positive feedback trial after learning. Activity in the network during response selection (minus phase) and feedback (plus phase). DA burst, due to the positive feedback, activates the direct pathway, reinforcing the selected response. The level of activity of the units corresponds to the scale reported at the bottom right of the figure.

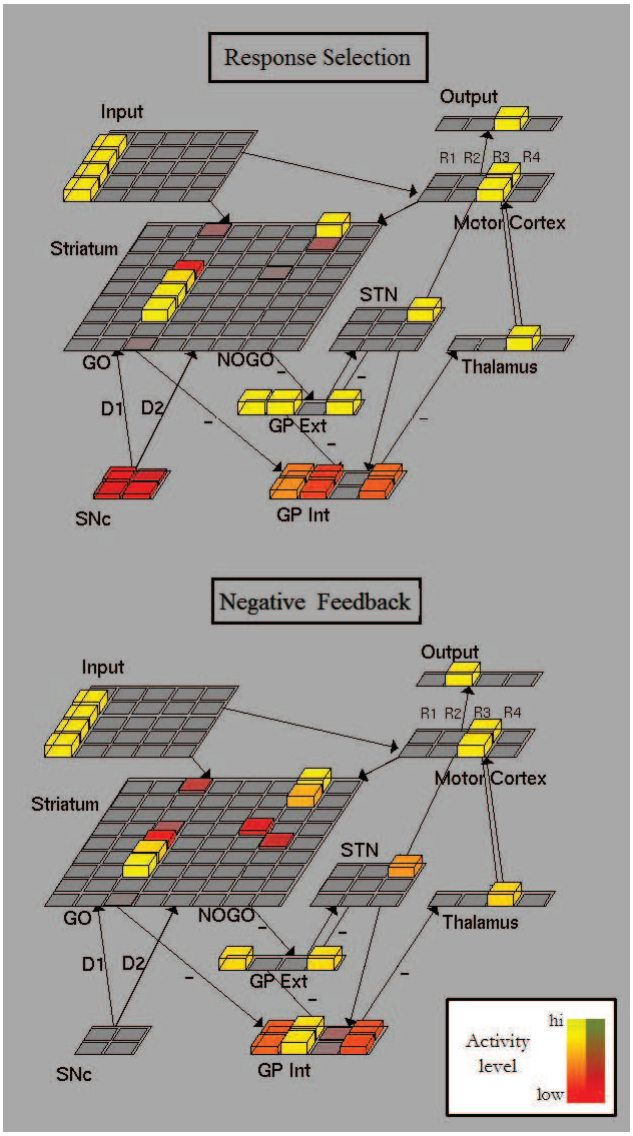


Figure 3.5 A negative feedback trial during training. Activity in the network during response selection (minus phase) and feedback (plus phase). Phasic DA dip, due to the negative feedback, activates the indirect pathway, thus suppressing the selected response. The level of activity of the units corresponds to the scale reported at the bottom right of the figure.

In Figure 3.4 the network selects the correct response during minus phase. Therefore a DA burst, due to the positive feedback, activates the direct pathway, reinforcing the selected response.

In Figure 3.5 the network selects an incorrect response during the minus phase. Therefore, a phasic DA dip, due to the negative feedback, activates the indirect pathway, thus suppressing the selected response.

Therefore the modulatory effect of the dopamine allows the striatum to learn which responses to facilitate and which to suppress in the context of the incoming sensory input.

A more extensive and detailed description of the BG network and its predictions can be found in [37, 38].

3.3 The Cerebellum

As for the basal ganglia, several theories have been proposed about the CB and its functions in motor control and learning. These theories have had their origins in many fields of interest, including anatomy, physiology, clinical neurology, and electrical or communications engineering.

This section reviews the theories the cerebellum model here developed is based upon. More comprehensive surveys about cerebellar theories and models reported in the literature can be found in [8, 57, 62].

3.3.1 Cerebellar theories

Most of the models presented in the literature have been based on extensions of the theories proposed by Marr [83] and Albus [1]. In Marr and Albus's theory, PFs would provide the cerebellar cortex with a large amount of information from the cerebral cortex. In turn, the activity of individual PCs, in the cerebellar cortex, would regulate elemental movements. The inferior olive(IO), through the CFs, would transmit the essential information that guides motor learning, training PCs how to perform their regulatory functions. Indeed, CFs activity adjusts the synaptic weights of PFs synapses,

thus teaching PCs to recognize specific patterns signaled by their input vectors. However, these theories are based on different assumptions regarding the specific nature of the signals provided by the CFs.

Marr [13, 83] postulated that the motor cortex was responsible for initiating limb movements and the CB provided, through the cerebellar nuclei, a positive feedback only for those actually needed. In particular, he suggested that the motor cortex activated a large set of cortical neurons related to many elemental movements and PCs fired in response to the input patterns and eliminated unneeded elemental movements through inhibition of the corresponding nuclear neurons.

This hypothesis is supported by the electrophysiological studies conducted by Ito [60], who demonstrated that inhibition was the sole action of the PCs that project out of the cerebellar cortex.

Therefore, according to Marr, the CB would exert its influence by inhibiting and disinhibiting motor control actions formulated in the cerebral cortex. Marr also hypothesized that the CB recognized appropriate contexts and emitted the same movements in a more automatic fashion through the training influence of the CFs that induce LTP in the cerebellar cortex. Particularly, Marr assumed that CFs carried specific instructions from the cerebral cortex designating which elemental movements needed to be executed. He suggested that CFs activated PCs and whenever the presynaptic ending (i.e. parallel fibers) and postsynaptic cell (i.e. Purkinje cell) simultaneously fired, the PF-PC synapse was strengthened.

Instead, Albus [1] proposed that PCs were trained to pause, rather than to fire, and pauses selected elemental commands controlled by the individual nuclear cells. Albus also envisioned a different learning rule, with an opposite sign and more complex properties. In his theory, Albus assumed that the IO compared sensory feedback with the desired output state and generates error signals. He postulated a three-factor learning rule, in which PF-PC synapses would be weakened (i.e LTD instead of LTP would occur) in the presence of simultaneous activation of climbing fiber

(training signal), Purkinje cell (postsynaptic factor), and parallel fiber (presynaptic factor). Studies conducted later by Ito [63, 64] supported the learning rule proposed in Albus's model. Indeed, he demonstrated that CF activity, when coupled with other factors, produced LTD.

With regard to the LTP, less is known about this mechanism in the CB, although one seems to exist. Indeed, Sakurai [113] induced LTP in cerebellar slices by stimulating PFs without CFs. This led Houk and Barto [55] to postulate that LTP occurs whenever PF fired without either postsynaptic depolarization or CF discharge.

3.3.2 The Cerebellum model

The CB neural network is shown in Figure 3.6 and comprises the lateral cerebellar cortex, the dentate nucleus and their anatomical connections with the inferior olive, thalamus and motor cortex.

The model learns to select a motor commands, depending on the task and input stimuli. This goal is achieved by the interaction of distinct modules, working in parallel, each related to a particular motor command. As for the basal ganglia, in the current implementation it is supposed that the model can select a response among four possible alternatives, but the model can be extended to include more responses.

The basic circuitry of the lateral cerebellar cortex is organized around the inhibitory PCs, from which the final and only output of the cerebellar cortex originates. The cerebellar cortex also comprises the inhibitory neurons (Stellate_Basket layer). In the model, each column of the cerebellar cortex (Purkinje and Stellate_Basket layer) corresponds to a microzone. Each microzone modulates the selection of an elemental movement directed to a particular direction (up, down, right, left). PCs show a spontaneous activity [30] that is influenced by two excitatory afferent inputs: PFs and CFs. Both fibers excite different parts of the PCs, with important consequences for the evoked activity. PFs stimulation results in a small monosynaptic excitatory postsynaptic potential (EPSP) and

disynaptic inhibitory postsynaptic potentials (IPSP) through the inhibitory interneurons, whereas CFs evoke large EPSPs, which trigger a large action potential in PCs.

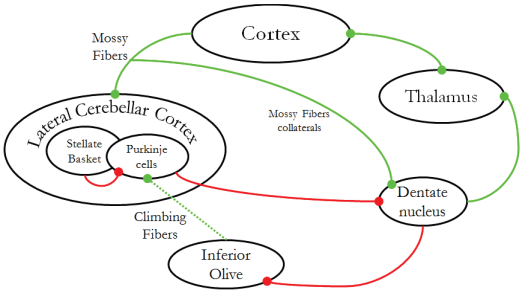
According to the cerebellar circuitry showed in chapter 1, PFs arise from the excitatory granule cells, which receive excitatory synaptic connections from the MFs. In the model, this disynaptic excitatory pathway has been simplified, considering only a monosynaptic pathway (indicated as mossy fibers in Figure 3.6), whose collaterals excite the nuclear cells (dentate and InhibDentate layers).

Since PFs project to a broad area in the cerebellar cortex (each PC receives more than $200,000$ synapses from the PFs that traverse its dendritic tree), the input layer sends spread projections both to Purkinje and Stellate_Basket layers, influencing the activity in several microzones.

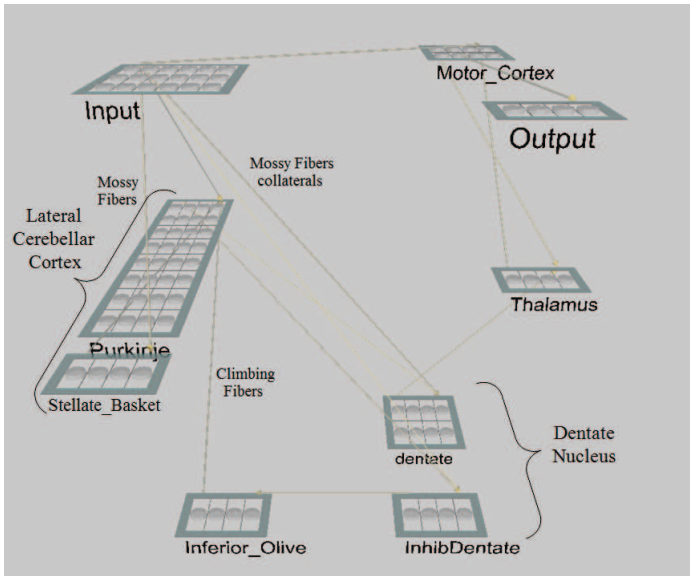
Each PC receives excitatory input from one climbing fiber that makes multiple synaptic contacts with the proximal dendrites of the PC. Therefore, in the model, each cluster of neurons in the IO give rise to distinct CFs, each innervating the corresponding microzone in the cerebellar cortex.

Each microzone converges on a small cluster of dentate nuclear cells, forming a microcomplex. The activity of each cluster of dentate cells is modulated by the inhibitory connections from the corresponding microzone and by the excitatory collaterals from the mossy fibers. In the model, the dentate nucleus comprises both excitatory (dentate layer) and small inhibitory neurons (InhibDentate layer). The excitatory dentate participates in a topographically organized recurrent circuit that includes thalamus and motor cortex. The small inhibitory dentate neurons give rise to the nucleo-olivary pathway.

As already mentioned, each microcomplex is related to a particular motor command and functions in an autonomous way. In other words, parallel subloops (each comprising a microcomplex) independently modulate each response, allowing selective facilitation of one response with concurrent suppression of the others.



(a)



(b)

Figure 3.6 The cerebellar model. (a) Schematic representation of the cerebellar circuitry incorporated in the model. (b) The neural network model developed using the Leabra framework [98]. Each module includes a positive feedback loop between a microzone, a cluster of dentate nucleus cells and a cluster of motor cortical cells. Each dentate cluster receives inhibitory input from a private set of Purkinje cells. Each set of Purkinje cells receives a private climbing fibers training input, convergent input from an array of parallel fibers, and inhibitory input from basket and stellate cells. A more detailed description of the model is provided in the text.

The IO provides the training signal that allows the cerebellum to learn the inverse model that predicts the motor command to select, according to the input signal representing the desired trajectory, as suggested by Gomi and Kawato [73]. In this respect, the model incorporates the theory proposed by Albus for LTD [1] and the theory proposed by Houk and Barto for LTP [55].

Therefore PF-PC synapses are weakened (i.e. LTD occurs) whenever PC fires in the presence of simultaneous activation of the CF and PFs that synapse on the PC. LTP occurs whenever there is PF activity without either postsynaptic depolarization or CF discharge. In order to simulate feedback effects, the learning algorithm involve two distinct phases: *minus* and *plus* phase.

During the "minus" phase the network selects a response, depending on the input stimuli and the network's weights (i.e. depending on what the network has learned in past experience).

In the "plus" phase, the activity of the IO changes depending on the correctness of the response chosen by the network in the "minus" phase. Particularly, IO activity increases whenever the network selects an incorrect response, whereas IO activity decreases whenever the network selects the correct response.

Connection weights of PF-PCs synapses change according to the difference between activity states of the network in the minus and plus phases as follows:

when $(CF_j^+ - CF_j^-) > 0$

$$\Delta w_{ij} = \epsilon_{LTD}[PF_i^-(CF_j^+ - CF_j^-)PC_j^-] \tag{3.1}$$

when $(CF_j^+ - CF_j^-) < 0$

$$\Delta w_{ij} = \epsilon_{LTP}[PF_i^-(CF_j^+ - CF_j^-)PC_j^-] \tag{3.2}$$

where w_{ij} represents the synaptic weight between the i_{th} PF and the j_{th} PC. PF_i^- represents the activation of the i_{th} PF (which synapses onto the j_{th} PC) during the minus phase. CF_j^- and CF_j^+ represent the activation of the j_{th} CF (which synapses onto the j_{th} PC) during minus and plus phase, respectively. PC_j^- represents

the activation of the j_{th} PC during the minus phase. Whenever LTD occurs, weights are adjusted according to the learning rate ϵ_{LTD}, whereas weights are adjusted according to the learning rate ϵ_{LTP} whenever LTP occurs.

Therefore, LTD and LTP sculpt the cerebellar cortical network according to previous experience, forming the basis for the acquisition of the inverse model. Simulation studies using the learning rule for LTD postulated by Albus and the mechanism for LTP mentioned above have already demonstrated the capability of finding correct PF weights in a simple learning task [11].

Since PCs show spontaneous activity, their inhibitory output prevents firing of the dentate nucleus cells when MFs (and therefore, PFs) are silent. As a movement has to be initiated, the MFs, which carry information about the movement to perform, modulates Purkinje cells activity (through the PFs) by a direct excitatory pathway and a disynaptic inhibitory pathway through the interneurons (Stellate_Basket layer). At the same time, collaterals from mossy fibers excite the dentate nucleus.

Early in learning, the excitatory influence of MFs has more influence on the discharge of Purkinje cells, increasing the activity of the already tonically active PCs. Consequently, despite dentate nucleus cells are excited by the excitatory collaterals of the MFs, increased activity in PCs makes dentate neurons more inhibited, preventing the selection of a response. The motor cortex is weakly active due to direct connections from sensory input. Therefore, the most active unit in the motor cortex determines the response.

If the selected response is incorrect, CFs activity increases and induces LTD in conjunctively active PF-PCs synapses. Instead, if the selected response is correct, CFs activity decreases, thus inducing LTP in PF-PCs active synapses.

After repeated trials, LTD and LTP in the cerebellar cortex, due to changes in CFs activity, allow the cerebellum to acquire the correct stimulus-response (S-R) associations. As learning proceeds, less error are made and then less activity in CFs is observed.

Later in training, after the cerebellum has learned the S-R

associations, whenever an input stimulus occurs, since the PF-PCs synapses related to the correct response are weakened and those related to the wrong responses are strengthened, inhibition from the cortical interneurons predominates over excitation from MFs to the PCs related to the correct response, whereas excitation from MFs predominates over inhibition from cortical interneurons to the PCs related to the incorrect responses. Consequently, excitation from MFs collaterals predominates over inhibition from PCs to the dentate neurons related to the correct response. These neurons excite the thalamus that, in turn, excites the region in the motor cortex related to the correct response.

Figures 3.7 and 3.8 show the neural activity within the network during response selection and feedback.

The network is provided by an input signal representing a stimulus (from the input layer). During minus phase, depending on the stimulus and past experience, the network selects a response, activating a particular unit in the output layer (each representing a movement toward a particular direction: up, down, right, left). The IO shows tonic activity. During the plus phase, depending on the response selected, IO activity changes, thus providing the network with an error signal.

Figure 3.7 shows the neural activity during learning, when the network selects an incorrect response and receives a negative feedback. In the example shown, the correct response to the input stimulus is represented in the model by the second unit in the output layer.

During minus phase the network selects an incorrect response and, at the same time, reduces IO activity in the corresponding column (during training, before the network learns the S-R associations, activity in the inhibitory dentate is reduced compared to that shown after learning). The remaining units of the IO show tonic activity.

Since the network selects an incorrect response, during the plus phase the activity in the IO units increases (with the exception of the IO unit related to the response selected, that is inhibited by the corresponding column of the inhibitory dentate).

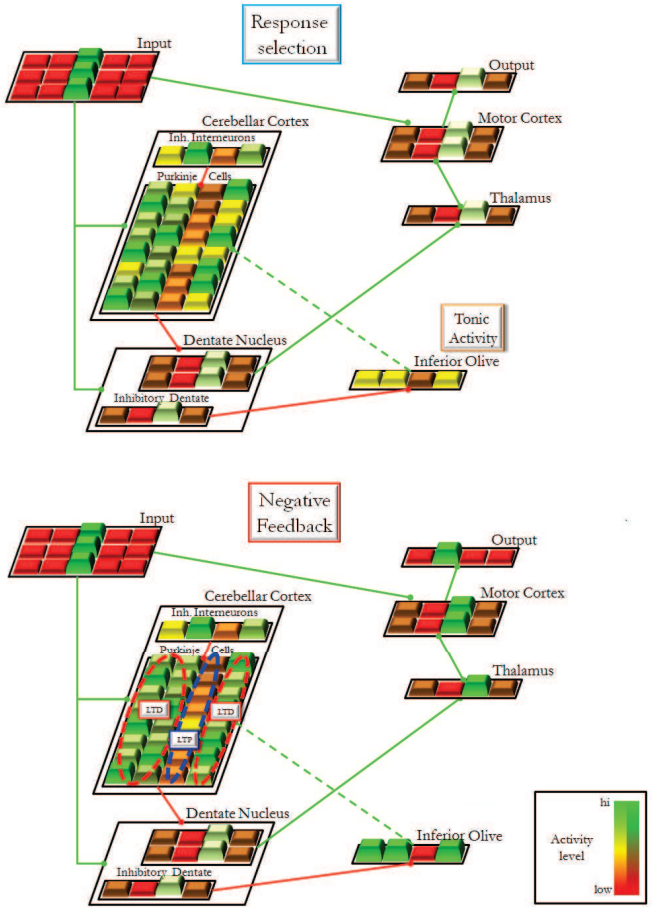


Figure 3.7 A negative feedback trial during training. Activity in the network during response selection (minus phase) and feedback (plus phase). During the plus phase activity in the inferior olive units increases, with the exception of the unit related to the selected response. LTD occurs in the active PF-PCs synapses that receives increased excitation from the inferior olive, whereas LTP occurs in the active PF-PCs synapses on the PCs that receives decreases excitation. Therefore, selected response is suppressed, whereas other responses are reinforced. Units activity corresponds to the scale reported at the bottom right of the figure.

Therefore, according to difference between activity states of the IO units in the minus and plus phases, LTD occurs in the active

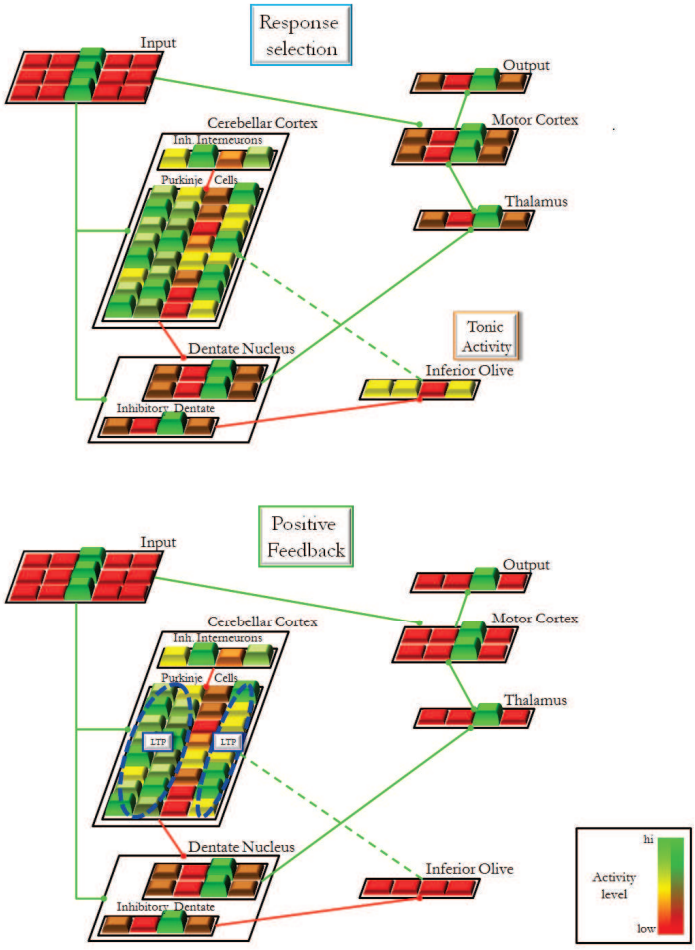


Figure 3.8 A positive feedback trial after learning. Activity in the network during response selection (minus phase) and feedback (plus phase). During the plus phase the activity in the inferior olive units decreases, with the exception of the unit related to the selected response. LTP, occurring in the active PF-PCs synapses that receives decreased excitation from the inferior olive, further suppress other responses. The level of activity of the units corresponds to the scale reported at the bottom right of the figure.

PF-PCs synapses on the PCs that receives increased excitation from the IO units, whereas LTP occurs in the active PF-PCs

synapses on the PCs that receives decreased excitation from the IO units.

Later in training, after the cerebellum has learned the S-R associations, whenever an input stimulus occurs, since the PF-PCs synapses related to the correct response are weakened and those related to the wrong responses are strengthened, only the nuclear cells related to the correct response are released from inhibition. These neurons excites the thalamus that, in turn, excites the region in the motor cortex related to the correct response.

Figure 3.8 shows the neural activity after learning, when the network selects the correct response and thus receives a positive feedback. In the example shown, the correct response to the input stimulus is represented in the model by the third unit in the output layer. Because of the previous experience, during the minus phase the microcomplex related to the correct response (the third column of the cerebellar cortex and dentate nucleus in the model) activates the correct output unit and, at the same time, reduces IO activity in the corresponding column. The remaining units of the IO show tonic activity. During plus phase the activity in the IO decreases because the network selected the correct response. Therefore, according to difference between activity states of the IO units in the minus and plus phases, LTP occurs in the active PF-PCs synapses on the PCs that receives decreased excitation from the IO units.

3.4 What is the goal in combining the Basal Ganglia and Cerebellum models?

According to the current knowledge of the anatomical and physiological features of the basal ganglia and cerebellum, it has been suggested that different computational processes occur within these neural systems, providing them the learning ability that allows humans to acquire and accurately execute motor

skills. It has been hypothesized by Doya [26] that the basal ganglia and cerebellum implement different learning algorithms. This author suggested that the basal ganglia are specialized for *reinforcement learning* and the cerebellum is specialized for *supervised learning*. In this view, the basal ganglia receive the reward signal from the substantia nigra through the nigrostriatal dopaminergic projections, whereas the cerebellum receives the teaching signal from the IO through the climbing fibers.

With regards to the role of dopamine as reward signal, it has been shown that phasic bursts and dips of dopamine occur during positive and negative feedback, respectively [52]. Instead, several hypothesis have been proposed about whether and how the error signal is encoded in the climbing fiber activity [12, 85]. Some cerebellar models reported in the literature are based on the assumption that the IO computes the discrepancy between the intended and the actual movement [62]. Others assume that the error signal is computed by the motor cortex and provided to the cerebellar cortex through the IO [72]. In both cases, it is supposed that the correct response is known and compared to the performed one. This mechanism lacks of biological plausibility because it is based on the hypothesis that the correct motor response, that the neural system should learn, is already known somewhere else.

In the cerebellum model here developed, the IO generates an error signal *without the explicit knowledge of the correct motor action*.

Indeed, whenever a phasic dip of dopamine occurs, meaning that the response selected is incorrect, a phasic burst of activity within the IO occurs (as reported in electrophysiological studies [12]). Otherwise, whenever a correct response is selected and a phasic burst of dopamine occurs, only the IO area related to that response has a phasic burst, whereas the remaining area has a phasic dip. As shown in Figure 3.8, as soon as the cerebellar network learns the task properly, no more increase in the IO activity occurs, because of the inhibitory connections from the dentate nucleus (that is more active when the motor sequence is acquired).

Moreover, according to the proposed hypothesis (discussed in chapter 2) and the studies presented in the literature, BG and DA critically mediates the acquisition of a behavior [53, 121], but they play a diminishing role in executing well-learned behaviors, because the motor sequence is maintained by the cortex-cerebellar system.

Therefore, the goal in combining the basal ganglia and cerebellum models is twofold:

- Provide further understanding about the learning mechanisms in the cerebellum, evaluating the role of LTD and LTP in CB learning, and the way the IO generates error signals.
- Provide further understanding about the role of the basal ganglia and cerebellum in procedural motor learning, testing the hypothesis that:
  - Early in learning, task performance is more dependent on the procedural knowledge maintained by the cortex-basal ganglia system.
  - After long-term practice, task performance is more dependent on the motor sequence maintained by the cortex-cerebellar system.

Chapter 4

Experimental Results

In order to validate the model, the behavior of the network in executing a motor task was evaluated. Particularly, the functions of motor loops, which comprise the interactions among the basal ganglia, cerebellum and motor cortex was investigated.

Neural activations within the network and the responses provided during learning of a simulated motor task were compared to the results reported in the experimental studies on motor learning presented in the literature.

Further experiments were carried out simulating lesions of the cerebellum and basal ganglia, and comparing the obtained results with those reported in experimental studies carried on patients affected by cerebellar and basal ganglia damage.

The analysis of the results obtained from simulations of the model provides some cues on the role of the basal ganglia and cerebellum in motor learning.

4.1 The motor task

The experiments involve the motor task shown in Figure 4.1, which consists in reaching an ordered sequence of points by selecting the appropriate sequence of motor commands. The network, provided by a sequence of input stimuli, learns the correct S-R associations

that allow the model to complete the task selecting the appropriate motor command, at the appropriate time, within the sequence.

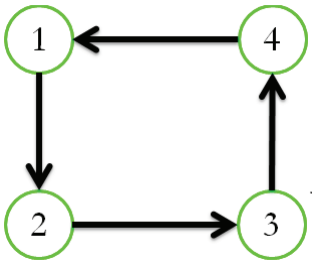


Figure 4.1 Simulated motor task. According to the input stimuli, representing the position of the current point, the network has to select the appropriate motor command to reach the next target point.

Therefore, after a certain number of training epochs, each consisting of four trials, the network learns the association and thus selects the correct sequence of motor commands to complete the task through the interaction of several modules within the basal ganglia and cerebellar circuitry.

4.2 The Neural Network

The network implementing the model, which comprises the basal ganglia and cerebellar circuitry, and whose behavior is analyzed in the experiments, is reported in Figure 4.2.

Simulations start with random weights, but the strength of the connections is reinforced or weakened during the course of training, depending on the feedback associated to the response selected by the network. This phenomenon allows the network to learn the S-R associations needed to complete the motor task properly.

At the beginning of each trial, in the minus phase, an input stimulus reaches the input nuclei of BG and CB, giving rise to a sequence of neural activations within BG and CB that leads to elicit a particular response. At the same time, the input stimulus directly activate multiple competing responses in the

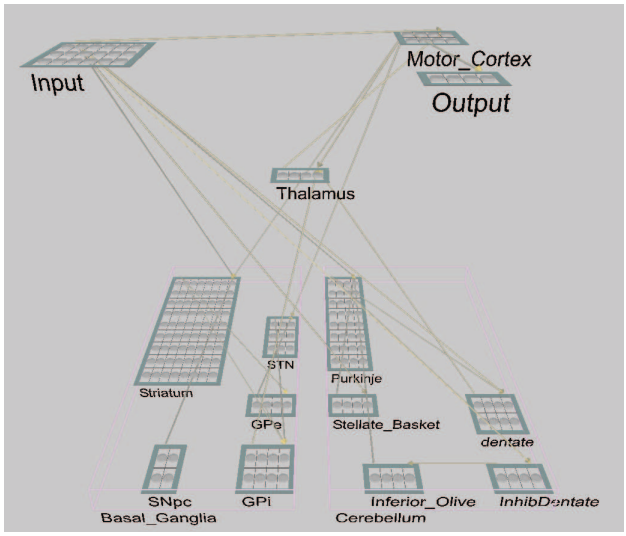


Figure 4.2 Neural network of the model for procedural motor learning, comprising the basal ganglia, cerebellum and motor cortex.

MC. However, these connections are not strong enough to select a response, therefore MC also needs support from the thalamus, whose activity is modulated by the BG and CB output nuclei.

Recalling that within BG and CB there are four distinct subloops working in parallel, each modulating a particular response, selection is achieved by the interaction of these four distinct modules. In the "plus" phase, the activity of the SNpc and IO changes depending on the correctness of the response chosen by the network in the "minus" phase. Particularly, activity changes in the network according to the following criteria:

- Whenever the network selects *the correct response* SNpc activity increases (thus providing a DA burst) and IO activity decreases (thus CFs do not provide an error signal).

- Whenever the network selects *the incorrect response* SNpc activity decreases (thus providing a DA dip) and IO activity increase (thus CFs provide an error signal).

As a result, connection weights change according to the difference between activity states of the network in the minus and plus phases.

4.3 The Cerebellum model

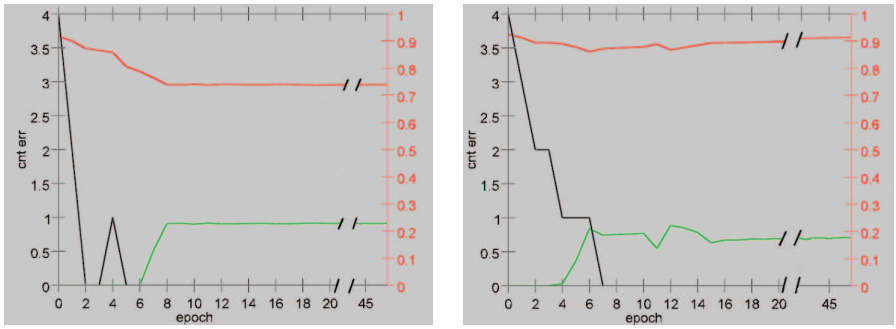
This section evaluates the CB model, analyzing the behavior of the network instantiating the cerebellar neural circuitry. Neural activations within the network were compared to those reported in the neuroimaging studies discussed in chapter 2. Furthermore, the hypothesized learning rule in the cerebellum was analyzed, evaluating the contribution of LTP and the way in which the activation within the IO changes during error feedback.

4.3.1 Neural activity in the Cerebellum

The results provided by several neuroimaging studies (as discussed in chapter 2) showed that the cerebellar cortex is more active during the initial phase of learning and its activity decreases progressively as learning proceeds. Simultaneously, activity in the dentate nucleus increases.

Figure 4.3 shows the neural activity in the cerebellar cortex and dentate nucleus while training the model on the motor task. In particular, Figure 4.3(a) shows neural activity in the networks in which only the phenomenon of LTD occurs in the cerebellar cortex, while Figure 4.3(b) shows the neural activity in the networks in which both LTD and LTP occur in the cerebellar cortex.

As shown in the figure, the neural activity is in accordance with the results reported by the neuroimaging studies previously analyzed. Indeed, during the initial phase of training, when the model selects a greater number of incorrect responses, cerebellar cortex is more active and its activity decreases progressively as learning proceeds. Dentate nucleus shows an opposite pattern of activation, being less active during the initial phase of training and becoming more active when the network learns the motor task and thus selects correct responses.



(a) (b)

Figure 4.3 Neural activity in the cerebellum. *Black lines* represent the number of errors made by the model. *Red lines* represent the average unit activity in the cerebellar cortex. *Green lines* represent the average unit activity in the dentate nucleus. (a) Learning rule without LTP. (b) Learning rule with LTP.

A subtle distinction between the two cases is that LTP causes a subsequent slow increase of the cerebellar cortex activity (Figure 4.3(b)).

Figure 4.4 reports the IO activity during training. As shown in the figure, IO activity increases whenever the networks selects incorrect responses and reduces as errors decrease.

4.3.2 Evaluation of the cerebellar learning rule

The cerebellum model incorporates a learning rule based on the theory proposed by Albus [1] for LTD and the theory proposed by Houk and Barto [55] for LTP. The mechanism of LTD proposed by Albus was supported by the later studies conducted by Ito [63, 64], while less is known about LTP.

Although activations within cerebellar networks without LTP best follow the cerebellar activations reported in the neuroimaging studies, it is noteworthy to observe that, with regard to the learning performance, LTP allows the cerebellum to unlearn a previously learned wrong S-R association. In other words, since LTD leads to PF-PC synaptic strength weakening, if during the

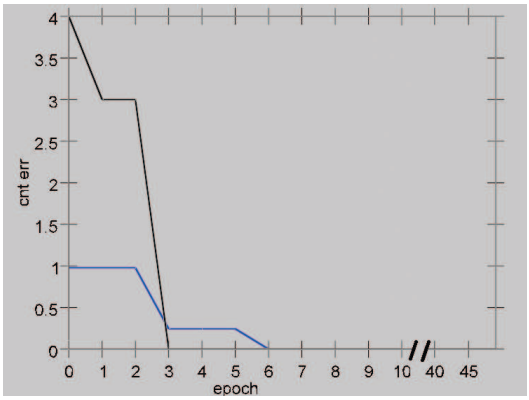
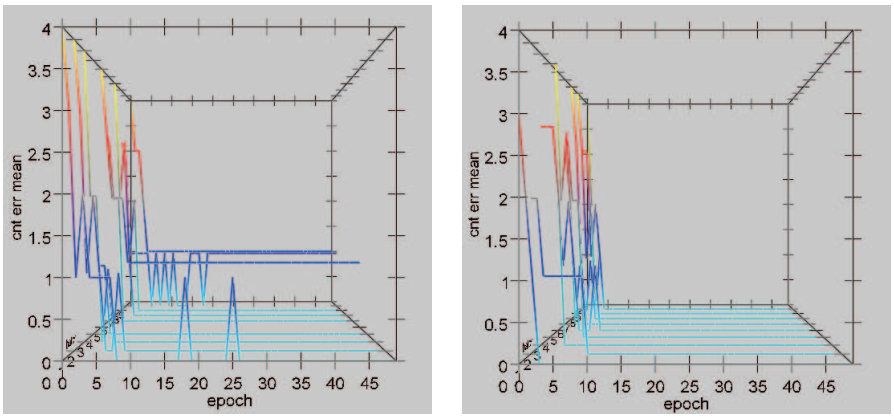


Figure 4.4 Neural activity in the inferior olive. *Black lines* represent the number of errors made by the model. *Blue lines* represent the average unit activity in the inferior olive.

initial phase of training a large number of errors occurs, it can happen that wrong PF-PC synapses are weakened, leading to the selection of the wrong response. Without LTP there is no possibility of unlearning the wrong S-R association, as shown in Figure 4.5(a).



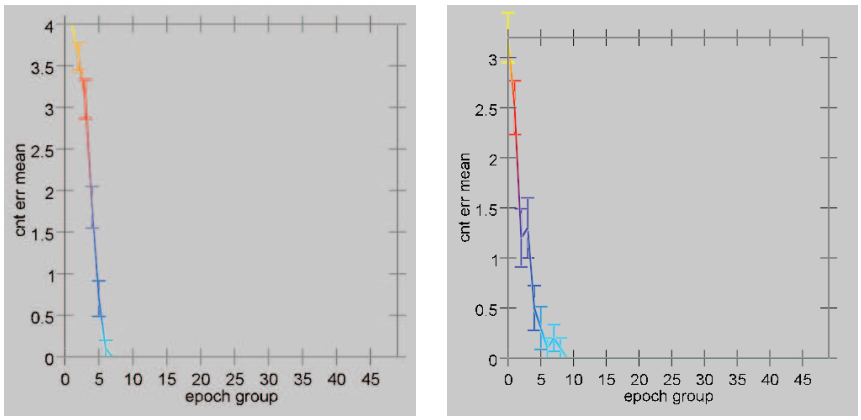
(a) (b)

Figure 4.5 Learning curves of 20 networks, trained for 50 epochs. (a) Learning rule without LTP. (b) Learning rule with LTP.

Therefore, the mechanism of LTP in the cerebellar cortex is necessary to perform the task properly. Moreover, section 4.6 will show that LTP is also essential to adapt the response when S-R associations are changed in the motor adaptation task.

As already mentioned in chapter 3, whereas most of the previous work on cerebellum is related to supervised learning, here the error signal is generated by the IO without the explicit knowledge of the correct motor action.

In Figure 4.6 are shown the learning curves of a pure cerebellum model with supervised learning 4.6(a) and those of the combined BG-CB model 4.6(b).



(a) (b)

Figure 4.6 Learning curves of 20 networks, trained for 50 epochs. (a) Pure cerebellum model with supervised learning. (b) Combined BG-CB model.

As shown, both models properly learn the S-R associations. However, although the cerebellum model provided with a supervised signal shows a slightly faster learning as compared to the combined BG-CB model, it is noteworthy that the this last is more biologically plausible because it learns the associations without an explicit teaching signal.

4.4 Simulated dopamine depletion during training and retention

According to the proposed hypothesis for procedural motor learning, the role of BG and DA is more important during the early stage of learning, when the spatial sequence of movements is acquired.

As reported in the literature [53, 121], dopamine critically mediates the acquisition and expression of a behavior during the initial stage of learning, whereas it plays a diminishing role in executing well-learned behaviors. Smith-Roe and Kelley [121] showed that co-activation of glutamate (NMDA) and dopamine (D1) receptors within the striatum (in the nucleus accumbens core) of rats had a key role for the acquisition of a new motor behavior (lever pressing), but it did not for the expression of the behavior after it was well-learned. Indeed, inhibition of NMDA-D1 receptors (through NMDA and D1 receptor antagonists) impaired learning, whereas it did not affect the performance in executing a previously acquired behavior.

Further support to this hypothesis comes from the observation that Parkinson's patients are able to perform automatic motor responses elicited by a stimulus, but they have difficulties in executing novel motor actions [77].

In order to evaluate this hypothesis, DA depletion was simulated at different epochs, from the beginning of the training phase to the retention phase. DA depletion was achieved by lesioning SNpc so that dopaminergic neurons were tonically inactive. As a result, tonic DA and phasic DA were absent during minus and plus phase, respectively.

A set of experiments was conducted changing the starting epoch of the lesion, from the first (epoch 0) to the last one (epoch 50). Each experiment was carried on 20 networks, each trained for 50 epochs. Each epochs consisted of 4 trials.

Figure 4.7 illustrates the results obtained, showing the number of errors after 50 epochs of training as a function of the lesion epoch.

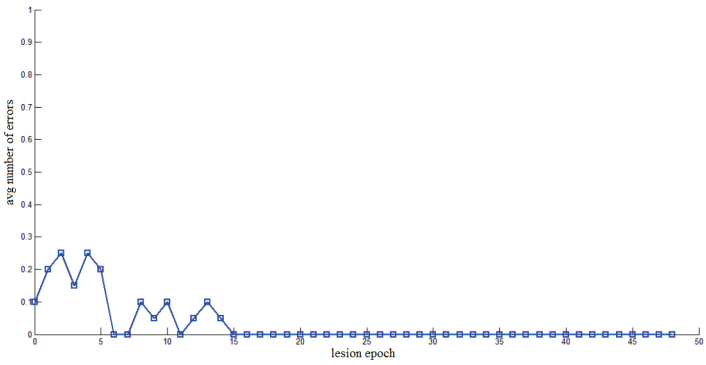


Figure 4.7 Simulated dopamine depletion. Number of errors made by the network after 50 epochs as a function of the epoch from which the SNpc is lesioned. Results are averaged over 20 network, for each epoch of lesion.

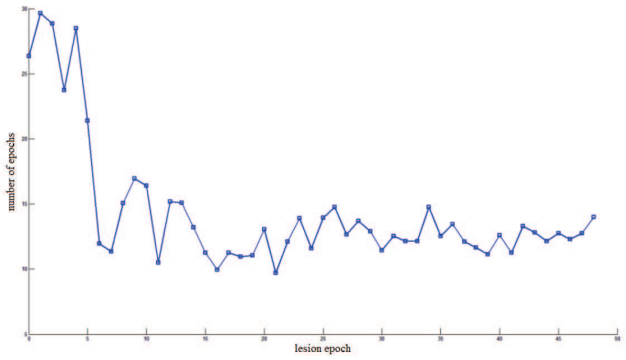


Figure 4.8 Simulated dopamine depletion. Number of epochs the network needs to properly learn the task, as a function of the epoch from which SNpc is lesioned. Results are averaged over 20 network, for each epoch of lesion.

These results show that DA depletion during the early stage of learning impairs the ability to learn and execute the task properly, whereas DA depletion does not impair the ability to properly perform the task after it is acquired by the cerebellum (that occurs approximately after 15 epochs).

As expected, the later the SNpc lesion occurs, the less the number of epochs are needed to properly learn the task, as shown

in Figure 4.8. The curve shows slight variations because the results are averaged over 20 networks (each starting with different random weights) for each epoch of lesion.

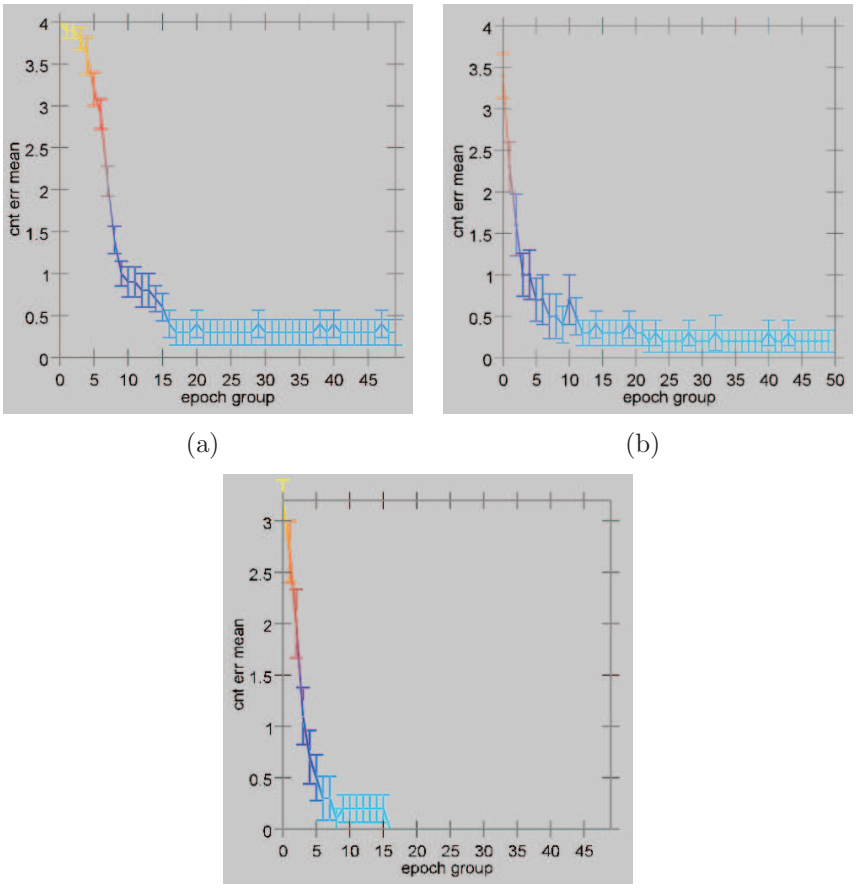


Figure 4.9 Simulated dopamine depletion. Learning curves, averaged over 20 networks, obtained with dopamine depletion occurring (a) at the beginning of training (epoch 0), (b) during training (epoch 10), and (c) after learning (epoch 25).

Figure 4.9 shows learning curves obtained in three particular conditions: DA depletion at the beginning of training 4.9(a), during training 4.9(b), and during retention 4.9(c), after the

cerebellum learned the motor task.

4.5 Simulated cerebellar damage

In order to test the hypothesis that the cerebellum function is more critical late in learning, thus after the sequence of motor commands is acquired, we simulated cerebellar damage after learning.

Cerebellar damage was simulated by lesioning 25% of the cerebellar cortex units after epoch 25 (after the network learned the motor task). The experiment was carried on 20 networks, each trained for 50 epochs. Each epochs consisted of 4 trials.

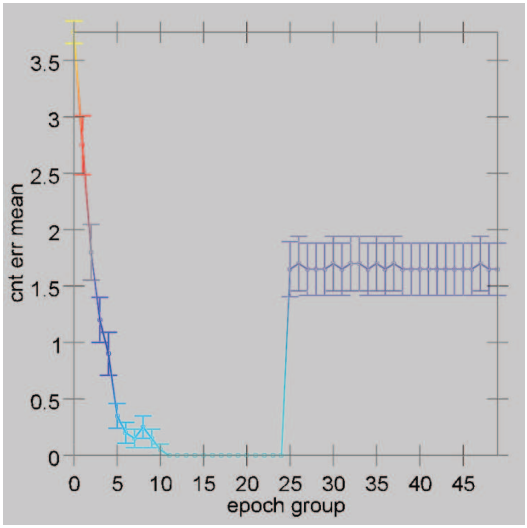


Figure 4.10 Simulated cerebellar damage. Learning curves, averaged over 20 networks, obtained by lesioning 25% of the cerebellar cortex units. Lesion occurs at epoch 25, thus after the networks learned the motor task. After cerebellar damage the networks are impaired in executing the previously acquired motor task.

As shown in Figure 4.10, after cerebellar damage, the network is impaired in executing the motor task previously learned.

4.6 Motor Adaptation task

In a motor adaptation task the participants are required to learn how to adapt their movements according to some external changes, artificially imposed by the experimenter. Usually, the ability of motor adaptation is tested asking to the subject to reach some targets on a screen, through a cursor, moving a joystick. The experiment involves two kind of conditions, "normal" and "adapted". During "normal" conditions task, the movements of the joystick correspond to the same movements of the cursor on the screen. Instead, during "adapted" conditions task, the relation between movements of joystick and cursor is changed, as shown in Figure 4.11.

A motor adaptation task is simulated in the model considering two training stages, in which the model learns S-R associations under "normal" conditions and "adapted" conditions. During the first stage of training, the model learns the motor task reported in Figure 4.1, as in the previous experiments. After 25 epochs of training, S-R associations are changed as in Figure 4.11. Figure 4.12 shows the obtained results.

As already mentioned, the mechanism of LTP is essential in the motor adaptation task, since the cerebellum has to unlearn the previously learned S-R associations and learn the new ones.

As shown in Figure 4.13 without LTP the cerebellum cannot unlearn the previously acquired S-R associations. Therefore, during the adaptation stage, the cerebellum is unable to learn new S-R associations.

Another experiment was carried out varying the duration of the first stage of training under normal conditions. It would expect that, extending training under normal conditions it should be more challenging for the subject to adapt the movements in the second training phase, when the relation between movements of joystick and cursor is changed.

In the model, this experiments was carried out by switching between normal and adapted conditions at different epochs, from epoch 25 to epoch 45 (each experiments lasts 70 epochs).

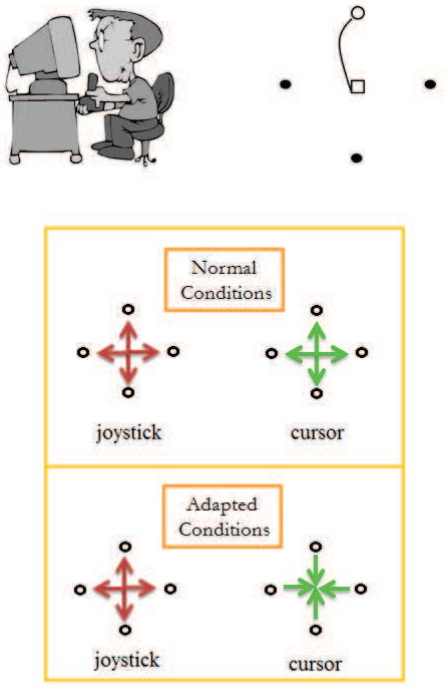


Figure 4.11 Motor Adaptation task. The subject has to reach some targets on a screen, through a cursor, moving a joystick. At some point, during training, the relation between movements of joystick and cursor is artificially changed by the experimenter, and the subject has to learn how to adapt the movements.

Figures 4.14 and 4.15 illustrate the results obtained for each switching epoch. Figure 4.14 shows the error rate in the adaptation phase at the end of training as a function of the switching epoch. Figure 4.15 reports the number of epochs the networks need to properly learn the motor task under adapted condition as a function of the switching epoch.

As expected, later switching between conditions occurs, the higher the error rate at the end of training is (as shown in Figure 4.14), because the network needs more time to adapt the responses. Indeed, the longer the duration of training under normal conditions, the greater the number of epochs required to

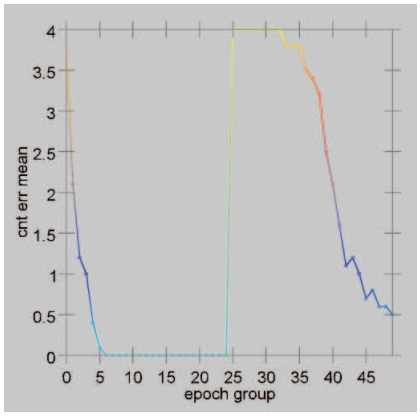


Figure 4.12 Motor Adaptation learning curves, averaged over 20 networks. Each stage lasts 25 epochs and each epoch consists of 4 trials. Changes in S-R associations occur at epoch 25.

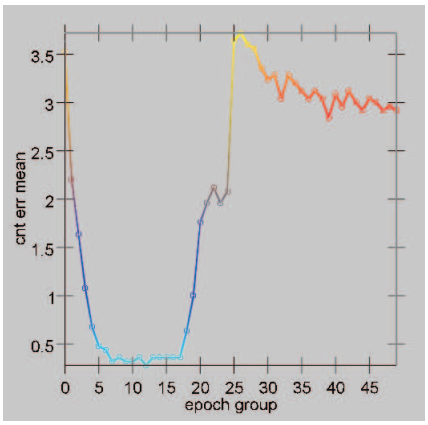


Figure 4.13 Motor Adaptation learning curves with a learning rule that involves only LTD. The learning curves are averaged over 20 networks. Each stage lasts 25 epochs and each epoch consists of 4 trials. Changes in S-R associations occur at epoch 25. The networks are impaired in learning new S-R associations during the adaptation stage.

learn the task during adaptation stage, as shown in Figure 4.15.

Figure 4.16 reports the learning curves obtained by switching between normal and adapted conditions at different epoch: after 10 (Figure 4.16(a)), 25 (Figure 4.16(b)), 40 (Figure 4.16(c)), and

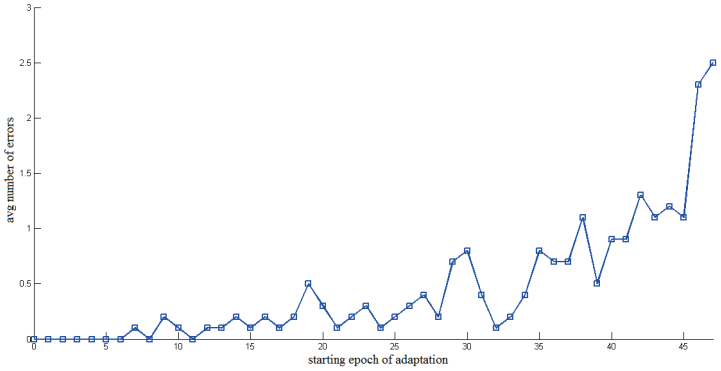


Figure 4.14 Motor adaptation task. Number of errors made by the network, at the end of adaptation stage, as a function of the starting epoch of adaptation. Results are averaged over 20 networks for each starting epoch of adaptation stage. Since the network selects four responses per epoch, max number of errors is four.

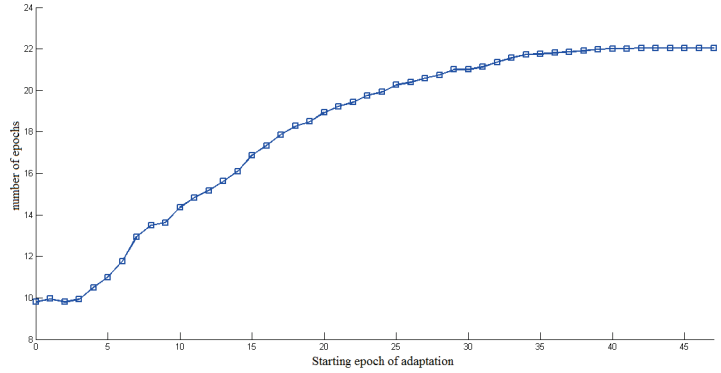


Figure 4.15 Motor adaptation task. Number of epochs the network needs to properly learn the task, as a function of the epoch from which adaptation stage starts. Results are averaged over 20 networks for each starting epoch of adaptation stage.

60 (Figure 4.16(d)) epochs.

As reported in the study of Smith and Shadmehr [119], patients affected by cerebellar damage are profoundly impaired in adapting to altered arm dynamics, whereas HD patients, which are affected

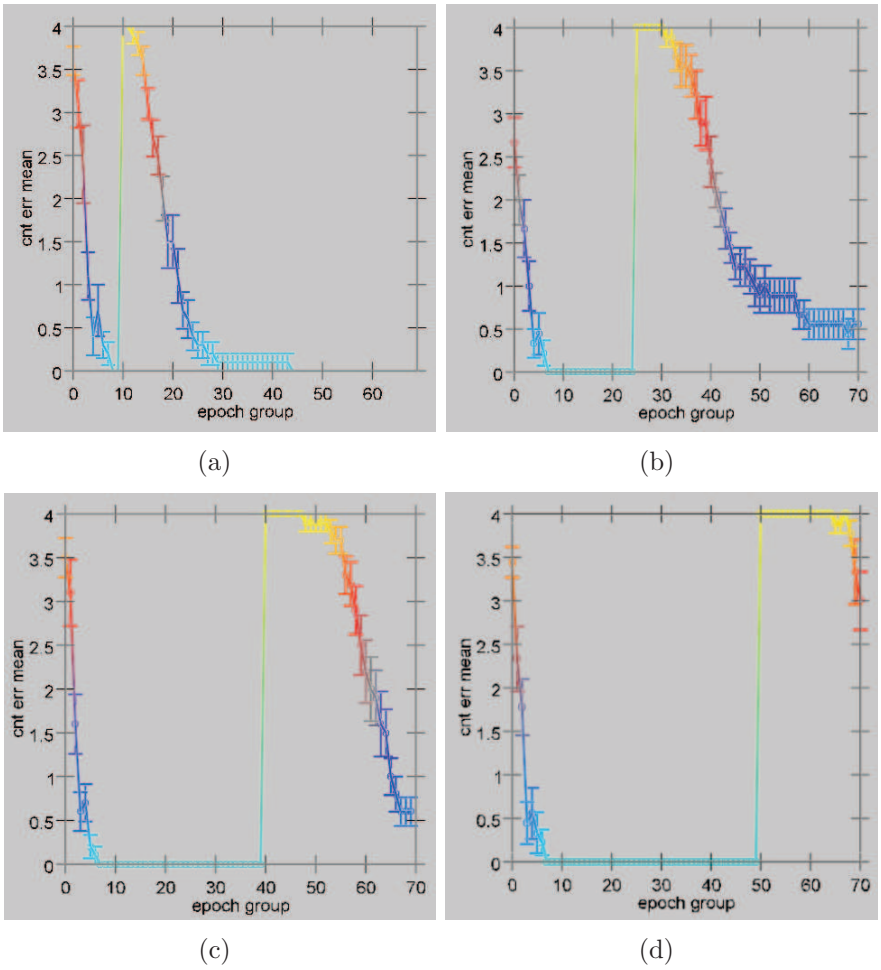


Figure 4.16 Motor adaptation task. Learning curves, averaged over 20 networks, obtained by switching between normal and adapted conditions at (a) epoch 10, (b) epoch 25, (c) epoch 40, and (d) epoch 60.

by striatal damage, exhibit no significant deficits. Furthermore, an experimental study conducted by Marinelli and colleagues [82] showed that PD patients and healthy subjects perform the motor adaptation task in a similar way.

In the model, cerebellar damage was simulated by lesioning 25% of the cerebellar cortex units, HD was simulated by lesioning

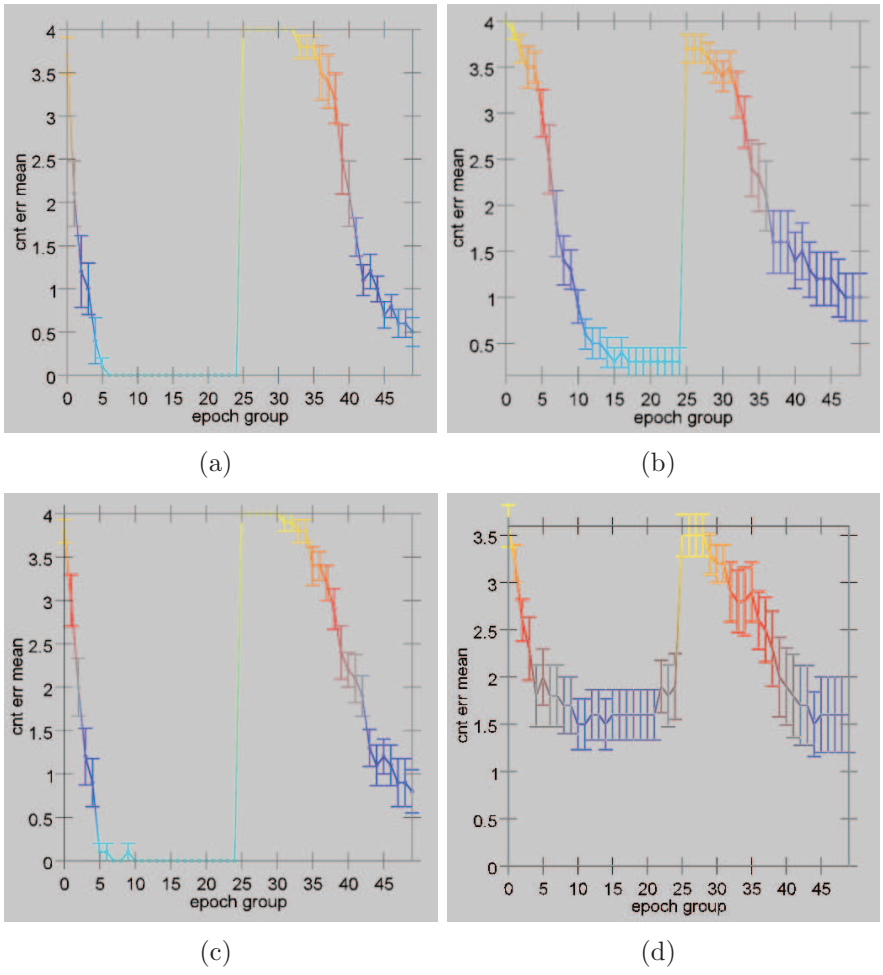


Figure 4.17 Motor adaptation learning curves, averaged over 15 networks. (a) intact network, (b) network with DA depletion, (c) network with striatal damage, and (d) network with cerebellar damage. Each stage lasts 25 epochs and each epoch consists of 4 trials. Changes in S-R associations occur at epoch 25. Since the network selects four responses per epoch, max number of errors is four. Learning is spared in (b) and (c), whereas the ability to adapt movements is impaired in (d).

25% of the striatal units and PD was simulated by lesioning 75% of SNpc units.

Figure 4.17 shows the learning curves obtained for each

condition: for intact networks (Figure 4.17(a)), DA depleted networks (Figure 4.17(c)), striatal damaged networks (Figure 4.17(b)), and CB damaged networks (Figure 4.17(d)).

Results reported in Figure 4.17 are consistent with those reported in the above mentioned experimental studies. Indeed, although the striatal damaged networks (Figure 4.17(b)) show a little impairment, i.e. slowed learning in both phases, they learn the S-R associations properly. DA depleted networks (Figure 4.17(c)) also show slowed learning, but in some cases they do not learn the S-R associations (in accordance with the results on dopamine depletion shown in section 4.4). Finally, learning is severely impaired in both phases in CB-damaged networks (Figure 4.17(d)).

According to the study of Smith and Shadmehr [119], patients with CB degeneration show impaired performance both in normal and adapted conditions, although performance is worse in the adaptation phase. In order to investigates whether the model shows the same behavior, different percentages of damaged CB units were simulated in the network. Figure 4.18 reports the obtained learning curves for each condition.

Results show that learning is impaired in CB damaged networks, although networks affected by more extended lesions show worse performance in the adaptation phase (as shown in Figure 4.18(d)).

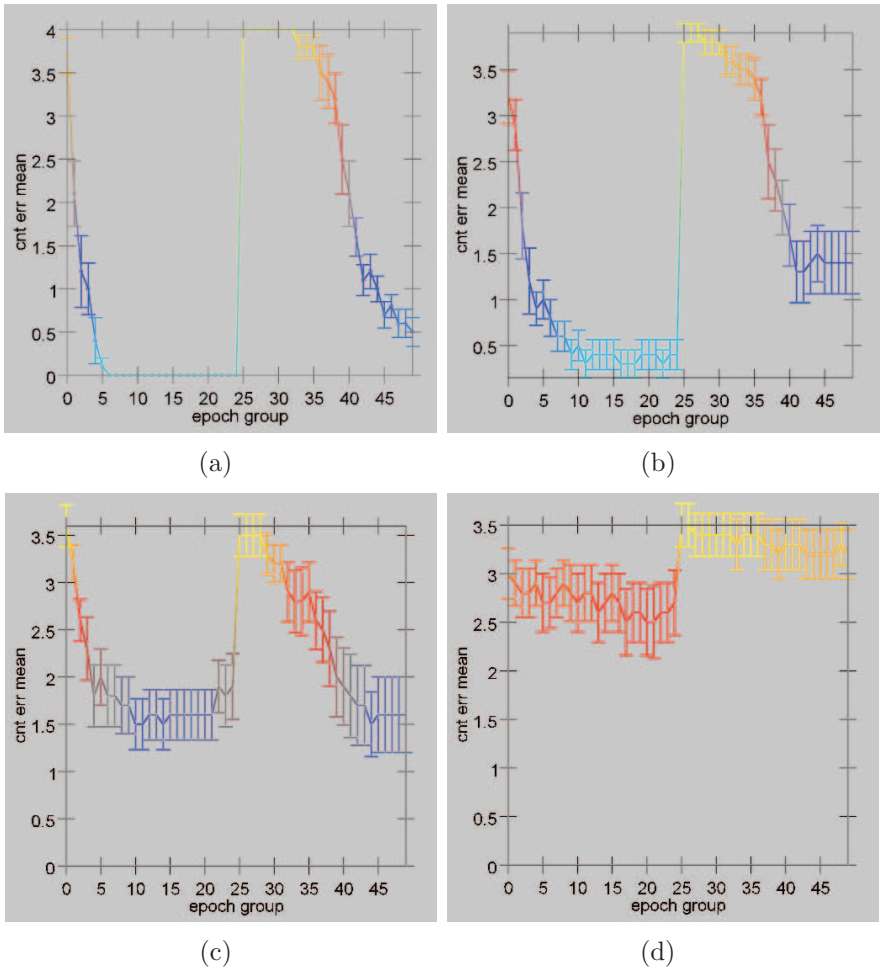


Figure 4.18 Motor adaptation learning curves of networks with different percentage of CB-damaged units. Results are averaged over 15 networks. (a) CB intact network, (b) networks with 12% of CB-damaged units, (c) networks with 25% of CB-damaged units, and (d) networks with 37% of CB-damaged units. Each stage lasts 25 epochs and each epoch consists of 4 trials. Changes in S-R associations occur at epoch 25. Learning is spared only in intact networks, whereas damaged networks show impairment in both phases. Figure (d) shows that with more extended cerebellar lesions (37%) performance is worse in the adaptation vs initial phase.

Conclusions

This thesis investigates the processes underlying the execution of complex sequences of movements and provides some insights about how different levels of the nervous system interact and contribute to the gradual improvement of motor performance during learning.

We propose a new hypothesis about the computational processes occurring during acquisition and retention of novel motor skills.

According to our hypothesis, a sequence of movements is stored in the nervous system in the form of a spatial sequence of points and a sequence of motor commands.

We propose that learning novel motor skills requires two phases, in which two different processes take place.

Early in learning, when movements are slower, less accurate, and attention demanding, the motor sequence is performed by converting the sequence of target points into the appropriate sequence of motor commands. During this phase, the trajectory plan is acquired and the movements rely on the information provided by the visuo-proprioceptive feedback, which allows to correct the sequence of movements so that the actual trajectory plan corresponds to the desired one and the lowest energy is spent by the muscular subsystem involved.

During the late learning phase, when the sequence of movements is performed faster and automatically, with little or no cognitive resources needed to complete it, and is characterized by anticipatory movements, the sequence of motor commands is acquired and thus, the sequence of movements comes to be executed as a single behavior.

We suggest that the **Basal Ganglia** and the **Cerebellum** are involved in learning novel motor sequences, although their role is crucial in different stages of learning.

Accordingly, we propose a neural scheme for procedural motor learning, comprising basal ganglia, cerebellum and cortex, which envisages that the basal ganglia, interacting with the cortex, select the sequence of target points to reach (composing the trajectory plan), whereas the cerebellum, interacting with the cortex, is responsible for converting the trajectory plan into the appropriate sequence of motor commands.

Consequently, we suggest that early in learning, task performance is more dependent on the procedural knowledge maintained by the cortex-basal ganglia system, while after a long-term practice, when the sequence of motor commands is acquired within the cerebellum, task performance is more dependent on the motor command sequence maintained by the cortex-cerebellar system.

The neural scheme (and the hypothesis behind it) was evaluated through a computational model that incorporates the key anatomical, physiological and biological features of these brain areas in an integrated functional network.

We analyzed the behavior of the network in learning a motor task, evaluating the neural activation within the network and the error rate of the responses provided. We found that the results obtained, both in terms of the neural activations and motor response, fit those reported by many neuroimaging and experimental studies presented in the literature.

We also carried out further experiments, simulating neurodegenerative disorders (Parkinson's and Huntington disease, which affect the basal ganglia) and cerebellar damages. Results obtained by these experiments validates the proposed hypothesis, showing that the basal ganglia play a key role during the early stage of learning, whereas the cerebellum is crucial for motor skill retention.

In order to evaluate the role of the cerebellum in motor adaptation, we performed a set of experiments simulating a motor

adaptation task. The results obtained (which resembled those reported in the literature) showed that cerebellar damages impair the ability to adapt movements.

The model also provide some insights about how the error signal needed for training the cerebellum is generated, and the learning mechanisms occurring within the cerebellar cortex. Indeed, one of the network's emergent properties is that the phenomenon of Long-Term Potentiation (whose role is still debated in the literature) is essential for motor learning.

Therefore the model provides novel predictions about the role of basal ganglia and cerebellum in motor learning and motivates further investigations of their interactions.

The model does not comprise the (recently found) two-way path linking the basal ganglia and cerebellum that is independent of the cerebral cortex [14, 54]. Therefore, a future development of this work could be the introduction in the model of these pathways, in order to investigate whether these anatomical connections are the base of a functional interaction, and maybe, provide an answer to the questions proposed by these researchers:
"Is the cerebellar input associated with motor and cognitive disorders that are characteristic of basal ganglia dysfunctions?"
"When basal ganglia activity is abnormal, is cerebellar input part of the problem or part of the solution?".

Appendix A

Implementational details

The model is implemented using a subset of the Leabra framework [98]. Particularly, the model incorporates two properties of this framework:

- the *point neuron activation function*;
- the *k Winner-Take-All* ***(kWTA)*** *inhibition function*

Following sections describe these functions and the learning algorithms incorporated in the model. The parameter used in the model are reported in the last section.

A.1 The point neuron approximation

As implemented in [98], the neurons in the model operate according to a *point neuron approximation*. This approximation models a neuron simplifying its geometry to a single point, therefore using a single equation to describe its electrophysiological properties. This equation is derived from the basic dynamics of information processing of real biological neurons.

Excitatory, inhibitory and leak synaptic input channels are simulated and their conductance g_c and reversal potential E_c contribute to the net current I_{net} as follows:

$$
\begin{aligned}
I_{net} &= \sum_c g_c(t)\overline{g}_c(V_m(t) - E_c) \\
&= (g_e(t)\overline{g}_e(V_m(t) - E_e) \\
&+ g_i(t)\overline{g}_i(V_m(t) - E_i) \\
&+ g_l(t)\overline{g}_l(V_m(t) - E_l)) \qquad \text{(A.1)}
\end{aligned}
$$

where the three basic channels activating the neuron are: e excitatory input, i inhibitory input and l leak current. The excitatory input channels are activated by the neurotransmitter glutamate, the inhibitory input channels are activated by the neurotransmitter GABA and the leak channel are always open and passing the K^+ (potassium) ion.

The total conductance of each channel is decomposed into two terms: $g_c(t)$ represents the fraction of open channels for the ion c at time t, whereas $\overline{g}_c$ represents the maximum conductance for that ion. The net current influences the membrane potential V_m of the neuron, which is updates as follows:

$$V_m(t+1) = V_m(t) - \tau I_{net} \qquad \text{(A.2)}$$

Therefore:

$$
\begin{aligned}
\delta V_m(t) &= \tau \sum_c g_c(t)\overline{g}_c(E_c - V_m(t)) \\
&= \tau(g_e(t)\overline{g}_e(E_e - V_m(t)) \\
&+ g_i(t)\overline{g}_i(E_i - V_m(t)) \\
&+ g_l(t)\overline{g}_l(E_l - V_m(t))) \qquad \text{(A.3)}
\end{aligned}
$$

where τ represents a time constant, which captures the speed of updating the membrane potential for the neuron.

Therefore, the membrane potential (Eq. A.2 and A.3) changes according to the excitatory and inhibitory inputs from other neurons. The equilibrium potential V_m^{eq} represents the value of the membrane potential for which the excitatory input balances

the inhibitory input and leak current. Therefore, this value is obtained by setting I_{net} to zero in Eq. A.1 and solving for the value of V_m. We obtain:

$$V_m^{eq} = \frac{g_e \overline{g}_e E_e + g_i \overline{g}_i E_i + g_l \overline{g}_l E_l}{g_e \overline{g}_e + g_i \overline{g}_i + g_l \overline{g}_l} \tag{A.4}$$

The excitatory input conductance $g_e(t)$ is the average over all the inputs coming into the neuron, weighted by the strength of the connections:

$$g_e(t) = \langle x_i w_{ij} \rangle = \frac{1}{n} \sum_i x_i w_{ij} \tag{A.5}$$

The inhibitory conductance for a unit is computed from the net input of the sending units. Instead, inhibition within a layer is computed using the kWTA inhibition function above mentioned, which is explained in the following section. Finally, the leak conductance is constant.

The activation function, which provides the firing rate associated to the membrane potential of the neuron, is a thresholded sigmoidal function of the membrane potential, having a *X-over-X-plus-1* form:

$$\begin{aligned} y_j &= \frac{\gamma[V_m - \Theta]_+}{\gamma[V_m - \Theta]_+ + 1} \\ &= \frac{1}{1 + (\gamma[V_m - \Theta]_+)^{-1}} \end{aligned} \tag{A.6}$$

where:

$$[V_m - \Theta]_+ = \begin{cases} V_m - \Theta & \text{if } V_m - \Theta > 0 \\ 0 & \text{if } V_m - \Theta \leq 0 \end{cases}$$

In the equation, y_j is the activation value, γ represents a gain parameter and Θ is the threshold. In order to take into account the

effect of the processing noise of biological neurons, the activation function is convolved with a Gaussian-distributed noise:

$$y_j^*(x) = \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi\sigma}} e^{-\frac{x}{2\sigma^2}} y_j(z-x)dz \tag{A.7}$$

where $y_j^*(x)$ is the noise-convolved activation and x represents the value returned by the $[V_m - \Theta]_+$ expression.

A.2 k Winner-Take-All inhibition function

The inhibitory interneurons within a layer provide a level of inhibition that is proportional to the level of excitation coming into the layer, maintaining the level of activity roughly constant. This effect is simulated in the model via the kWTA function. This function guarantees that among the units that receive the most excitatory input, no more than k units are active at the same time. The value of the inhibitory conductance as a function of the excitatory input that put the equilibrium membrane potential just at the threshold is obtained by setting V_m^{eq} to the threshold Θ in Eq. A.4 and solving for the value of g_i. We obtain:

$$g_i^{\Theta} = \frac{g_e \overline{g}_e (E_e - \Theta) + g_l \overline{g}_l (E_l - \Theta)}{\Theta - E_i} \tag{A.8}$$

where g_i^{Θ} represents the value of inhibitory conductance that puts the unit just at the threshold.

Depending on the flexibility in determining how many units are active, two versions of kWTA function can be distinguished, the basic kWTA function and average-based kWTA function.

Sorting the units by the level of excitatory conductances, the basic kWTA algorithm selects the value of g_i between the g_i^{Θ} values of the kth and $k+1$th most excited units, as follows:

$$g_i = g_i^{\Theta}(k+1) + q(g_i^{\Theta}(k) - g_i^{\Theta}(k+1)) \tag{A.9}$$

where $0 < q < 1$ (usually set to 0.25) is a constant and determines where to place the inhibition between $g_i^{\Theta}(k+1)$ and $g_i^{\Theta}(k)$.

This version of the kWTA is used in the striatum layer, with $k = 3$ and $q = 0.25$.

The average-based kWTA algorithm provides more flexibility regarding to the level of activity within the layer. Indeed, the value of g_i is chosen between the average of the g_i^{Θ} values for the kth most active units $\langle g_i^{\Theta} \rangle_k$ (Eq.A.10), and the average of the g_i^{Θ} values for the remaining units $\langle g_i^{\Theta} \rangle_{n-k}$ (Eq. A.11).

$$\langle g_i^{\Theta} \rangle_k = \frac{1}{k} \sum_{i=0}^{k} g_i^{\Theta}(i) \tag{A.10}$$

$$\langle g_i^{\Theta} \rangle_{n-k} = \frac{1}{n-k} \sum_{i=k+1}^{n} g_i^{\Theta}(i) \tag{A.11}$$

Therefore, the expression for g_i is the following:

$$g_i = \langle g_i^{\Theta} \rangle_{n-k} + q(\langle g_i^{\Theta} \rangle_k - \langle g_i^{\Theta} \rangle_{n-k}) \tag{A.12}$$

The average-based kWTA is used in the motor cortex layer, with $k = 1$ and $q = 0.6$.

A.3 Learning algorithms

In order to simulate feedback effects, the learning algorithms involve two distinct phases: *minus* and *plus phase*.

During the "minus" phase the network settles into activity states and selects a response depending on the input stimuli and the network's weights. In the "plus" phase, dopamine release (i.e. SNpc activity) and climbing fibers firing (i.e. IO activity) change depending on the selected response.

With regard to the SNpc, dopaminergic neurons increase from tonic to high level of activity (i.e. from activation value of 0.5 to 1) for a correct response, whereas an incorrect response causes a

decrease from tonic to zero level of activity (i.e. from activation value of 0.5 to 0). Synaptic connection weights in the BG model change according to the version of reinforcement learning rule of the Leabra framework [98]. The learning mechanism combines Hebbian model and error-driven task learning (a more detailed explanation can be found in [98]).

The equation for the Hebbian weight changes is:

$$\Delta_{hebb} w_{ij} = \epsilon(x_i^+ y_j^+ - y_j^+ w_{ij}) = \epsilon y_j^+ (x_i^+ - w_{ij}) \tag{A.13}$$

where ϵ represents the learning rate parameter. The equation for error-driven task learning is:

$$\Delta_{err} w_{ij} = (x_i^+ y_j^+) - (x_i^- y_j^-) \tag{A.14}$$

In order to keep weight changes within the 0-1 range, the error-driven weights are bounded:

$$\Delta_{sberr} w_{ij} = [\Delta_{err}]_+ (1 - w_{ij}) + [\Delta_{err}]_- w_{ij} \tag{A.15}$$

Therefore, the amount of weight changes is computed adding together the weight changes obtained by Hebbian model with those obtained by soft-bounded error-driven learning:

$$\Delta w_{ij} = \epsilon[k_{hebb}(\Delta_{err}) + (1 - k_{hebb})(\Delta_{sberr})] \tag{A.16}$$

where k_{hebb} is a parameter that controls the relative proportion of these two types of learning.

With regard to the CB model, the learning rule (eq. A.17) takes into account the theory proposed by Albus for LTD [1] and the theory proposed by Houk and Barto for LTP [55]. PF-PC synapses are weakened (i.e. LTD occurs) whenever the PC fires in the presence of simultaneous activation of the CF and PFs that synapse on the PC, whereas LTP occurs whenever there is PF activity without either postsynaptic depolarization or CF discharge. Depending on the response selected, climbing fibers firing changes in the opposite way of SNpc: IO units activity

increases for incorrect responses (i.e. from an activation value of 0.5 to 1) and decreases for correct responses (i.e. from an activation value of 0.5 to 0, except for the IO unit related to the response). Therefore, synaptic connection weights change according to the following equation:

$$\Delta w_{ij} = \epsilon[PF_i^-(CF_j^+ - CF_j^-)PC_j^-] \tag{A.17}$$

where ϵ represents the learning rate parameter. In the experiments reported in chapter 4 the values of the learning rate parameters for LTP and LTD are $\epsilon_{LTP} = 0.02$ and $\epsilon_{LTD} = 0.06$, respectively.

A.4 Model parameters

The model parameters of the Basal Ganglia, Cerebellum, Motor Cortex and Thalamus are reported in Tables A.1, A.2 and A.3. The parameters are obtained from the associated biological values through a process of normalization (described in [98]).

In order to simulate contrast enhancement in the striatum [37, 38], gain γ and threshold Θ parameters for striatal neurons change during DA phasic bursts and dips as follows:

$$\gamma = \begin{cases} 10000 \cdot k & \text{for positive feedback DA+} \\ 600 - 300 \cdot k & \text{for negative feedback DA-} \end{cases}$$

$$\Theta = \begin{cases} 0.25 + 0.04 \cdot k & \text{for positive feedback DA+} \\ 0.25 & \text{for negative feedback DA-} \end{cases}$$

where $(0 \leq k \leq 1)$ represents the percentage of intact SNpc units (k=1 for intact networks).

	Parameter								
Layer	E_e	g_e	E_i	g_i	E_l	g_l	V_{rest}	Θ	γ
Striatum	1	1	0.15	1	0.15	1	0.15	0.25	600
GPi	1	1	0.15	1	0.275	3	0.26	0.25	600
GPe	1	1	0.15	2.5	0.275	1	0.26	0.25	600
STN	1	1	0.15	1	0.2	1	0.25	0.25	600

Table A.1 Basal ganglia model parameters.

	Parameter								
Layer	E_e	g_e	E_i	g_i	E_l	g_l	V_{rest}	Θ	γ
Purkinje	1	1	0.15	1	0.275	3	0.26	0.25	600
Stellate_Basket	1	1	0.15	1	0.15	0.1	0.15	0.25	600
Dentate	1	1	0.15	1.5	0.15	0.1	0.15	0.25	600
Inf. Olive	1	1	0.15	2	0.15	0.1	0.15	0.25	600

Table A.2 Cerebellum model parameters.

	Parameter								
Layer	E_e	g_e	E_i	g_i	E_l	g_l	V_{rest}	Θ	γ
MC	1	1	0.15	1	0.15	0.1	0.15	0.25	600
Thalamus	1	0.5	0.15	1.7	0.15	0.07	0.15	0.25	600

Table A.3 Motor cortex and thalamus parameters.

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