General discussion

The main results of this thesis revealed how the simple spike activity of Purkinje cells of Crus 1, Crus 2, and simplex lobule can affect whisker and respiratory movements. The simple spikes of Purkinje cells can accelerate the respiratory and whisker movements, mainly during training and/or adaptation. In Crus1, Crus2, and simplex lobule, simple spike facilitation was the primary neural correlate of the whisker movement adaptation, and Purkinje cell potentiation appears to be the crucial cellular mechanism sustaining the simple spike facilitation. Conversely, the fact that suppression of simple spike activity was observed only in a minority of cells suggests that the type of whisking and breathing adaptation that we examined in this thesis is unlikely to depend on Purkinje cell depression in this cerebellar area. In addition to the main results of this thesis, other considerations on the specific results of the various chapters will be discussed in the following paragraphs grouping the results relative to simple spikes, complex spikes, as well as Purkinje cell potentiation.

THE ROLE OF SIMPLE SPIKES

In chapter 2, the simple spike activity of Purkinje cells lacking protein phosphatase 2B was more regular than in wild type mice, and the learning of a whisker-based object localization task was inefficient. In these mice, the lack of the protein phosphatase 2B, which impaired Purkinje cell potentiation, did not affect motor performance of the vestibular ocular reflex, but principally its adaptation (Schonewille et al., 2010). The learning deficits presented in chapter 2 increased depending on the level of challenge that the mice were presented with. This suggests that the unimpaired simple spike firing pattern is particularly important when mice have to learn to perform fast sensory-motor integration.

In chapter 3, we examined the ability of two Purkinje cell-specific knockout mouse lines (one for protein phosphatase 2B and one lacking the gene for AMPA receptor GluA3 subunit) to adapt their reflexive whisker protraction (i.e., a forward whisker sweep induced by sensory stimulation). The whisker adaptation was induced by applying a training paradigm consisting of 20 seconds of 4 Hz air-puff stimulation. In these mouse lines, the altered simple spike modulation did not result in any detectable deficit of the motor performance of the untrained reflexive whisker protraction. However, it impaired the capability of Purkinje cell-specific knockout mice to adapt their whisker reflexive protraction. When we compared the trial-by-trial variation in instantaneous simple spike firing with that of the whisker position, we noted that there was a positive correlation. This means that trials with relatively many simple spikes typically displayed stronger whisker protraction. We found that the correlation was maximal with a zero lag, implying that simple spike modulation neither preceded nor followed the whisker movement, but occurred at the same time. This result did not emerge in a previous study in which the correlation between simple spike modulation and whisker position had been calculated at a population level (Brown & Raman, 2018). Our result indicates that simple spikes were

unlikely to drive the untrained reflexive whisker protraction. After the training paradigm, the simple spikes correlated with the magnitude of the whisker movement with a lead of about 20 ms. This temporal relationship corresponded to what could be expected for the simple spike driving whisker movement via the cerebellar nuclei and the pre-motor whisker neurons in the brainstem (Bellavance et al., 2017; Deschenes et al., 2016; Moore et al., 2013; Teune, 2000). Thus, the result of chapter 3 indicates that the simple spikes represent the untrained reflexive whisker protraction, but they can anticipate and amplify the reflex execution under particular circumstances.

The findings of chapter 5 offer a new way of looking at simple spike modulation during the performance of simultaneous movements. After the investigation of how Purkinje cell activity could affect whisker movements, we have evaluated their impact on respiration. At rest, simple spikes encode but do not anticipate, the phase of the respiratory cycle. Instead, upon air puff sensory stimulation, an increase of simple spike activity preceded and potentially accelerated the subsequent respiration cycle. This facilitation was not only necessary for the anticipation of the subsequent cycle but also predicted the magnitude of the inhalation on a trial-by-trial base of about 20ms. Therefore, during the resting condition, the simple spikes were representing the phase of the ongoing respiratory cycle; then, in response to external environmental conditions, the simple spikes potentially contributed to the adaptation of respiration. In addition to these findings, another important aspect links chapter 3 and chapter 5. About half of the cells involved in the adaptation of respiration also exhibited neural correlates of whisker position. This result suggests that Purkinje cells are a suitable candidate not only for adjusting respiration upon sensory stimulation but also for the synergistic control of breathing and whisking. In fact, the optogenetic stimulation of the Purkinje cells correlating with whisking and breathing was able to affect both respiration and whisker movements. Therefore, Purkinje cells that are thought to control one single motor behavior could, in principle, coordinate that particular behavior with others that tend to occur simultaneously.

Besides the Purkinje cell contribution to behavior described, the results in chapter 6 indicate that the impact of simple spike burst on primary motor and sensory cortices depends on the state of the animal. We compared the impact of air puff and optogenetic Purkinje cell stimulation on the coherence between primary somatosensory and motor cortices. Purkinje cell optogenetic stimulation affected mainly the coherence between primary somatosensory and motor cortices within the gamma band. The effect of Purkinje stimulation was stronger in the trials with larger whisker movement than in those with smaller movements. This result suggests that similarly to what resulted from chapter 3 for whisking and chapter 5 for respiration, the extent to which the cerebellar output affects other brain areas, like the primary motor and sensory cortices, also depends on behavioral context: “stronger impact of the cerebellar activity during larger movements.” It would be interesting to test whether the theta sensory stimulation used (to induce plasticity in Purkinje cells and enhance whisker protraction) in chapter 3 could have an impact on the coherence between primary somatosensory and motor cortices. This because

it has been proposed that, during whisking, the transfer of information between the neocortex and other brain structures, such as the hippocampus, occurs in the theta rhythm (Grion et al., 2016; Kleinfeld et al., 2016). Considering that also the cerebellar activity is enhanced in the theta band (D'Angelo et al., 2009; Moscato et al., 2019; Ramakrishnan et al., 2016; Roggeri et al., 2008) it is likely that Purkinje cell stimulation at theta frequencies could be particularly effective to modulate the coherence between primary somatosensory and motor cortices in the gamma band (as described in chapter 5), but also in other ranges of frequencies.

In conclusion, during whisker movement, the simple spikes rate of Purkinje cells of Crus 1, Crus 2 mainly increases, and more simple spikes correlate with bigger whisker protraction (Brown & Raman, 2018; Chen et al., 2016). In addition to previous works, we propose that simple spikes of lobule simple Crus 1 and Crus 2, which always modulate during movements, can affect movement only when particular environmental circumstances intensify their activity. This was demonstrated for whisker movement in chapter 3 and respiration in chapter 5. In this respect, the cerebellum appears to monitor the ongoing movements, which is represented by the simple spike activity and boost this activity via external stimuli when the environment calls for adaptation and/or learning.

THE ROLE OF COMPLEX SPIKES

In chapter 3, we used 4 Hz air-puff stimulation that increased the simple spike responses to the subsequent air-puff stimulation. The enhancement of the simple spike responses required intact Purkinje cell potentiation and depended on the low complex spike response probability of each Purkinje cell. Thus, the potentiation of simple spikes, described in chapter 3, was negatively correlated with the occurrence of complex spikes. This result was predicted by in vitro studies (Coesmans, Weber, De Zeeuw, & Hansel, 2004; Hirano, 1990; Linden & Ahn, 1999; Shibuki & Okada, 1992), but also suggested by in vivo studies on compensatory and saccade eye movements (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). Indeed, in the long run complex spikes can control simple spike firing (De Zeeuw et al., 2011). However, also other mechanisms can contribute to the complementarity of simple spikes and complex spikes. It has been demonstrated that simple spike activity can control the discharges of their climbing fibers via disynaptic connection involving the cerebellar nuclei (Badura et al., 2013; Chaumont et al., 2013; X. Chen et al., 2010). In line with these studies, signs of reciprocal control between simple and complex spikes were detected in Purkinje cell-specific knockouts used in this thesis. In fact, the basic complex spike firing rate, as well as its modulation during the whisker-based object localization task and whiskers reflexive protraction of chapter 2 and chapter 3, were affected even when the mutation did not directly affect the olivary neurons. These results can then be explained by Chris Miall's theory in which

there is a reciprocal control between simple and complex spike activity. This reciprocal control is mediated by the disynaptic connection between Purkinje cell, cerebellar nuclei, and inferior olivary cells and serves as a mechanism to maintain the Purkinje cell homeostasis between potentiation and suppression (Miall, Keating, Malkmus, & Thach, 1998). Thus, there is converging evidence on the role of complex spikes in regulating Purkinje plasticity mechanisms (Gao, van Beugen, De Zeeuw, 2012).

More controversial is the impact of the complex spike on whisker reflexes and respiration. In chapter 3, the presence of air puff induced complex spike consistently predicted a bigger whisker reflexive protraction. In chapter 5, instead, the respiratory cycles associated with the occurrence of complex spikes were not different than the rest of the respiratory cycles. On the other hand, at rest, spontaneous complex spike activity was particularly high in a very specific phase of the respiratory cycle. The fact that the preferred complex spike phase was right after the phase of maximum simple spike increase fits again with Chris Miall's theory (Miall et al., 1998). According to this theory, a brief increase of simple spikes can trigger complex spikes, via disinhibition of the nucleo-olivary pathway. In turn, this reduces the simple spike activity to maintain the Purkinje cell homeostasis in a certain firing range. From these results, the role of the complex spike in shaping simple spike firing patterns seems clearer than its role in controlling behavior. Complex spikes may induce pauses in simple spike firing, and this could affect the behavior, but we couldn't see any sign of their effect on respiration. Different experiments, in which complex spike activity is optogenetically modulated, could indeed clarify the actual complex spike contribution to the actions. Manipulating complex spike activity using specific spatio-temporal patterns would be needed to be conclusive on the impact of the complex spike on motor actions. However, the fact that optogenetic activation of olivary neurons has not yet been reported indicates that these types of neurons are more difficult to manipulate. Considering that complex spikes can be triggered by external stimuli, in chapter 5, we investigated the extent to which we could manipulate the inferior olivary activity using particular temporal patterns of sensory stimulation. The fact that in chapter 5, the average olivary spiking rate (i.e., complex spike frequency) was not affected by any patterns of sensory stimulation confirmed that it is indeed difficult to increase the rate of the occurrence of the complex spike experimentally. Thus, while we manipulated the simple spikes activity to establish their contribution to the adaptation of respiration and whisker reflexes, manipulation to assess the impact of the complex spike on movement has not been performed yet, and this leave opens the possibility of an impact of complex spikes on behavior. From the result of chapter 3, we conclude that there is at least an indirect impact of complex spikes on behaviors, and it is mediated by a more long-term impact of complex spike on simple spikes.

THE ROLE OF PURKINJE CELLS POTENTIATION

Although Purkinje cell depression as the sole mechanism underlying cerebellar learning has been extensively questioned in the past decade (De Zeeuw & Ten Brinke, 2015; Galliano et al., 2013; Galliano et al., 2018; Ke, Guo, & Raymond, 2009; Schonewille et al., 2011), whether Purkinje cell potentiation and suppression co-occur in different sub-population of Purkinje cells during specific types of learning is not yet understood. It has been proposed a predominance of potentiation or suppression mechanisms for memory formation in different cerebellar areas (De Zeeuw & Ten Brinke, 2015). One of the main results of this thesis is the demonstration that Purkinje cells potentiation is a key mechanism underlying whisker adaptation. In addition to the findings in chapter 3, the results of chapter 2 and chapter 5 demonstrate that Purkinje cell potentiation is essential for several forms of cerebellar learning, especially those requiring fast sensory-motor integration.

Originally, the object discrimination task, described in chapter 2, has been used to study neural correlates of associative learning in the cerebrum (Huber et al., 2012; O'Connor, Peron, Huber, & Svoboda, 2010). However, whether the cerebellum was involved at all, it was completely unknown. Showing that Purkinje cell potentiation was required for the acquisition of that object discrimination task, sheds light on the importance of the cerebellum and its plasticity for that type of associative learning. It has been discovered that cerebellar preparatory activity precedes the execution of a similar task (Gao et al., 2018), but what is the cerebellar neural correlate of this type of learning is still unknown. Our results in chapter 2 show that the contribution of Purkinje cell potentiation was particularly relevant when the task needs to be performed rapidly. Whether Purkinje cell depression is also required for the learning of the object discrimination task remains to be tested. However, in contrast with what hypothesized in James S. Albus's theory (Albus, 1971), Purkinje cell potentiation was required to learn the discrimination task of chapter 2 efficiently. Furthermore, I interpret the bigger impairment of potentiation-deficient mice when the response window was narrower, as Purkinje cell potentiation is particularly important in learning how to perform fast sensory-motor integration.

In chapter 3, we collected several independent pieces of evidence, all pointing towards an essential role of Purkinje cell potentiation as cellular mechanisms for the enhancement of the whisker reflexive protraction. This enhancement consisted of larger, but also faster, whisker forward sweeps in response to air-puff stimulation. The correlation between simple spike facilitation and occurrence of complex spike indicates that this type of potentiation follows the rule of parallel fiber to Purkinje cells LTP derived from slices physiology studies (Coesmans et al., 2004). However, upon 4 Hz air-puff stimulation, even the cells with the highest complex spike response probability did not exhibit significant depression of their simple spike responses. One reasonable possibility is that in this subgroup of cells, the complex spike responses do suppress the simple spike responses but not upon 4 Hz air-puff stimulation. Our protocol was meant to maximize the parallel fibers activity by exploiting the resonance property of the granular

layer (D'Angelo et al., 2009; Roggeri et al., 2008). Regardless of whether those cells, with high complex response probability, can also undergo Purkinje cells simple spike depression upon sensory stimulation, the majority of the cells (66%) exhibited facilitated simple spike responses. This form of Purkinje cell plasticity was prevented in Purkinje cell potentiation-deficient mice. The results that emerged under our experimental condition suggest that in lobules Crus1 and Crus2, Purkinje cells potentiation, rather than depression, is the main mechanism underlying the facilitation of the whisker reflexive protraction. Even in this case, the optogenetic modulation of the climbing fiber activity could reveal if long-lasting Purkinje cell depression can be induced and if this would result in suppressed whisker reflexive protraction. From the evidence collected so far, we propose Purkinje cell potentiation as a cellular mechanism to make faster and bigger whisker reflexive protraction.

In chapter 5, the sensory-induced adaptation of the respiration was tightly associated with simple spike facilitation. The fact that the mice with impaired Purkinje cell potentiation could not promptly adapt their respiration suggests that this cellular mechanism could be required for performing fast sensory-motor integration. Also, the fact that the simple spike facilitation is outstanding in the area between medial Crus 1 and simple lobule suggests that in this cerebellar area, potentiation could dominate on depression. Another alternative explanation could be that the area with a predominant simple spike increase receives more excitatory synaptic inputs from the parallel fibers. Even in this scenario, however, the massive activation of the parallel fibers would lead to potentiation of both intrinsic firing property and involved synapses. Potentiation could take place, especially because in that area, the climbing fibers activity was relatively low compared to the surrounding areas. Conversely, the area that received a lot of climbing fiber inputs, located in some lateral parts of the hemispheres, could be dominated by Purkinje cell depression. What would be the biological function of such segregation between areas dominated by one of the two competing plasticity mechanisms must be elucidated with further experiments. The results of our experiments, however, suggest that they do exist.

CONCLUSION

In summary, cerebellar activity reflects a representation of multiple and diverse ongoing behaviors such as whisking and breathing, even at the level of individual Purkinje cells. This modulation does not affect movement during unperturbed conditions, because it does not precede it in time. When adaptation is required, the temporal relationship between simple spike and movements changes, and Purkinje cells lead the adapted movement. Thus, a conspicuous part of cerebellar activity does not have any direct impact on the execution of basic movements, such as breathing, but it just continually supervises them in case adaptation is required. From our results, Purkinje cells potentiation is an instrumental mechanism for achieving faster discrimination (chapter 2), faster and bigger whisker reflexive protractions (chapter 3), and

faster adaptation of respiration (chapter 4). The link between Purkinje potentiation and faster sensorimotor integration has not been established before and explains why the cerebellar patients are slower and why they need to supervise their actions consciously.

Furthermore, I believe that Purkinje cell depression, in adjacent cerebellar areas, is also important to take actions faster. To test this hypothesis, specific studies need to be done. Based on the findings collected so far, I propose that the cerebellum, as the Big Brother of Orwell's novel, continuously supervises us: it operates omnipresent surveillance of our actions and uses mechanisms, such as Purkinje cell potentiation, to facilitate the simple spike activity to achieve goals such as faster sensory-motor integration, when it is required. Indeed, our Small Brother is Watching us!

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