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A liaison brought to light: Cerebellum-Hippocampus, partners for spatial cognition

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Outline

Introduction: Cerebellum and spatial cognition

1- A cerebellum-hippocampus centered network for spatio-temporal navigation

2- Anatomical and physiological foundations of cerebello-hippocampal interaction

- *When the cerebellum talks to the hippocampus, it listens*
- *A possible theta pathway*
- *The Head-direction pathway*

Abstract

This review focuses on the functional and anatomical links between the cerebellum and the hippocampus and the role of their interplay in goal-directed navigation and spatial cognition. We will describe the interactions between the cerebellum and the hippocampus at different scales: a macroscopic scale revealing the joint activations of these two structures at the level of neuronal circuits, a mesoscopic scale highlighting the synchronization of neuronal oscillations and finally a cellular scale where we will describe the activity of hippocampal neuronal assemblies following a targeted manipulation of the cerebellar system. We will take advantage of this framework to summarize the different anatomical pathways that may sustain this multiscale interaction. We will finally consider the possible influence of the cerebellum on pathologies traditionally associated with hippocampal dysfunction.

Introduction: Cerebellum and spatial cognition

The cerebellum, which literally means “little brain”, has in reality a surface corresponding to 80% of the neocortex in humans [1] and contains more than 50% of the brain’s nerve cells of the whole brain. This makes it an intriguing structure that has been shown to play a major role in motor and cognitive functions (see reviews in [2–5]).

The idea of cerebellar involvement in cognitive functions emerged around late 80s, early 90s with the study of cerebellar patients [6]. Patients with bilateral cerebellar damage displayed impairments in visuo-spatial organization, reported difficulties in the planning of their daily activities [7] or even presented deficits in the acquisition of spatial procedures [8,9]. Deficits in spatial learning were also observed in mice with cerebellar mutation or rats with hemocerebellectomy (see review in [10–12]). However, the presence of motor disorders in patients and in most of the cerebellar models studied has long hindered the acceptance of a specific role of the cerebellum in such cognitive functions by the scientific community [13]. To assess whether spatial disabilities were a mere byproduct of motor disorders or not, novel behavioral paradigms were developed. In particular, the SmithKline, Harwell, Imperial College, Royal Hospital, Phenotype Assessment (SHIRPA) was developed for a rapid assessment of forty-two measurements of motor activity, coordination, postural control, muscle tone, autonomic functions, and emotional reactivity, as well as reflexes dependent on visual, auditory, and tactile modalities. Following the development of this standardized SHIRPA procedure, it has been possible to quantify the individual sensory-motor abilities of each mouse [14,15]. Thus, the individual motor scores could be correlated with the individual performances in the spatial memory test. The absence of correlation made it possible to propose the existence of cognitive deficits independent of the motor disorders. In addition, inspired by the precise behavioral procedures settled in spatial learning (see for example [16]), tests were developed to evaluate visuo-motor abilities along with spatial learning and memory, in particular by including probe tests for memory evaluation and a visible platform task in the overall water maze procedure (see review in [17,18]). The visible platform task assesses the visuo-motor abilities of the animal under the same conditions as the spatial memory tests themselves. Therefore, a deficit in the memory tests in the absence of a deficit in the visible platform test leads to the conclusion of a cognitive deficit independent of any visuo-motor problem. Finally, a very precise scoring of the goal search behavior was included [19,20] enabling a better characterization of the behavioral strategies used to acquire the task(s). As previously observed, all experimental models showed deficits in the acquisition of spatial tasks. However, the fact that these were not correlated with possible motor deficits, confirmed the cerebellum as a crucial brain region for goal-directed navigation, independently of its motor role ([21–23] but also see [24]). Subsequently, the development of directed mutagenesis has made it possible to create experimental models with cerebellar-specific alterations while avoiding motor deficits [25,26]. The cognitive evaluation of these models has further confirmed the specific implication of the cerebellum in goal-directed navigation ([27,28] but also see [29]) and revealed that cerebellar computations are particularly involved when the spatial context is required to perform efficient trajectory.

On the same line, the studies targeting the deep cerebellar nuclei (dentate, interpositus, fastigial) and the vestibular nuclei, which are output channels of the cerebellum to the rest of the brain, have also documented the involvement of the cerebellum in spatial navigation. Multiple effects on hippocampal function have been reported following lesions of the vestibular nuclei (see review in [30]). The dentate nucleus has been specifically

demonstrated to be involved in the acquisition of the Morris water maze task with a hidden platform, but not in the long-term retention of spatial memory or the visuomotor guidance necessary for swimming toward a visible goal [31,32]. Following the lesion of dentate nuclei, the acquisition of a self-motion-based motor sequence was also reported to be altered [33]. Recently however, muscimol inactivation of deep cerebellar nuclei resulted in a memory deficit in the water maze task when all nuclei were inactivated but not when only the dentate was inactivated. These results suggested that the fastigial, interpositus and/or vestibular nuclei are also key structures in spatial navigation and may contribute particularly to the process of consolidation of an allocentric spatial memory [34]. The authors also proposed that inactivation of the fastigial and/or vestibular nuclei may prevent the offline integration of self-motion information with external signals within the navigation network. This interpretation is in line with our view that self-motion information processed by the cerebellum feeds the navigation system [3].

Altogether, decades of convergent results have constituted a strong and convincing body of evidence for the involvement of the cerebellum in spatial cognition and have convinced the community to consider the cerebellum as an essential actor of the navigation brain circuit. To date, the cerebellum is not only considered as a key brain structure for the acquisition of spatial-related procedures but also an essential element for pre-processing multimodal sensory information that will then be conveyed to the navigation system.

1- A cerebellum-hippocampus centered network for spatio-temporal navigation

The involvement of the cerebellum in spatial navigation behavior raised the question of the functional link between the cerebellum and the hippocampus, one of the key players in spatial memory (see for example [35] for a viewpoint review).

To highlight the involvement of the cerebellum along with more classical navigation structures, and evaluate possible functional connectivity between the hippocampus and the cerebellum during goal-directed navigation, we used imaging approaches, which provide a global view of the brain networks involved in different navigation strategies. We thus combined a goal-directed navigation task with network analysis based on either fMRI in humans or fos imaging in mice.

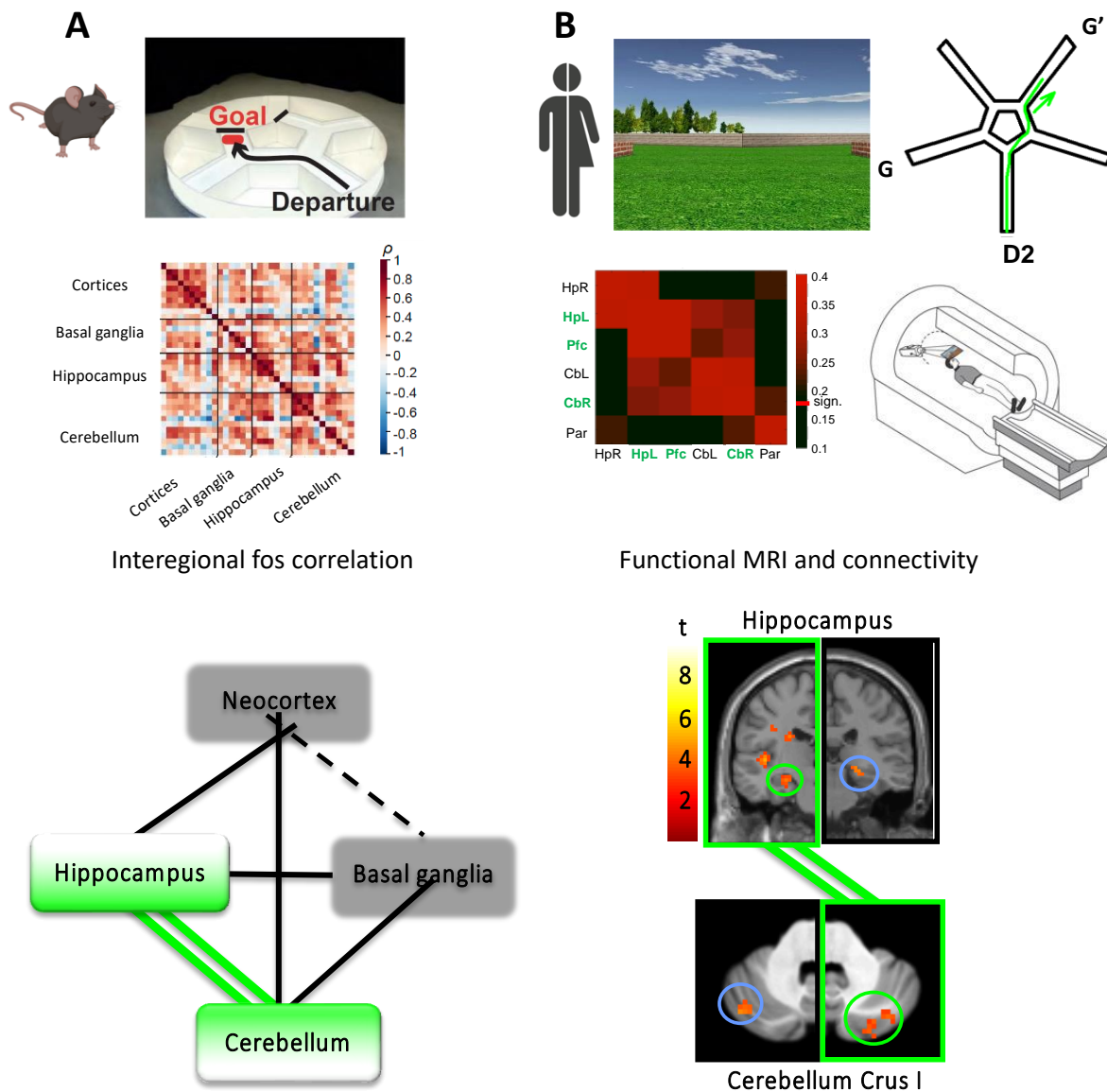


Figure 1. The Starmaze paradigm. Evaluation of the hippo-cerebellum functional interaction during goal-directed navigation. **A.** The Starmaze was first developed for mice as a water maze in which the animals have to swim until they find a hidden platform under the water surface [36]. By analyzing the fos activity just after the mice correctly completed the task, we were able to show a correlation between the hippocampus and the cerebellum underlying the execution of a learned spatiotemporal sequence [41]. **B.** We then developed the Starmaze task as a serious video game in humans [37]. The use of virtual reality in humans has made it possible to combine navigation behavior with the visualization of brain activity and the analysis of functional connectivity, thanks to functional magnetic resonance imaging (fMRI). We also found functional connectivity between the cerebellum and the hippocampus during sequence-based navigation [39]. Hp: Hippocampus; L: Left; R: Right; Pfc: Prefrontal Cortex; Cb: Cerebellum; Par: medial parietal.

We took advantage of the Starmaze paradigm [36] which allows us to characterize the navigation strategies used by the navigator, be it a mouse or a human, to reach their goal

(Figure 1). The design of the Starmaze environment combines distal landmarks and walls structuring the maze into alleys and intersections so that two types of strategies can be used and distinguished: a 'place-based' strategy in which the participants rely on a mental representation of the location (place) of the goal with respect to the distal landmarks, and a 'sequence-based' strategy in which the participants rely on a memorized path (sequence of turns at successive route intersections). In both species, we found that the two strategies could be memorized simultaneously and used spontaneously or according to the context of the task [37,38].

Using fMRI during the Starmaze task in humans, we found that specific and different cerebellar lobules were involved in sensory-motor or cognitive aspects of the task [39] confirming the existence of a functional topography in the cerebellum [40]. We also reported functional co-activations between cerebellum and hippocampus, which suggested that the role of the cerebellum is not limited to sensory-motor processing. In details, we observed activation of lobule VIIA Crus1 combined with contralateral hippocampus and either the medial prefrontal or the medial parietal cortex depending on whether the navigator would rely on mnemonic representations of sequences or places to perform the task. Notably, these results highlighted the prominent role of the human cerebellum part Crus1 in cognitive aspects of navigation, and specified its strong functional interaction with the hippocampus and prefrontal cortex during the sequence-based navigation. In mice, the combination of a behavioral task in the aquatic Starmaze with cellular fos imaging further revealed the central involvement of the functional connectivity between the hippocampus and the cerebellum, including crus1, lobules VI, IV/V as well as lobule IX and X, during sequence learning and execution [41].

Functional connectivity of cerebellum, hippocampus and prefrontal observed in sequence-based navigation is reminiscent of results on early motor sequence learning [42] review in [43]), and has also been associated with accurate spatio-temporal prediction of finger movements [44]. Interestingly, hippo-cerebellar interactions support not only spatio-temporal prediction of accurate movements but also the perception of visuo-spatial changes such as perspective or 3D configuration [45]. The left hippocampus and the bilateral cerebellum were found to be part of a domain-general pattern separation network, active in a delayed match-to-sample task whether the task focused on spatial or temporal conditions [46]. In our navigation study, we found this connectivity when the sequence was spontaneously used by the participants. We additionally showed that the connectivity between cerebellum (Via Crus I) and the left hippocampus during the task was correlated with the tendency of the participant to use the sequence-based strategy. This suggests that, unlike classical motor sequence learning where hippo-cerebellar interactions only appear early on, this functional loop is also involved in the use of a well-known spatio-temporal sequence during navigation. This suggests that the hippo-cerebellar coupling may be important when larger time intervals between actions need to be memorized.

Remarkably, the cerebellum and the hippocampus are thus co-activated in many tasks that combine multiple dimensions, both spatial and temporal. Indeed, Onuki's finger tapping task requires a spatio-temporal prediction of the movement [44]. Similarly, in the delayed match-to-sample task, the pattern separation can be done in the temporal domain as well as in the spatial domain, and always requires memorization of a spatio-temporal configuration. Finally, in the Starmaze task, the sequence-based strategy is particularly interesting for behaviorally modeling the "what, where, and when" of episodic-type memory [47]. Indeed,

according to Eichenbaum and Cohen [48] see also [49]), the role of the hippocampus in a navigation task is to memorize the relationships between different elements regardless of the nature of these elements, i.e. spatial, olfactory, or even motor. Thus, the memory used in navigation can be compared to episodic memory (see Figure 2).

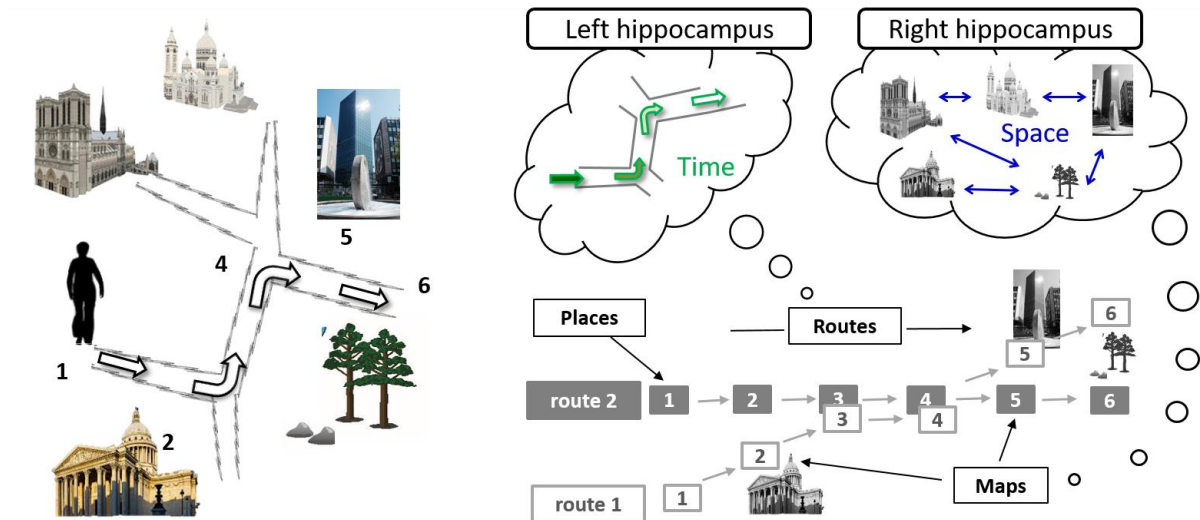


Figure 2. Spatio-temporal representations in navigation and episodic memory. The events of our life that follow one another in time form episodes that are the origin of our memories. In a similar way, when we navigate in our environment, we encounter several successive places along the route taken. The places represent the events and the path to follow is assimilated to an episode composed of several events of our life (adapted from [48]). Our memories or representations in the hippocampus can then be organized as maps relying on the spatial relationships between places/events or as routes/sequences taking into account the temporal order in which these events/places were encountered. In humans, a functional lateralization was observed with the right hippocampus for memory organized in space and the left hippocampus for memory organized in time [50,51].

Our results in humans suggest that, rather than providing a single common function, the two hippocampi provide complementary representations for navigation, concerning places in the right hippocampus and temporal sequences in the left, both of which likely contribute to different aspects of episodic memory. Remarkably, functional connectivity between the hippocampus and the contralateral cerebellum Crus 1 was only observed during sequence-based navigation. A possible interpretation of these results is that in navigation requiring temporal organization of encountered places, the hippocampus could provide contextual information (e.g. the memory of past actions; see [41]) to the cerebellum, which may implement a learning module performing model-free reinforcement learning. In turn, the influence of self-motion vs. environmental information on hippocampal activity may depend on the sensory prediction performed by the cerebellum when monitoring self-motion (Figure 3).

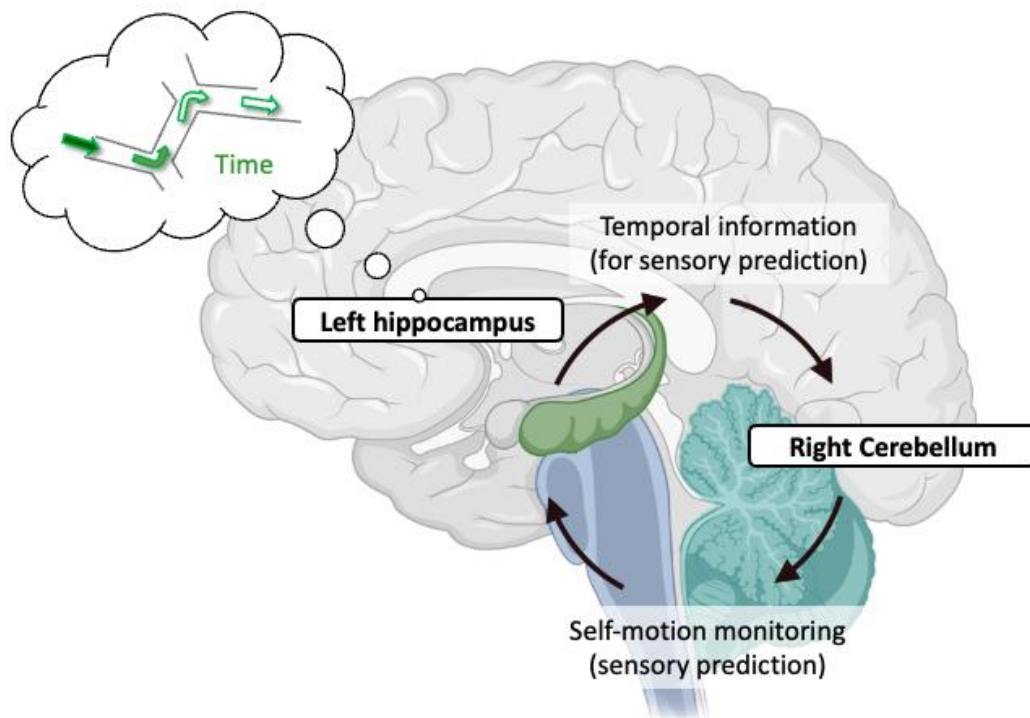


Figure 3. Hippocampus and cerebellum interplay in sequence-based navigation. Note that the lateralization of the two structures depending on the type of memory or strategy used to navigate was only observed in humans. A similar task in mice showed no lateralization [41]. Part of the figure used a BioRender image.

The cerebellar-hippocampal interaction was associated with synchronous activity between the two structures. This interaction involves bidirectional communications such that the cerebellum can influence hippocampal activity and vice versa (see review in [52]). In this scheme however, it remains unclear how information is exchanged between the cerebellum and the hippocampus, a question that has been targeted by work focusing on the anatomical and physiological foundations of their interaction.

2- Anatomical and physiological foundations of cerebello-hippocampal interaction

When the cerebellum talks to the hippocampus, it listens

Several lines of research suggest that the cerebellum impacts hippocampal activity. A major breakthrough in the field came with the observation that cerebellar activation or manipulations could modulate the activity pattern of hippocampal neurons [see review in 53]. Hippocampal place cells have been described as exhibiting robust firing selective to the animal's location in an environment [54] and being key elements of a "cognitive map" [55]. These cells are driven by a combination of environmental inputs (allocentric; see Figure 6; [56,57]) and internal measures of direction and traveled distance (self-motion or Idiothetic; [56,58,59]). Two studies suggest that the cerebellum is involved in the processing of the sensory inputs driving hippocampal cells. These studies show that the suppression of proteins involved in the induction of specific plasticity mechanisms at parallel-fiber to cerebellar

Purkinje cells synapses alters the balance between allothetic and idiothetic drives of place cell activity [60,61]. These results question the mechanisms behind this balance. It has been proposed that different modules of the cerebellum use different temporal schemes to sustain learning and memory as well as subsequent behaviors [62,63]. Therefore, we cannot exclude that distinct cerebellar modules might be altered differently in L7-PKCI and L7-PP2B and sustain the differences observed in navigational abilities and space coding. Another possible interpretation that would be interesting to evaluate, relies on the adaptive-filter model of the cerebellum (proposed by [64] and discussed in the framework of navigation in [3]). In that framework, PKC- and PP2B-dependent computations may differently contribute to the weighting of cerebellar inputs at the Purkinje cell layer of the cerebellum (see Hypothesis Figure 4), and then to the overall integration of self-motion signals. The hippocampus eventually receives all combined sensory inputs, including this integrated self-motion signal.

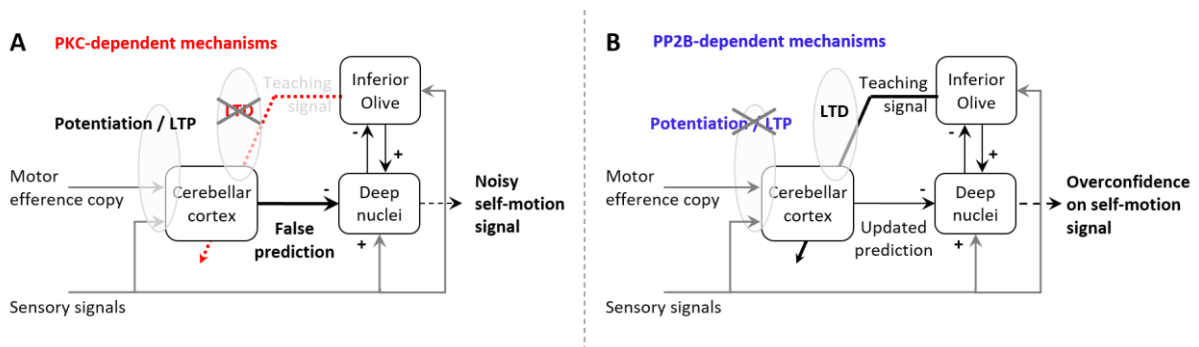


Figure 4. Hypothesis: PKC- and PP2B-dependent cerebellar computations may modify the weight put on self-motion cues. Relying on a computational model of the cerebellar function, PP2B-dependent mechanisms (in blue) including long-term potentiation (LTP) may have a major role in filtering the multi-sensory and motor signals entering the cerebellar cortex to extract self-motion information and from this predict the sensory inputs to come (internal cerebellar model). PKC-dependent mechanisms (in red) including long-term depression (LTD) would rather be involved in correcting the internal model following prediction errors (teaching signal). A. The cerebellum of L7-PKCI transgenic mice, with suppressed PKC-dependent mechanisms, would have impaired teaching signal leading to false predictions. The cerebellum would then provide the navigation system with noisy and unreliable self-motion information. B. The cerebellum of L7-PP2B knock-out mice, with suppressed PP2B-dependent mechanisms at the Parallel-fiber-Purkinje cell synapses, may have impaired ability to properly integrate all entering sensory information. However, it could keep strong control on the prediction error with the maintained ability to update the internal model and predictions through LTD-dependent correction, leading the navigation system to develop overconfidence in the self-motion information provided by the cerebellum, especially if other types of information such as visual inputs are otherwise altered.

Subsequent studies, using optogenetics combined with fMRI and/or electrophysiology, have shown sustained activity within the dorsal hippocampus [65] as well as retrosplenial cortex following the activation of cerebellar output nuclei in head-fixed mice [66]. Altogether, these studies suggested an influence from the cerebellum to the hippocampus but questioned the anatomical link between the two.

The debate on the anatomical connectivity between the cerebellum and the hippocampus goes back to the 70s. Although early studies using electrical stimulation of the cerebellar vermal and paravermal regions in cats and rats have suggested the existence of a possible direct pathway between the cerebellum and the hippocampus [67–71], it is now clear that it is not the case in mice, where we have shown that the cerebellum is connected to the

dorsal part of the hippocampus via at least one intermediate structure ([72] but also see [73] in human using tractography, and [74] in chicken).

A possible theta pathway

To better understand the functional link between the cerebellum and the hippocampus, several teams focused on the intermediate structures anatomically linking the two structures. Three structures can possibly receive direct influence of the cerebellum on the way to the hippocampus: the supramammillary nucleus (SuM), the raphe nucleus as well as the nucleus incertus. All these potential intermediate structures contribute to the generation of hippocampal theta rhythm including the medial septum-diagonal band of Broca (MSDB; see review in [75]). First, the nucleus incertus receives projection from the caudal fastigial [76] and projects towards the MSDB and the hippocampus [77–79]. As reported in [80], the nucleus incertus not only synchronizes its activity with the hippocampus during theta period but is also able to evoke a phase reset of the hippocampal theta wave. Bidirectional communication between the nucleus incertus and the medial septum has also been described and could thus contribute to septo-hippocampal theta ([81] see review in [75]). Interestingly, the nucleus incertus and MSDB have been shown to play a role in spatial cognition including spatial goal-directed memory [82,83]. The second potential intermediate structure is the raphe nucleus [72] which receives direct projections from the deep cerebellar nuclei (in cat [84], rat [85] and Macaca [86]) and projects to the hippocampus as well as the medial septum [87]. The third intermediate structure is the SuM [72] which projects to the medial septum [88] and exhibits theta rhythmic neuronal activity independent of septum ([89] see [90] for a comprehensive review).

Altogether, these intermediates structures constitute potential pathways for cerebellar influence on hippocampal theta rhythmic activity (Figure 5).

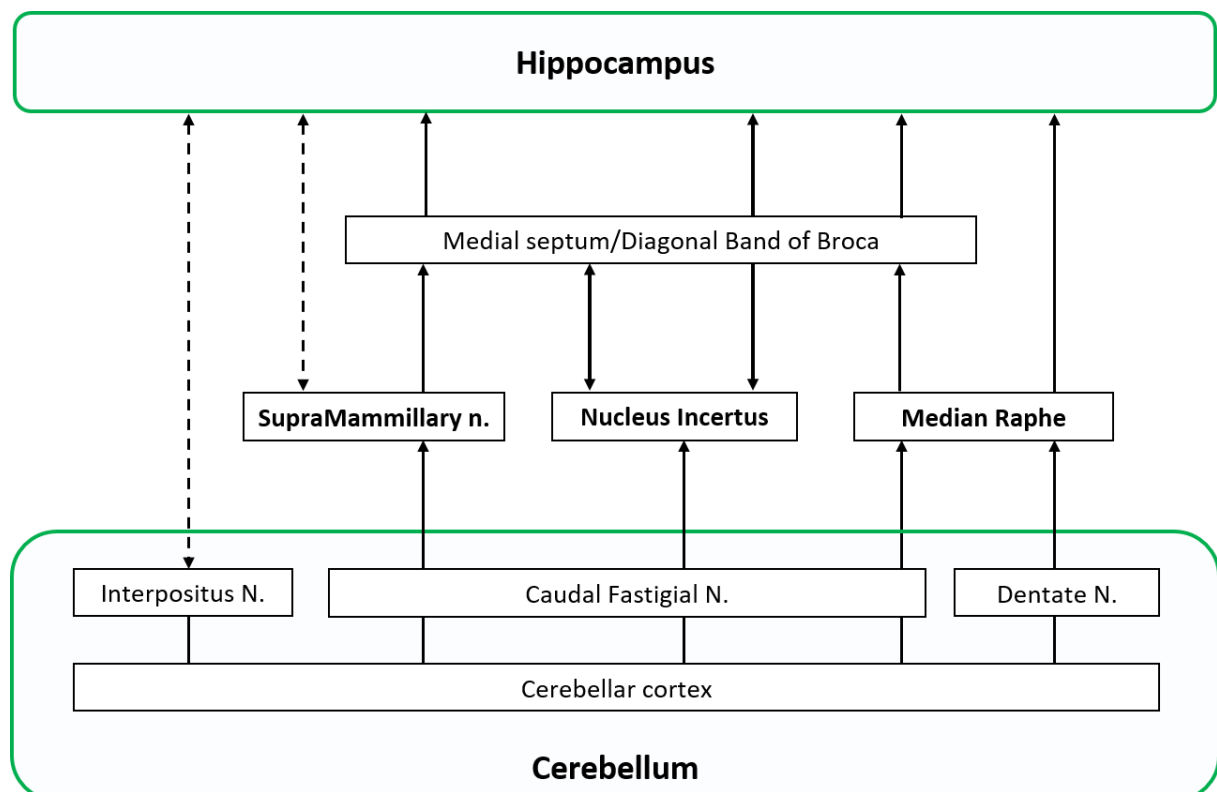


Figure 5. The “theta pathway”. Three structures can be identified as potential candidates for mediating the influence of the cerebellum on the hippocampus in the theta-frequency range. These structures receive afferents from the cerebellum via specific deep cerebellar nuclei. They in turn project toward the hippocampus either directly or via the medial septum-diagonal band of Broca. Some projections have been found bilateral (double arrows). Solid arrows stand for validated anatomical connections. Dotted arrows indicate that there was only indirect (functional/electrophysiological) evidence for a connection between the two structures.

Interestingly, an eye-blink conditioning task in rabbits revealed a coupling in theta oscillations between the hippocampus and the cerebellum. This observation is twofold interesting: first, because eye-blink conditioning is a typical cerebellum-dependent task which is traditionally not thought to involve the hippocampus; second because this coupling was seen when the unconditioned stimulus (UCS) and the conditioned stimulus (CS) were presented separately with an interval of time in between [91–93]. The learning was enhanced in the presence of hippocampal theta and led to rhythmic theta-band (6–7 Hz) oscillations in the interpositus nucleus and the cerebellar cortex, suggesting a cross-talk between the hippocampus and the cerebellum in the theta-band. Once the conditioning is acquired, the presentation of a conditioned stimulus can then induce theta when an animal is in a non-theta state, a phase reset of theta when presented during spontaneous theta, and increasing hippocampal-cerebellar theta synchrony ([91,92,94,95], reviewed in [52]). In line with these observations, simultaneous local field potential recordings from the dorsal hippocampus and cerebellar regions in mice has shown a theta-range synchronization (6–12 Hz frequency range) between the vermis either lobule 6 or crus I regions of the cerebellum and the hippocampal CA1 in awake freely moving mice [72].

During natural sleep, we observed a bidirectional communication between hippocampal and cerebellar Crus I, lobule VI and lobules II/III [96]. Beyond theta, we have described a prominent cerebellar delta oscillation (<4 Hz), acting as a temporal coordinator within the cerebellar network and between the cerebello-hippocampal networks during REM and non-REM sleep. In particular, our data revealed discrete cerebellar phasic sharp potentials (PSPs) synchronized across cerebellar regions and triggered hippocampal sharp wave ripples (SWR) during non-REM sleep. The SWRs are particularly important oscillatory patterns for cognitive functions. The hippocampal ensemble activity is organized during sharp-wave ripples [97–99] potentially leading to the consolidation of recent spatial learning [100]. Additionally, the precise timing of SWRs with prefrontal delta waves is shown necessary for accurate decision making [101]. In this regard, several recent studies have pointed out the cerebellar role in synchronization of the hippocampus with multiple cortical regions including prefrontal regions [102,103]. Whether the cerebellum is involved in the synchronization of hippocampal SWRs with prefrontal delta events would be an interesting avenue to pursue in future.

Altogether, these results point toward functional synchrony between the two structures during both active behavior and different sleep states with a possibility that cerebellum may reset the hippocampal theta or the SWRs. In order to decipher the mechanisms behind synchronous communications or reset, characterizing the anatomical link(s) between these two structures and the associated mechanisms will be essential.

The Head-direction pathway

In addition to “theta pathway”, we have previously reported the existence of two additional and multi-synaptic pathways that may influence hippocampal coding (see [3] for a detailed review of these pathways). Recent anatomical tracing [76,104] have pointed to other intermediate structures along the non-theta pathways. One of these non-theta pathways from cerebellum to the hippocampus involves the head-direction system. Multimodal self-motion information from cerebellar circuit, including both vestibular and non-vestibular sensory inputs are fed to the head-direction system through multiple pathways (Figure 6).

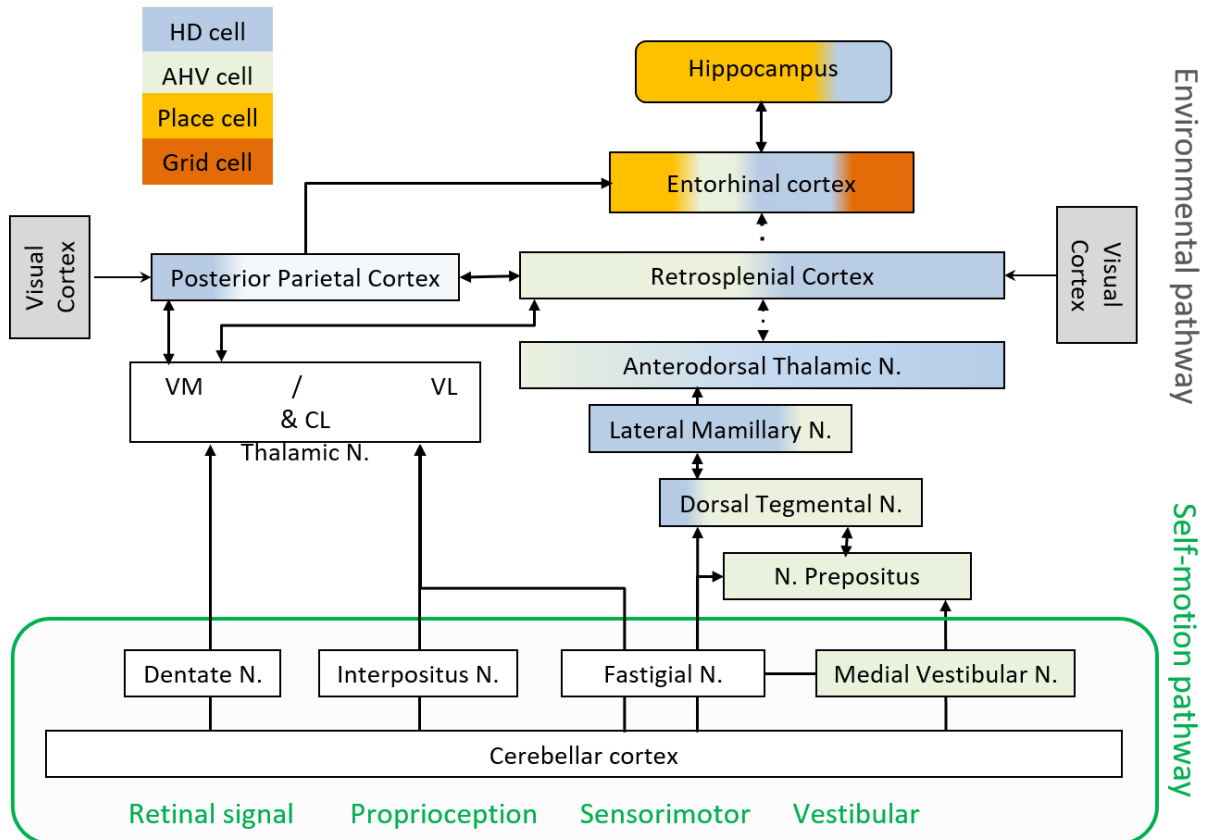


Figure 6. The “Head-Direction pathway”. HD: Head Direction, AHV: Angular Head Velocity, VL: ventral lateral, CL: centro lateral, VM: ventral medial, N.: Nucleus. [105,106]; see also [72,76,107].

Upstream to the hippocampal circuit, the head-direction system is a candidate pathway for bringing the information related to the animal’s head translation into the navigation system [3,108]. Neurons in the head-direction system exhibit firings selective to the animal’s head direction [109,110] and are part of multiple interconnected brain structures including, the brainstem, mammillary bodies, anterodorsal thalamic nucleus, and several cortical areas such as retrosplenial cortex [105,111]. The head-direction system is another element of the brain’s navigational system and is essential for the emergence of entorhinal grid cells and stable hippocampal place cell firing [112–114]. Despite clear anatomical pathways of cerebellar afferents arriving on the head-direction system, there hasn’t been any

direct evidence on the cerebellum's role in head-direction cell activity. Most explicit pathway is the interconnections between the cerebellum and the vestibular nuclei which mediate the control of posture and balance [115,116] and encode head tilt-translation [117–119]. The cerebellar interconnections with medial vestibular nuclei through fastigial nuclei might be particularly important for generating head-direction signal as the lesions to the medial vestibular nucleus or occlusions of semicircular canals or otolith organs, all alter the head-direction signal (see [120] for review).

However, cerebellum might also tune the head-direction signal through other components of self-motions, such as motor/proprioceptive inputs [121]. For instance, the angular head velocity signal in the dorsal tegmental nucleus (DTN) displays a strong reliance on motor cues [122]. Further, the afferents from nucleus prepositus to the DTN are shown essential for head-direction cell activity when relying on self-motion inputs [123]. Accordingly, the known cerebellar afferents through the fastigial nucleus to the nucleus prepositus [76] may terminate on cells targeting DTN and mediate stable direction signal. Consistent with this idea, cerebellar manipulations, with potential sparing of vestibular interconnections, has shown presence of a normal head-direction signal but instead altered the strength of tuning by the self-motion information [124].

The overall effect of the cerebellar alterations to the place and head-direction cells suggests that the cerebellum may be involved in the integration of multimodal self-motion inputs driving place and head-direction cells. In this regard, a structure upstream of the hippocampus, the retrosplenial cortex is often argued for its role in the transformation between external and internal spatial-reference frames by employing both allocentric and self-motion information [125]. Consistent with this idea, neurons in the retrosplenial cortex encode different types of idiothetic and allocentric information, including routes, locomotion, head direction, animal position, visual landmarks, angular head, and linear velocities [122,126–128]. Interestingly, in one pathway, the retrosplenial cortex is sitting just two synapses away from the cerebellar dentate nucleus, bypassing the subcortical head-direction pathway [129]. However, there has not been any clear evidence of functional modulation of retrosplenial activity by the cerebellum until recently it is suggested that the cerebellum influences both speed and head-direction signals within the retrosplenial cortex [124]. The overall effects on speed and head-direction cells could subsequently affect the speed and grid codes within the medial entorhinal cortex [130] and the associated path-integration process within the hippocampus [49,131,132].

Conclusion and discussion

In summary, converging evidences point to a central role for the cerebellum in optimizing navigation and controlling neuronal code for space. The integration of self-motion information by the cerebellum appears to be essential for a reliable and stable representation of both location and direction. Besides, the ability of the hippocampus to organize the elements of an experience in time seems to favor the associative work of the cerebellum. Although bidirectional links between the cerebellum and the hippocampus have been revealed at different scales, most recent work has focused on the cerebellum-to-hippocampus direction. In this review, we propose that the influence of the cerebellum on the hippocampus relies on multiple convergent pathways including two main streams: the theta pathway and the head-direction pathway.

In addition, recent results have highlighted the complexity of cerebellar inputs on the hippocampus by describing the existence of multiple projections that nevertheless present a very specific topography. In Streng et al [104], the authors highlighted how only a very specific output of the fastigial nucleus can influence the hippocampal activity and inhibit seizures. Anatomically, Watson et al. [72] revealed that the hippocampus receives inputs from distinct but topographically restricted regions of the cerebellum, including the caudal fastigial described by Streng et al. [104]. The anatomical convergence of these inputs from different cerebellar modules including vermal, paravermal and hemispheric regions into the hippocampus suggests that hippocampal function may require the integration of multiple signals potentially computed at distinct cerebellar locations. These computations potentially include multi-sensory processing [133], sensory-motor combination [134,135] or even reward prediction and contingencies [136-137], a combination of these being required for optimal goal-directed behavior (see [72] for discussion). Functional investigations of the different cerebellar inputs to the hippocampus will be important to pursue in the future to understand how the outputs of these cerebellar computations are conveyed through the above-described pathways.

The evidence for communication between the cerebellum and the hippocampus has been a major discovery not only because it breaks with the prevailing dualistic view of two structures involved in distinct functions but also because it opens the way to therapeutic applications for hippocampal-related pathologies. In particular, cerebellar neurostimulation may carry a therapeutic potential in a diverse and increasing number of neurological and neuropsychiatric conditions [138]. For instance, a recent study has proposed targeted cerebellar manipulations for treating temporal lobe seizures ([104]; see comment in [139]). Beyond the seizure treatment, neurostimulation of the cerebellum can interest a wider range of applications including those related to orientation problems. As an example, developmental topographical disorientation disorders [140,141]) are reported in patients who are unable to orient themselves even in familiar environments in the absence of any noticeable brain lesions. To date no mechanism has been found explaining this phenomenon, let alone to remedy it. The fact that cerebellar-dependent mechanisms are able to provoke instability of spatial representation both in the hippocampus and in the head-direction system, opens up new avenues of research, with the possibility that the mechanisms behind disorientation disorders can be related to an alteration to cerebellar function or cerebellar communications with the hippocampus. Finally, the contribution of the cerebellum to cognitive functions including episodic memory extends the clinical interest of this brain structure to various neurodegenerative and neuropsychiatric disorders. For instance, Jacobs et al., [142] proposed an integrative hypothesis of a cerebellar contribution to the cognitive and neuropsychiatric deficits in Alzheimer's disease. In light of these studies, modulating hippocampal activity through cerebellar stimulation brings prospect in treatment of hippocampal-dependent memory disorders such as Alzheimer's disease. We expect that future studies will reveal further exciting roles for this "little brain".

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