Introduction

CEREBELLAR SURVEILLANCE AND CORRECTION OF ACTIONS

Life is a continuum of receiving environmental information and formulation of responses for survival, satisfaction, and, in the best-case scenario, also happiness. The central nervous system is specialized in processing information conveyed by the sensory organs and elaborates reactions effectuated by the muscles and the endocrine system.

The process of reacting to environmental stimuli can be very simple, like the knee-jerk reflex in which the touch of the knee causes the movement of the leg. In everyday life, however, reacting to environmental stimuli can be incredibly complex. When a person is playing soccer or when a prey runs away from a predator, the sensory information, from multiple modalities, flows into the nervous system as a continuum, and it is continually used to adjust the ongoing movements. The complexity of this process is further increased by the possibility of moving some of the sensory organs to optimize the collection of information. The process by which sensory and motor systems communicate and coordinate with each other to couple perception and action is called sensory-motor integration. While simple reflexes, like the knee-jerk reflex, are mediated by the spinal cord (McHenry, 1969), more complex forms of sensory-motor integration involve several brain structures, including the cerebellum (Devi & Reddy, 1972; Doba

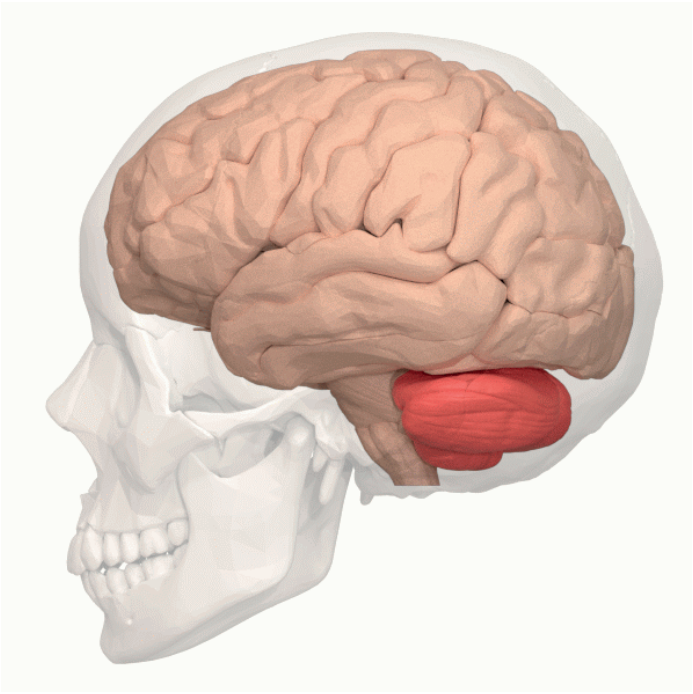

Figure 1. The human brain has three main parts: the cerebrum, brainstem, and cerebellum, the latter of which is highlighted in red. Image from Wikimedia Commons, created by DBCLS and distributed under Creative Commons Attribution.

& Reis, 1972; Fujita, 1982; Higgins, 1987; Mnukhina, 1951; Pellegrini & Evinger, 1997; Shinoda & Yoshida, 1974). The cerebellum is an essential part of the central nervous system that integrates the inputs coming from the sensory organs and several parts of the brain, to control the spatial accuracy and the temporal coordination of the muscles during movements (for a review see (Fine, Ionita, & Lohr, 2002). This structure was named cerebellum, which in Latin means "small-brain" because, in almost all vertebrates, its volume is far smaller than the volume of the cerebrum, the "big-brain" (Figure 1), (Sultan & Glickstein, 2007). Despite the cerebellar volume being approximately one-tenth of the volume of the cerebrum, it contains the majority of the neurons of the whole central nervous system (Williams & Herrup, 1988). However, cases of severe deficiencies in the development of the cerebellum suggest that this structure is not required for human survival (Glickstein, 1994). For instance, in a recent and well-described case of complete cerebellar agenesis, "...only mild to moderate motor deficiency, dysarthria and ataxia" were reported (Yu, Jiang, Sun, & Zhang, 2015), (Figure 2). The fact that the person without the cerebellum was only diagnosed when she was 24-year-old, already married, and gave birth to a daughter suggests that the cerebellum is dispensable for many body functions.

Nevertheless, even though there was initially no critical need to have a clinical diagnosis, even in this patient, many suboptimal sensorimotor functions were already present during early life (Yu et al., 2015). Accordingly, the cerebellum has been found to play many roles in a great number of processes that range from sensorimotor to autonomic and cognitive functions (Fine et al., 2002). This seeming contradiction between contributing to many things and being dispensable for many others suggests that the cerebellum is an auxiliary structure that gets involved specifically in optimizing the acquisition and the execution of functions that could still take place, but with less accuracy. This hypothesis could explain why the abovementioned person without cerebellum did start to walk and speak only around the age of 7-years-old. A similar conception has also emerged in a very different context, including experimental settings. For instance, a genetically modified mouse line, in which the activity of the majority of cerebellar

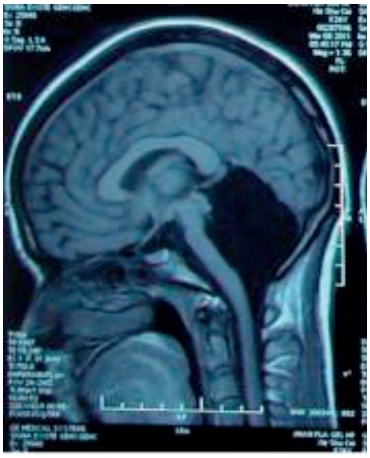

Figure 2. Sagittal MRI of a case of cerebellar agenesis. Adapted from (Yu et al., 2015).

neurons was suppressed, showed impairments in learning but not in the execution of classical behavioral tests (Galliano et al., 2013). It is known that compensatory mechanisms are likely to occur in the cases of human cerebellar agenesis, as well as in cerebellar specific mouse models (Jin et al., 2019). However, it was surprising that symptoms associated with spinocerebellar ataxia such as intention tremor, dystonia and ataxia were absent also in many other cerebellar specific knockout mice (Schonewille et al., 2010; Schonewille et al., 2011). In these mouse mutants, the intact cerebellum is essential only for the acquisition of new complex actions like the more challenging adaption of the oculomotor activity (Galliano et al., 2013; Galliano et al., 2018). The cerebellum, however, modulates its activity along with several types of basic movement (Becker & Person, 2019; Cerminara, Apps, & Marple-Horvat, 2009; Chen, Augustine, & Chadderton, 2017; Krauzlis & Lisberger, 1991; Sarnaik & Raman, 2018). For example, experiments on mouse whisker movements have shown that, even though the cerebellar neuronal activity encodes the execution of simple motor behaviors, it does not clearly show the temporal features required to drive the movement (Chen, Augustine, & Chadderton, 2016; Chen et al., 2017). Anatomical studies suggest that the modulation of the cerebellar activity during movements could be driven by proprioceptive reafferent inputs coming from large part of the body (G. Sengul, Y. H. Fu, Y. Yu, & G. Paxinos, 2015). During movement, the cerebellum also receives an efferent copy of inputs that from the motor areas, such as the primary motor cortex, target primary motor neurons (Wolpert, Ghahramani, & Jordan, 1995). According to this scenario, the cerebellum receives information about ongoing movements but does not necessarily always contribute to its execution. Therefore, the fact that the cerebellum continually keeps an eye on the ongoing motor performance could serve to adapt rapidly, compensate, and correct for any unforeseen circumstance or perturbation. To adjust ongoing movements rapidly, it has been proposed that the cerebellum generates an internal representation (i.e., neuronal model) of the sensory-motor consequences of the motor command (Wolpert et al., 1995). Whether the cerebellum generates predictions or bases the adaptation of the ongoing motor program just on the somatosensory feedback, the existing body of literature lets us envision a scenario in which the cerebellum oversees our actions - a bit like the big brother that George Orwell described in 1984. In his marvelous novel, Orwell recounts the omnipresent government surveillance in the imaginary super-state of Oceania. Anytime anything would deviate from the desires of Big Brother, the leader of the single-party of Oceania, the Thought Police would intervene to correct anything related to that deviation. If we imagine our body as the super-state of Oceania, then indeed, we would have the cerebellum as the Big Brother of Orwell's novel, which controls the execution of all our actions. Whenever correction is required, the "observer" goes into action, outputting the specific spike patterns that can be read out by the downstream pre-motor nuclei. Before going into detail about the aim of my research, I will briefly introduce some basic anatomical and physiological background.

CEREBELLAR ANATOMY, CIRCUITRY, AND FUNCTIONS

Gross anatomy

In all mammals, the cerebellum can be subdivided into three main lobes. The primary fissure separates the anterior and posterior lobes. The posterolateral fissure, instead, divides the posterior from the flocculonodular lobe. Phylogenetically, the flocculonodular lobe is the most primitive, and it is also named "vestibulocerebellum." Later the medial portion of both the anterior and the posterior lobes developed (which includes the vermis and medial part of the hemispheres), which is named "spinocerebellum." Finally, the lateral hemispheres or "cerebrocerebellum" developed (Kandel, 2013). The three lobes can be further subdivided into ten lobules indicated by the roman numbers (Larsell, 1952) or using an alternative nomenclature that emphasizes the relative independence of the vermis and hemispheres (Bolk, 1906). In Bolk's nomenclature, the hemispheres corresponding to lobules six and seven are named Simplex, Crus 1, and Crus 2 (Figure 3). In rodents, these lobules receive sensory inputs from the whisker system (Bosman et al., 2010; S. T. Brown & Raman, 2018; Kleinfeld, Berg, & O'Connor, 1999; Shambes, Gibson, & Welker, 1978), and their stimulation can elicit whisker movement (Esakov & Pronichev, 2001; Lang, Sugihara, & Llinas, 2006). Since the whisker system is the model that we have selected to study the cerebellar functions, in this thesis, we investigated the neural activity of Simplex, Crus 1, and Crus 2 lobules.

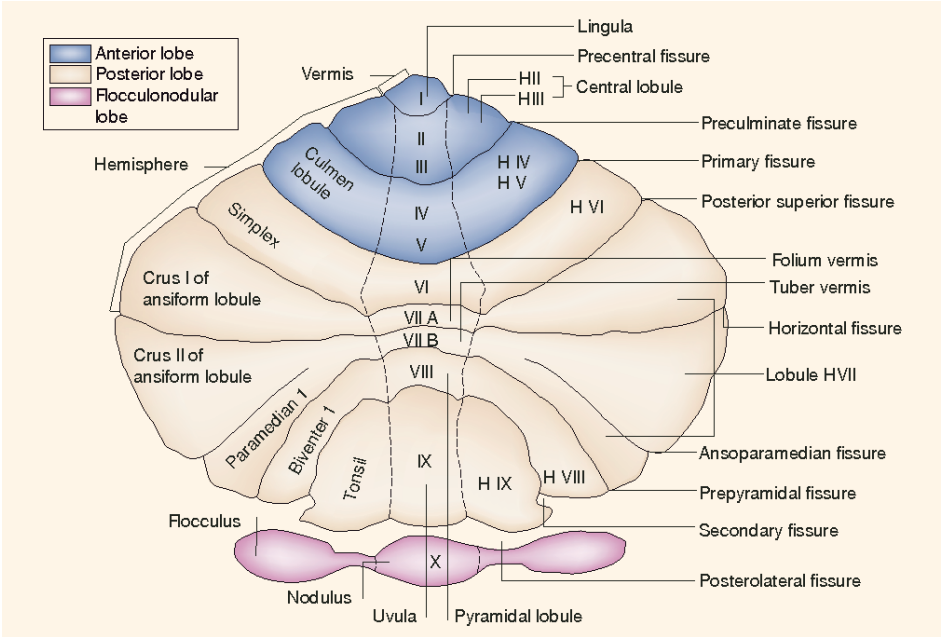

Figure 3. Representation of the cerebellar lobules. From (Manni & Petrosini, 2004) with permission.

Cytoarchitecture of the cerebellar cortex

Despite some minute differences that have been recently discovered (Cerminara, Lang, Sillitoe, & Apps, 2015), the cytoarchitecture of the cerebellar cortex is highly homogeneous (Kandel, 2013). It constitutes of three layers throughout all lobules. The granular cell layer represents the input layer of the cerebellar cortex and the mossy fiber system innervates it. The mossy fiber afferences provide excitatory glutamatergic inputs coming from many areas of the central and peripheral nervous system (Berretta, Perciavalle, & Poppele, 1991; Schafer & Hoebeek, 2018; G. Sengul, Y. Fu, Y. Yu, & G. Paxinos, 2015) to granular and Golgi cells in a particular structure called the glomerulus. The climbing fiber system, instead, targets Purkinje cells forming one of the strongest excitatory synapses of the whole brain (De Zeeuw et al., 2011). These fibers contact the proximal part of the dendrites of the Purkinje cells, which are extended up to the peripheral end of the molecular layer. The molecular layer forms the outmost portion of the cerebellar cortex; this layer contains the parallel fibers, which originate from granular cells and provide direct excitatory glutamatergic input to Purkinje cells and inhibit Purkinje cells via the molecular layer interneurons (stellate and basket cells), (Figure 4). Thus, the Purkinje cells integrate the inputs from the mossy fiber – parallel fiber system with those carried by the climbing fibers (De Zeeuw et al., 2011). These inputs control the spike activity of the Purkinje cells, which consist of relatively rare complex spikes (1-2Hz) and more frequent simple spike (30-150 Hz) (De Zeeuw et al., 2011). While parallel fibers modulate the simple spike firing, the climbing fibers elicit complex spikes whose calcium transients regulate several plasticity mechanisms in a synergistic fashion (Gao, van Beugen, & De Zeeuw, 2012).

Neuronal activity and information processing by Purkinje cells

Within a Purkinje cell, a very high level of input integration takes place. Their primary input source is represented by the granular cells. These cells are more numerous than all the other neurons of the brain taken together. In humans, for instance, there are an estimated 70 billion granular cells (Williams & Herrup, 1988). Each granular cell has an ascending axon that reaches the molecular layer where it bifurcates to form two parallel fibers running orthogonally for several millimeters and potentially reaching up to hundreds of Purkinje cells dendritic trees (Palkovits, Magyar, & Szentagothai, 1971). Thus, the inputs coming from thousands of mossy fibers are conveyed into granular cells with a high level of divergence, and with billions of parallel fibers, these inputs converge onto the massive Purkinje cell dendritic tree (which is one of the, if not the, largest of all neurons), (Kandel, 2013). Since the Purkinje cells form the sole output station of the cerebellar cortex, the activity of all cerebellar cortical neurons is eventually integrated into the Purkinje cells. Due to these Purkinje cell peculiarities, the axonal spiking of the Purkinje cells represents the final output of all cerebellar cortex computations. Thus, given that Purkinje cells can be considered to be the main computational unit of the cerebellar cortex (An et al., 2019; A. M. Brown et al., 2019), I have taken their electrical activity as the main outcome measure of this thesis.

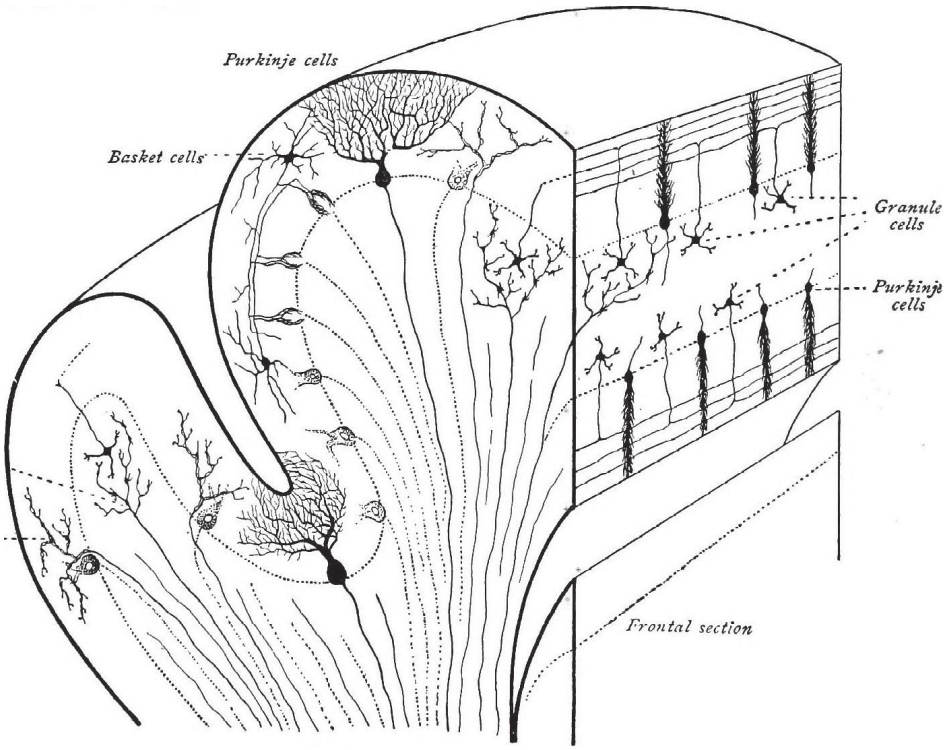

Figure 4. Cytoarchitecture of the cerebellar cortex. From (Villiger & Piersol, 1912) via Wikimedia Commons.

Anatomical pathway of the olivo-cerebellar system

Besides the cerebellar cortical circuit, discussed in the previous paragraph, the activity of Purkinje cells gets integrated within a series of other circuits that involve several areas of the central nervous system. The inputs from the Purkinje cells provide a powerful convergent inhibition onto the vestibular and cerebellar nuclei (Figure 5). The cerebellar nuclei neurons, together with axons of the Purkinje cells that target the vestibular nuclei, constitute the sole output of the entire cerebellum (Kandel, 2013). The cerebellar output then targets downstream pre-motor neurons located in the brainstem (Teune, van der Burg, van der Moer, Voogd, & Ruigrok, 2000), the spinal cord (Berretta et al., 1991) and, several portions of the cerebral cortex via the thalamus (Kelly & Strick, 2003). Some of those brainstem nuclei, in turn, project back to the cerebellum generating a series of feedback loops. The most remarkable loops are represented by the projections from the cerebellar nuclei to the inferior olive that can provide direct mono-synaptic inhibition or indirect di-synaptic excitation via the nuclei of the meso-diencephalic junction (De Zeeuw & Ruigrok, 1994). The olivo-cerebellar loops are organized in parasagittal modules (Ruigrok, 2011). Purkinje cells of a longitudinal zone of the cerebellar cortex, via the corresponding part of cerebellar nuclei, target the portion of the inferior olive from which originate their own climbing fibers (Voogd, 2011). The cerebellar nuclei also project

to the cerebral cortex via the thalamus. In turn, projections from the cerebral cortex go directly or indirectly to the cerebellum via the pontine nuclei and inferior olive, from which mossy fibers and climbing fibers originate, respectively (Schafer & Hoebeek, 2018). The presence of these recurrent connectivities implies that the cerebellum operates in close relationship with other brain areas and that behavior is likely to emerge by their reciprocal influence. Some pieces of evidence in this respect are presented in chapter 6 of this thesis. In particular, we tested the impact of the Purkinje cell stimulation onto the primary somatosensory and motor cortex and on whisker movements. The whisker system has been used as a model to study the cerebellar functions throughout all the experiments presented in this thesis.

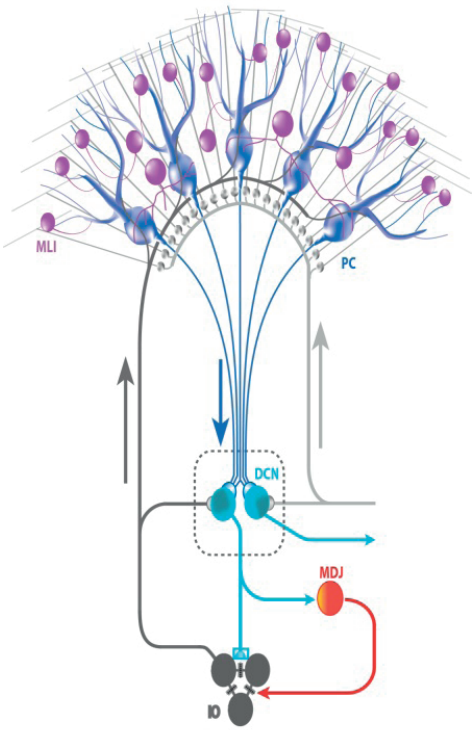

Figure 5. Schematic representation of the Olivo-cerebellar loops

The whisker system as a model to study the cerebellar function

The whisker system has been proposed as an ideal model to study sensory-motor integration (Bosman et al., 2011; Bosman et al., 2010; Kleinfeld, Ahissar, & Diamond, 2006). Among mammals, mice are preferably used in neuroscience, mostly because specific genes can be easily inserted or knocked out from their genome, increasing the possibility of manipulating a certain system dramatically. The main sensory modality by which mice explore their environment is represented by tactile sensory information coming from the facial whiskers (Ahl, 1986;

Prescott, Diamond, & Wing, 2011). Thus the whisker system is highly ethologically relevant for mice, and mice are highly relevant for neuroscience studies. The whisker system combines the movements of the mystacial vibrissae with direct sensory feedback. The cerebellum receives whisker inputs via both the mossy fiber and climbing fiber pathways. From the trigeminal nuclei, whisker inputs go directly to the cerebellar cortex (via the mossy fibers) and indirectly via the inferior olive (Bosman et al., 2011; Kleinfeld et al., 1999), where the climbing fibers originate (Torvik, 1956). Other trigeminal nuclei projections reach the mossy fiber system via the pontine nuclei and a thalamo-cerebro-pontine loop (Kleinfeld et al., 1999). It was proposed that the cerebellar output reach the portion of the facial nucleus responsible for whisker movements via the motor cortex (Lang et al., 2006). Recently, connections from the cerebellar nuclei to the whisker related pre-motor nuclei in the reticular formation have been proposed as a more direct pathway for the cerebellar control of whisker movements (S. T. Brown & Raman, 2018). Thus, whiskers and cerebellum are reciprocally connected via multiple sensory and motor pathways as expected for a system performing sensory-motor integration processes. For this reason, the whisker system can be used as a model to study how cerebellar neurons convert sensory inputs to motor commands. The whisker system can be also be used to study the neural control of its coordination with other motor domains. For instance, in chapter 5, we used the knowledge that the whisker movement can be phase-locked with breathing (Moore et al., 2013) to explore whether the same cerebellar area controls multiple motor domains. Besides, the whisker system is likely to be plastic and undergo adaptation upon specific training. Whether this is indeed the case and whether the cerebellum plays any possible role in whisker adaptation was completely unknown. This motivated us to study the cerebellar contribution to whisker sensory-motor integration and to the adaptation of the whisker system in chapter 3. In fact, if the whisker system undergoes cerebellar-mediated plastic changes, it could be used as a new model for the study of the neural correlates of cerebellar learning.

Neuronal correlates of cerebellar learning

In general terms, the cellular substrate of learning and memory is the neuronal plasticity. Neuronal plasticity is the capability of neurons to adapt their morphology and/or their functioning based on their antecedent activity. During the last fifty years, a great number of cellular mechanisms underlying neural adaptation have been discovered (for a review see (Gao et al., 2012)). Among these many forms of neuronal plasticity, the modification of the synaptic strength has been historically proposed as the main mechanism underlying learning and memory (Bliss & Collingridge, 1993; Hawkins, Abrams, Carew, & Kandel, 1983; Hebb, 1949; Shaw, 1986). For a few decades, the depression at parallel fiber to Purkinje cell synapses (PF-LTD) has been considered to be the main mechanism underlying cerebellar learning (Gilbert & Thach, 1977; Ito, 1972, 1982; Koekkoek et al., 2003; Medina & Lisberger, 2008; Simpson & Alley, 1974). The original cerebellar learning theory, proposed by David Marr in 1969, foresaw the facilitation of the parallel fiber to Purkinje cell synapses (PF-LTP) rather than their

depression (Marr, 1969). Two years later, this original hypothesis has been changed because James S. Albus, in his legendary article, stated that "the learning process to be stable must be accomplished principally by weakening synaptic weights rather than by strengthening them" (Albus, 1971). This last theory hypothesizes that the cerebellar motor learning is supervised by the activity of the climbing fibers that act as a teaching signal. Within the Purkinje cells, the signal representing the ongoing movement is compared with the signal representing the desired movement, and the teaching signal (i.e., the complex spike activity) adjusts the cerebellar output to correct the movement. James S. Albus's prediction received strong support from the Masao Ito's experimental results about the capability of the climbing fiber activity to induce PF-LTD (Ito, 1982). Consequently, the possible role of parallel fiber to Purkinje cells facilitation in learning processes was relatively diminished while the Marr-Albus-Ito's theory with PF-LTD as main neuronal correlates of learning has constituted one of the main milestones of the cerebellar doctrine. In this thesis, however, I will focus on the importance of the facilitation of Purkinje cells, as originally proposed by David Marr exactly fifty years ago. In this respect, this can be seen as my modest tribute to David Marr for the fiftieth anniversary of his "A theory of cerebellar cortex."

Multiple forms of plasticity underlying motor learning

Beside the PF-LTD (Konnerth, Dreessen, & Augustine, 1992), long term potentiation at the parallel fiber to Purkinje cell synapses (PF-LTP) was demonstrated to exist (Hansel, Linden, & D'Angelo, 2001), and the directionality of these competing forms of plasticity depends on the climbing fiber activity (Coesmans, Weber, De Zeeuw, & Hansel, 2004; Hirano, 1990; Linden & Ahn, 1999; Shibuki & Okada, 1992). Further studies showed that many other cerebellar neuron types undergo plastic changes of their structure, intrinsic excitability, and synaptic strength (for a review see (Gao et al., 2012)). In this scenario, multiple types of plasticity act together at several levels of the cerebellar circuitry in a synergistic manner to more efficiently adapt the computation and so the behavior. Among all these plasticity mechanisms, PF-LTD has been the most extensively studied in association with learning paradigms such as eye-blink conditioning and saccadic eye movements adaptation (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2018; Koekkoek et al., 2003; Medina & Lisberger, 2008; ten Brinke et al., 2015; Ten Brinke et al., 2017; Voges, Wu, Post, Schonewille, & De Zeeuw, 2017). However, increased simple spike activity was observed during saccadic eye movement adaptation and acquisition of VOR gain-increase (Herzfeld et al., 2018; Medina & Lisberger, 2008; Voges et al., 2017). Thus, during this type of learning, the increased simple spike activity could be caused by cellular mechanisms such as the potentiation of Purkinje cell-intrinsic excitability and parallel fiber to Purkinje cell synapses (*for simplicity I will refer to the combination of these two mechanisms as Purkinje cells potentiation, while considering Purkinje cell depression as the opposite mechanism*). This also emerged with learning deficits reported in Purkinje cell potentiation-deficient mutant mice (Schonewille et al., 2010; Schonewille et al., 2011). Conversely, no cerebellar learning deficit could be detected

in three independent mutant mouse lines with impaired PF-LTD (Schonewille et al., 2011). Thus, the specific plasticity mechanisms that sustain the different types of cerebellar learning are still not well understood. To test whether a learning-induced simple spike's facilitation requires Purkinje cell potentiation, in chapter 3 of this thesis, we developed a new training paradigm for the adaptation of whisker reflexive protraction and applied it to two independent PF-LTP deficient mouse lines.

Differential prevalence of Purkinje cell potentiation or suppression in cerebellar lobules encoding for different forms of cerebellar dependent learning

The fact that LTP deficient mice showed more severe learning deficits than LTD deficient mice suggested that some types of cerebellar motor learning could require Purkinje cell potentiation more than Purkinje cell depression (De Zeeuw & Ten Brinke, 2015; Galliano et al., 2013; Galliano et al., 2018; Schonewille et al., 2011). It has also been shown that the instructive climbing fiber signal, by which Purkinje cell depression is induced, is not required for one of the most classical cerebellar dependent learning paradigm (Ke, Guo, & Raymond, 2009). The group of Jennifer Raymond induced the vestibular ocular reflex adaptation using a training paradigm in which the "instructive" climbing fiber signal was absent. The induction of learning in absence of climbing fiber signal suggested that "other neural instructive signals make a substantial and independent contribution to motor learning." However, experiments involving other forms of cerebellar dependent learning, such as saccade adaptation and eyeblink conditioning, have shown to be dependent on climbing fiber activity and consequent Purkinje cell simple spike suppression (Attwell, Ivarsson, Millar, & Yeo, 2002; Herzfeld et al., 2018; Koekkoek et al., 2003; Medina & Lisberger, 2008). Importantly, these different types of cerebellar learning depend on different lobules of the cerebellum. Therefore, it has been proposed that in some cerebellar lobules, memory formation is predominantly sustained by suppression mechanism while potentiation mechanisms prevail in other cerebellar zones (De Zeeuw & Ten Brinke, 2015). More specifically, in Purkinje cells located at the floor of the primary cerebellar fissure, which is the area linked to conditioned eyelid behavior, suppression of simple spike activity, and not facilitation, appears to be the most prominent correlate of learning (ten Brinke et al., 2015). Conversely, the main neural correlate of learning in Purkinje cells located in the flocculus, which instead is an area associated with VOR adaptation, appears to be potentiation and simple spike facilitation (Voges et al., 2017). Therefore, we know which plasticity mechanisms are likely to sustain specific types of cerebellar learning only for a few specific parts of the cerebellar cortex. Conversely, we do not know which plasticity mechanisms may prevail in other parts of the cerebellar cortex and what are their ultimately impact on behavioral functions. For instance, even if we know that the adaptation of locomotion is cerebellar dependent and, we know which portion of the cerebellar cortex is more related with this particular type of behaviour (Darmohray, Jacobs, Marques, & Carey, 2019), we still don't know which are the main plasticity mechanisms underlying its

adaptation. Similarly, while we know that, in mice, large parts of Crus 1 and Crus2 lobules are anatomically and functionally related to the whisker system (Bosman et al., 2010; S. T. Brown & Raman, 2018; Chen et al., 2016; Kleinfeld et al., 1999; Lang et al., 2006; Shambes et al., 1978), we do not know which is the cerebellar contribution to whisker movement and which particular forms of plasticity in these areas are responsible for the adaptation of whisker kinematic. In this respect, the research reported in this thesis predominantly aimed to elucidate the relatively unknown contribution of the spike activity of Purkinje cells of Crus 1 and Crus 2 lobules on whisker movement and the plasticity mechanisms underlying its adaptation.

SCOPE OF THE THESIS

Continuing on the efforts of this laboratory, which provided pioneering evidence on the importance of parallel fiber to Purkinje cell potentiation in cerebellar motor learning, this thesis aspires to elucidate further the role of Purkinje cell potentiation and simple spike facilitation in several behavioral circumstances.

After the brief introduction of **Chapter 1**, we want to address the following questions:

- **Chapter 2:** To what extent does the discrimination between two object positions depend on potentiation at parallel fiber to Purkinje cell synapses? Is Purkinje cells potentiation particularly relevant when a whisker-based discrimination task has to be performed in a shorter time interval?
- **Chapter 3:** Can sensory stimulation induce long term increase of simple spike activity and associated plastic changes in the whisker system? Is Purkinje cells potentiation a required mechanism for such an increase of simple spike and its ultimate impact at the behavioral level?
- **Chapter 4:** To what extent can the rhythmicity of climbing fiber discharges be induced by applying external stimuli to behaving mice or to a realistic tissue-scale computational model?
- **Chapter 5:** Can the Purkinje cells of the same cerebellar area contribute to the synergistic control of breathing and whisking?
- **Chapter 6:** How does the cerebellar output affect the interplay between primary motor and somatosensory cortex during sensory-motor processing?

Finally, in **Chapter 7**, the main results of all the chapters are summarized and discussed, highlighting the significance of these findings and the future direction of our research.

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