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REVIEW

The Cerebellar Thalamus

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Abstract
The thalamus is a neural processor and integrator for the activities of the forebrain. Surprisingly, little is known about the roles of the "cerebellar" thalamus despite the anatomical observation that all the cortico-cerebello-cortical loops make relay in the main subnuclei of the thalamus. The thalamus displays a broad range of electrophysiological responses, such as neuronal spiking, bursting, or oscillatory rhythms, which contribute to precisely shape and to synchronize activities of cortical areas. We emphasize that the cerebellar thalamus deserves a renewal of interest to better understand its specific contributions to the cerebellar motor and associative functions, especially at a time where the anatomy between cerebellum and basal ganglia is being rewritten.

Keywords Cerebellum · Thalamus · Movement · Spike · Burst · Rebound · Cognition · Tremor · Inverse model · Dynamical system

The cerebellar system is currently considered as a major subcortical circuit encompassing cortico-cerebello-cortical parallel closed loops modulated by peripheral inputs and involved in sensorimotor, limbic, and associative functions. It is also heavily connected to brainstem nuclei, such as reticular nuclei. The corticocerebellocortical loops represent the anatomical substratum of functional networks governing behavior: executive, salience, default-mode, dorsal attentional, and motor networks. The anatomical paths pass through specific subnuclei of the thalamus [1, 2]. Therefore, a major question regarding the physiology of cerebellocerebral interactions is to elucidate the contribution of thalamic nuclei. This will impact on our understanding of cerebellar disorders.

The "cerebellar" thalamus can be subdivided into several, more or less segregated anatomo-functional territories. Major part of the thalamus receives cerebellar inputs and plays a central and active role in transferring/transforming cerebellar output to the cortex in order to optimize or to correct its computation [3, 4]. Currently, the thalamus is no longer regarded as a simple passive relay of information to the cerebral cortex and to the striatum. It is viewed as a genuine processor for neural information.

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Thalamus

In the present paragraph, we shall summarize and emphasize on some major histological, anatomical, and physiological of this paired nuclear complex situated in the wall of the diencephalon (for a broad and thorough overview: [5–7]) (Fig. 1).

First, from a brief gross anatomy standpoint, the thalamus is a large ovoid mass of gray matter located on each side of the third ventricle and can be subdivided into several subnuclei in function of their afferents and efferents. Two main parts can be distinguished in the thalamus: the dorsal region, its major body, and the ventral region, i.e., the reticular thalamus. The reticular thalamus, which is bordered by the internal capsule on one side and by the external medullary lamina on the other side, covers rostro-caudally the two thirds of the dorsal thalamus. The dorsal thalamus is divided by a medial sheet of myelinated axons called internal medullary lamina whose most rostral part bifurcates and which delimits three main compartments enclosing dorsal thalamic subnuclei: (1) anterior (anterior nucleus), (2) lateral (ventral and lateral nuclei), (3) medial (dorsomedian nucleus), and (4) posterior (pulvinar). The medial part of the internal medullary lamina also contains intralaminar nuclei distributed into two groups: an anterior one (paracentral, central median, central lateral nuclei) and a

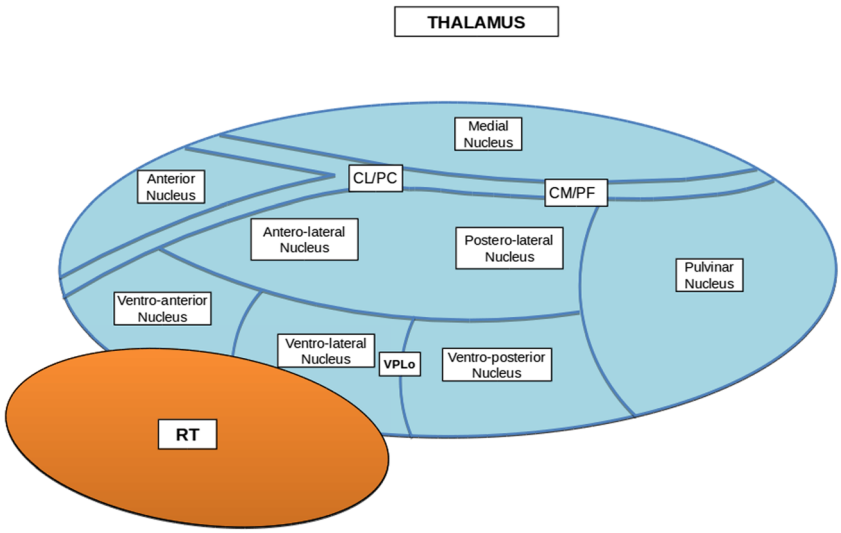

Fig. 1 Schematic drawing showing, in a lateral view, the main subdivision of the dorsal thalamus whose lateral part is covered by the reticular thalamic subnucleus. Note that the X area corresponding to the human nucleus ventralis intermedius is located medially to the ventral lateral nuclei. Centro-lateral/paracentral (CL/PC) and centro-médian/parafascicular subnuclei (CM/PF) are situated in the internal medullary lamina

posterior one (centromedian and parafascicular nuclei). More ventrally, medial and lateral geniculate bodies also belong to the thalamus. The dorsal thalamus receives its major afferents from the cortex, cerebellum, striatum, hypothalamus, reticular formation, and peripheral sensory pathways and sends its main efferents, more or less topographically organized, to the whole cortex, its main target, and to the striatum. Two main characteristics distinguish the dorsal thalamus from the reticular thalamus. The former contains glutamatergic neurons and GABAergic interneurons, whereas the latter contains only GABAergic neurons projecting to the dorsal thalamus. Moreover, the reticular thalamus receives exclusively collaterals of thalamocortical and corticothalamic fibers and can be parcellated into different anatomofunctional (somatosensory, visual, auditory, and motor) sectors.

Second, thalamic afferents have been subdivided into two classes (and some additional subclasses): "drivers" and "modulators" [6–8]. Put in a nutshell, driver inputs are represented by thick excitatory (glutamatergic) axons ending with dense terminal arborization upon proximal dendrites and soma of thalamic postsynaptic neurons where they activate ionotropic receptors (AMPA) inducing large excitatory postsynaptic potentials (EPSP) and capable of generating reliable spiking activity. Drivers comprise, for example, cortical infragranular layer 5, subcortical structures, and peripheral sensory tracts. Conversely, modulators consist of thin axons impinging upon distal (but sometimes proximal) dendrites of the postsynaptic neurons where they stimulate ionotropic (GABA-A/NMDA) or metabotropic (GABA-B/acetylcholine M1 muscarinic/noradrenergic/serotoninergic/histaminergic) receptors. These latter inputs elicit small EPSP or inhibitory postsynaptic potentials (IPSP) and, consequently, adjust responsiveness of their thalamic targets. NMDA receptors should control sustainedly the gain of transmission of thalamic relay neuron (TRN). Modulators encompass for instance: inhibitory (GABAergic) inputs, such as pallidum, substantia nigra, zona incerta, thalamic local inhibitory interneurons (LII) and reticular thalamic nucleus, and excitatory inputs, such as cholinergic or adrenergic reticular nuclei and glutamatergic cortical infragranular layer 6. Zona incerta displays strong synchronization with cortical oscillations [9] and can modify relay cell responsiveness to central or peripheral inputs [10].

Third, thalamic neurons mainly include glutamatergic TRN, GABAergic neurons of the reticular thalamus interconnected by dendritic gap junctions, and LII (20–25% of whole the thalamic neurons in monkeys) whose density varies from a subnucleus to another and which give rise to axonal and dendritic "axoniform" terminals.

Fourth, TRN receiving drivers can be classified as first-order or higher-order relay neurons according to their subcortical or cortical (layer 5) inputs (Fig. 2). Moreover, some TRN received convergent peripheral and cortical inputs, such as the posteromedial complex (PoM) in mice [11].

Fifth, within the thalamus, two kinds of projection systems coexist [6–12]: the core and the matrix. The former is composed of large paravalbumin-positive neurons mainly in relation to cortical granular layer 4 of specific brain areas, whereas the latter comprises smaller calbindin-positive neurons diffusely projecting predominantly to cortical superficial layer 1 of several areas, where they strongly and sustainedly activate inhibitory interneurons and pyramidal cells [13]. Matrix-based layer 1 activation could be involved in signal amplification and coincidence detection during concomitant activation of the core system [14]. Core and matrix neurons are preferentially observed in first-order thalamic and higher-order subnuclei, respectively. It is noteworthy that layer 1 receives feed-forward or feed-back inputs from other cortical areas, so that matrix cells can modulate cortical functional connectivity. In human, paravalbumin-immunoreactivity is present preferentially in the ventral nuclei and moderately in

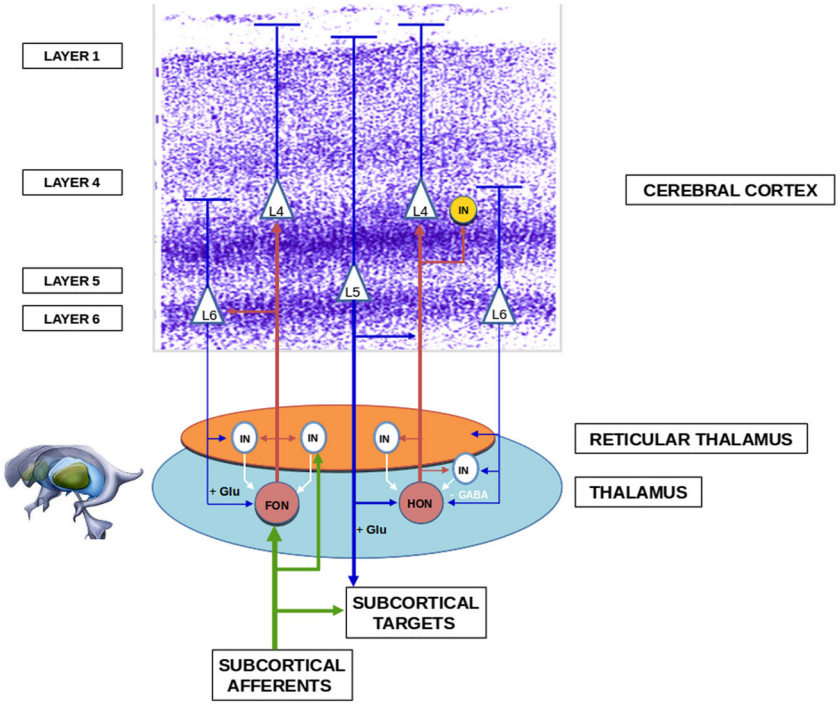

Fig. 2 Schematic diagram illustrating afferents to the dorsal thalamus (in blue) and the reticular thalamus (in orange), including glutamatergic first-order neurons (FON), high-order neurons (HON) and GABAergic local interneurons (IN), and thalamo-cortical efferents ending upon pyramidal cells and interneurons mainly in layers 4, 5, and 6. Projections from cortical pyramidal cells back to both thalamic nuclei are also shown

the mediodorsal nuclei [15]. Although present in all nuclei, dense calbindin- and calretinin-immunoreactivity was observed in rostral intralaminar and mediodorsal nuclei.

Sixth, TRN can exhibit several types of voltage-dependent response modes [3, 4]. There is evidence that the thalamus works as a relay in *tonic mode response*, i.e., when thalamic output neurons fire tonically and linearly, whereas it works phasically after a quiescence period in *burst mode*, i.e., when it responds nonlinearly by a burst firing [16]. The burst-mode is due to a low-threshold T-type calcium current (I_T), sometimes in collaboration with hyperpolarization-activated cation current (I_h). The balance between excitatory and inhibitory, modulatory inputs determine the responsiveness of TRN: weak and/or desynchronized excitatory inputs on one hand and strong and/or synchronized inputs on other hand can switch from tonic to burst mode. Burst mode allows transmission of low-frequency signal, with a weak selectivity for fluctuations, whereas tonic mode enables transmission of higher-frequency signal, with precise phase-locking in both cases [17]. Furthermore, thalamus can also exhibit *oscillatory mode* due to activation of intrinsic rhythmic currents of neuronal membrane and/or to recruitment of the thalamic reticular nucleus. Modulation of the thalamic activity and particularly, selection of the response mode are strongly influenced by several extra-thalamic systems, such as inhibitory inputs of basal ganglia and zona incerta, both of them being interconnected with the cerebellum or cholinergic inputs arising from the reticular pontine formation. Such diversity of thalamic responses would allow specific and faithful transfer or analysis of information (tonic mode) or filtering and amplifying new, salient, or unexpected inputs from expected ones (burst mode), as well as generation of thalamocortical rhythmic activities capable of coordinating several cortical areas. It has been assumed that in burst mode, the thalamus will function as a "wake-up call" or detection system selecting and preparing cortical neurons to receive subsequent information transmitted in the tonic mode. However, recently, it was also demonstrated that TRN can encode and "multiplex" a rich variety of information within burst activity and with a high temporal resolution [18]. Stimulus characteristics can be encoded in burst time onset, intraburst spike timing, and counting. Finally, TRN activates in the cortex not only principal cells but also interneurons. In mouse, thalamocortical bursts were shown to strongly depolarize, at least in layer 5, principal cells, and somatostatin (dendritic targeting) interneurons [19]. Higher-order TRN can target slow or fast interneurons in layers 4–2 [20]. In rats, nonspecific TRN activates preferentially slow adapting interneurons, inducing feedforward delayed inhibition and defining a time window for activation, whereas specific TRN causes rapid inhibition due to fast interneuron recruitment [21]. Therefore, the TRN mode response may differentially act on cortical principal cells, while they simultaneously and selectively influence interneurons which "determine the temporal structure of the cortical response" [21].

Seventh, thalamus participates in three main, potentially intermingled, corticothalamocortical loops [22] (Figs. 2 and 3). Cortical layer 6 innervates TRN and LII in the dorsal thalamus with a quasi-linear divergent axonal terminal arbor [23], after sending collaterals to the reticular thalamus and cortical layer 4. Conversely, cortical layer 5 branches to the dorsal

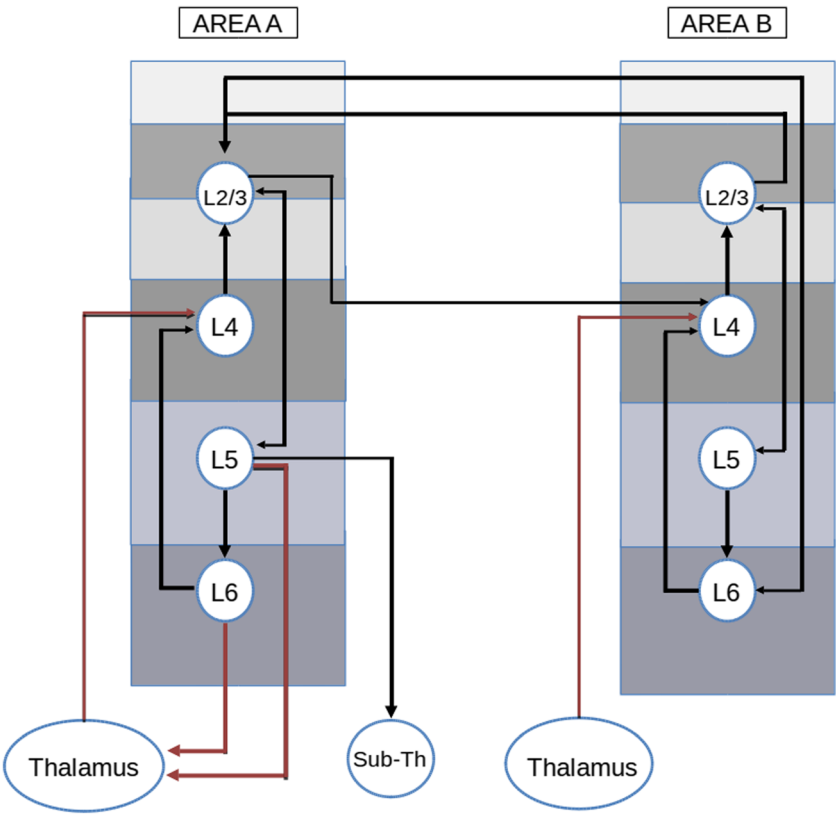

Fig. 3 Schematic diagram illustrating intra-areal and inter-areal connections in relation with layer-specific thalamocortical afferents and corticothalamic efferents

thalamus with a compact and convergent terminal arbor, as well as locally to the upper supragranular layer 1 through collaterals, and to the adjacent cortex through basal dendrites. Layer 6 corticothalamic neurons (CTN) impinge predominantly upon proximal dendrites of core TCN, while layer 5 CTN terminate predominantly upon matrix CTN. A laminar organization of the corticothalamic projections can be found [24]. For example, mediodorsal and ventral anterior/ventral lateral motor thalamus receives projection from prefrontal CTN located in the deep part of layers 6 (80%) or 5 (20%), and from equal proportion of these CTN in the upper part of layers 5 and 6, respectively [20]. It is noteworthy that, in rodent, a specific subgroup of orexin-sensitive cortical neurons located in layer 6b projecting upon higher order thalamic nuclei without sending any collateral to the reticular nucleus has been described [25]. The reticular thalamus receives collaterals of thalamocortical and corticothalamic axons. This nucleus is also in relation with the basal ganglia and the zona incerta. Therefore, (1) layer 5 CTN, as driver, exerts a focused and excitatory influence on relay neurons (and local interneurons) and can tune their receptive field [26]; (2) layer 6, as modulator, can directly facilitate signal transmission; (3) layers 5 and 6 CTN projecting upon matrix thalamocortical neuron (TCN) can recruit and likely coordinate several cortical and thalamic zones; and (4) layer 6 in relation with the reticular thalamus can inhibit relay neurons or switch their activity from tonic to burst mode. The switch or shift between suppressive and facilitative roles of layer 6 is frequency-dependent and based on short-term synaptic plasticity within the thalamus [27]. Moreover, a NMDA- and T-type calcium channel-dependent postsynaptic mechanism in TCN enables nonlinear amplification of synchronized EPSP caused by layer 6 CTN, so that the subsequent increased TCN responsiveness could determine temporal window for weak inputs to be relayed to cerebral cortex [28].

Eighth, it was demonstrated that, likely except for learning process, thalamic inputs contribute in a frequency-dependent manner to release specific spatiotemporal activity patterns due to intrinsic cortical dynamics and intracortical connectivity [29].

In conclusion, the histological and electrophysiological complexity of the internal thalamic organization, the diversity of the thalamic response modes to inputs, the divergence of the thalamo-cortical projections, and the existence of thalamocortical loops preclude to ascribe to the thalamus a role of simple relay. Without ruling out information transfer, it has been recognized that some thalamic nuclei may "enhance local cortical connectivity without relaying information" [30]. Based on recent data [11], Ahissar and Oram [31] suggested that, besides the traditional conception assimilating the thalamus as a multiway relay station, some thalamic subnuclei and cortical areas are organized in multiple thalamocortical closed loops allowing detection of phase difference in drivers inputs, filtering input like a logical gate (AND, OR, NOT), (linear or) nonlinear transfer to the cortex, and subsequent tuning of

cortical oscillations. Interesting too, the authors mentioned the dependence of the thalamic gate: AND versus OR, upon zona incerta input. In this example concerning the sensorimotor thalamocortical system involved in rat "whiskering," we can measure the remarkable complexity of the thalamic processing. More generally, TRN could partake in (1) complex modality- and context-specific information processing, such as synchronizing/binding (phase-locking) collaborative subcortical and cortical areas, for instance through the matrix system; (2) desynchronizing task-irrelevant areas, through the reticular thalamus and zona incerta, in a frequency band-dependent manner [32]; (3) sustaining durable thalamo-cortical activity through feed-back arising from layer 5 [33] (short-term memory); (4) integrating multiple peripheral and central neuromodulatory influences; (5) selecting; and (6) timing precisely appropriate intrinsic dynamical pattern of cortical activity [34–36]. In first-order relay core neurons, such as in lateral geniculate nuclei (vision), the burst-mode would first allow signal detection and attention reallocation to the target causing a switch of activity to the tonic-mode implicated in fine signal analysis. Finally, from a dynamical standpoint, cortical columns and associated thalamus have been modeled as weakly coupled oscillators (for example, [37]). In this model, thalamus can functionally and transiently bind cortical columns using rhythmic input (spiking) of proper frequency and can encode specific information in the phase of this input (interspike intervals). Moreover, the strength of the thalamo-cortical coupling governs the duration of phase synchronization, while the corticothalamic feed-back influences the cortical interareal synchronization [38]. Thus, the thalamus can, at least, precisely "clock" cortical activity, i.e., sequence and calibrate the duration of cortical column activation, what should be important for the cerebellar system. In this vein, Kasevich and LaBerge [39] and LaBerge and Kasevitch [40] suggested that thalamocortical loops passing through cortical layers 5 and 6 could transiently select cortical networks and segregate subcortical networks within these circuits. More precisely, recurrent thalamocortical loops would determine the frequency of subthreshold membrane oscillations of the apical dendrite of pyramidal cells, so that cortical pyramidal cells forced to oscillate at the same frequency would be synchronized and thus could specifically interact with each other. Moreover, layer 5 dendrites can also display a burst activity allowing selective amplification of the input signal. Therefore, layer 6 pyramidal cells within the thalamocortical loop would enable an oscillation frequency-based selection of global cortical network, within which layer 5 pyramidal cells would allow an amplitude-based segregation of subnetworks. In summary, thalamocortical loops would behave as a "clock" involved in (1) temporally grouping resonating neurons; (2) subgrouping in an amplitude-dependent manner neurons of the resonant circuit; and (3) isolating groups of distinct resonance frequency.

Afferents and Efferents of the Primate Cerebellar Thalamus

From a phylogenetic stand point in primates, the cerebellum-recipient thalamus is broadly characterized by (1) a clearer delineation between striatal and cerebellar projections in the ventroanterior and ventrolateral nuclei; (2) an increased number of local interneurons [41]; and (3) denser connections between thalamic subnuclei in relation and associative neocortices.

Histological tracing has unraveled which thalamic nuclei receive specific afferents from the cerebellum. All the "deep" cerebellar nuclei (DCN) project mainly to the contralateral thalamus through the superior cerebellar peduncle (brachium conjunctivum), which decussates within the ventral tegmental mesencephalon at the level of inferior colliculi. The ascending branch of this peduncle runs through and (dorsally) along the red nucleus towards the subthalamus in a region corresponding to the H1 field of Forel, before entering ventrally the thalamic external medullary lamina. DCN terminate mainly within the "cell-sparse" zone of the ventrolateral (VL) thalamus including [40]: the ventroposterolateral oral (VPLo), the ventrolateral caudal (VLc), the pars postrema of the ventrolateral (VLps), the X (the so-called: area X of Olszewski), and the ventrolateral oral (VLo) subnuclei, as well as within the caudal part of the ventral anterior (VA) and intralaminar (central) nuclei (IL) [43–48]. Some cerebellar afferents are traced in the depth of VA. A recrossed projection from the caudal and rostral dentate nuclei (DN) to the contralateral thalamus can exist. Let us also note that projections from the ventral DN to the (rostral) pulvinar have only been demonstrated in cat [49]. However, in monkey, the polymodal superior temporal sulcus (STS) projects to the basis pontis [50] and receives its main thalamic afferents from the pulvinar [51], and in human, there exists a loop between the right STS and the left crus I/VIIb [52] however through, seemingly, the right ventromedial thalamus. Further studies are thus required to determine, which cerebellar thalamic nucleus is connected with STS. Connections have also been described between DCN (except for the fastigial nuclei) and the rostral reticular nucleus in rat [53] and between DN and the reticular thalamus [54]. Moreover, the major termination zone of the fastigiothalamic and posterior interpositothalamic fibers is represented by the contralateral VPLo and medial area X, respectively [55]. Fastigio- and interposito-thalamic afferents end bilaterally within the thalamus. Terminals of the interpositus and DN interdigitate within the VL. The cerebellothalamic endings occupy an anteriorly convex dense territory constituted of longitudinally oriented bands in the ventral thalamus [12, 56], where the anterior part of dentate and interposed nuclei reaches the most lateral part of VL contrary to their posterior part in relation with medial VL. The DN also projects to the ventrolateral part of the mediodorsal (MD)

thalamic nucleus [57, 58]. More precisely, subregions of the DCN are specifically connected to thalamic subnuclei and to their associated cortical areas: dorsal ND-VPLo-motor cortex, lateral ND-X-premotor cortex, caudal ND-X-frontal eye field, ventromedian ND-VLc-parietal cortex, ventromedian ND-VLc/MD-dorsolateral prefrontal cortex (BA 9 dorsal), and VLc/MD-prefrontal cortex (BA 46 dorsal). Fastigial and posterior interpositus nuclei give off few fibers to prefrontal areas (BA 9 and 46) through X and VLc [59, 60]. In summary, the cerebellar thalamus receives mainly contralateral dentate projections and only sparse fastigial and interposed ones and comprises, at least, a motor (VPLo), premotor (area X), and associative (VLc, MD) regions. It is noteworthy that the (pre-)motor and nonmotor thalamus encompasses also the IL and (VA/)VL connecting DN and to a lesser extent, interpositus and fastigial nuclei, with the basal ganglia (striatum) [12, 61]. The motor thalamus has been characterized as a "super-integrator," since it received cerebellar, basal ganglia, and cortical afferents and may integrate peripheral and central sensorimotor and motivational information [62]. However, cerebellar and basal ganglia inputs are well-segregated in multiple "patches" in VA/VL. Potential communication between these two systems could rely however on common layer 6 feed-backs, dentato-striatal projections, and the reticular thalamus. The motor and cognitive domains of DN are linked to the indirect basal ganglia pathway passing through the external pallidum and the subthalamic nucleus. Figure 4 illustrates the main interconnections between the cerebello-cortical closed loops associated with a rubro-olivary loop with the striatal system.

Human Anatomy

MRI diffusion tensor imaging (DTI) enables to track white matter fascicles linking DCN, especially DN with thalami, using deterministic and probabilistic tractography. DTI has confirmed and complemented previous results obtained in monkey concerning dentatothalamic projections. First, tractograms have been calculated between DN and VA, VLc, VPL [63–67], parvocellular and medioventral DM, and intralaminar nuclei (central median, central lateral, and parafascicular nuclei) [68]. Second, VA and VLc (/VPLo) are preferentially connected with the dorsolateral prefontal cortex (and the supplementary motor area) and primary motor cortex, respectively [65]. Third, DN targets mainly contralateral thalamus, although some ipsilateral cerebellar projections have been described. The latter fibers might either emanate from another DCN or represent false tracking. However, recently, uncrossed dentatorubrothalamic projections, representing one fourth of the superior cerebellopeduncular volume, have been identified using tractography and microdissection validation [69]. Fourth, the density of dentatothalamic fibers displays a decreasing posterior-to-anterior gradient within the whole ventral thalamus. Fifth, the major dentatothalamic tract arises from the associative neocerebellum, including lobules VIIA (crus I and II), VIIB, and VIII. Sixth, the spatial resolution does not permit to distinguish between potential anatomical segregation and conversely, overlappings between cerebellar and basal ganglia afferents to the thalamus, especially in VA-VL and IL (see thorough discussion in [70]). In particular, projections from DN to centromedian nucleus in primate have not been reported [71], so that either these connections appeared in human and would be in charge of functional coordination between cerebellum and basal ganglia, or they could correspond to false tracking.

Histological and Physiological Considerations

The cerebello-cerebral pathway is mainly organized with a main feed-forward activating cerebello-thalamo-cerebral pathway and a feed-back modulatory dual cerebrothalamic pathway (Fig. 5). DCN, especially DN in human, send excitatory glutamatergic axons to the thalamus where they make synapses at the surface of perisomatic, large primary, and secondary dendritic trunks of TRN where monosynaptic unitary excitatory postsynaptic potential of large amplitude are elicited (in cat: [72]). Before reaching the thalamus, these axons also give off branches to spinal cord and brainstem structures, such as the red nucleus (mainly its parvicellular part in human), reticular formation, and basis pontis. A single TRN can receive convergent afferents from several neurons from each DCN and from both interpositus nucleus and DN, which potentially link the spino- and the neo-cerebellum. Moreover, numerous LII are present in VL in comparison with VA, where they can receive collaterals from DCN [73] as well as from reticular thalamus, and constitute a dense interconnected network through dendro-dendritic synapses [74]. TRN give off axons that can divide into several branches in the white matter before ending on one or several cortical areas in plexus form. Two classes of TRN may coexist: the main one connected to layer 3–4 and a second one connected to layers 1 and 6 [75]. At least in motor cortex, terminal arborizations are rostro-caudally oriented. In mouse, the density and size of these axon terminals and the correlated firing-response of the thalamic neurons vary between thalamic subnuclei. For instance, these responses are stronger in VL than in intralaminar centrolateral nucleus [76]. Cortical layer 6 of the same cortical column and to lesser extent of adjacent columns projects backward to the reticular thalamus and to TRN and LII. Therefore, activation from CTN and inhibition from TRN and LII may act as a high-pass filter depressing weak TRN receiving a weak cerebellar activation and neighbor TRN and conversely enhancing more strongly activated TRN [73]. TRN could participate in suppression of background surrounding noisy activity. Recently, it was

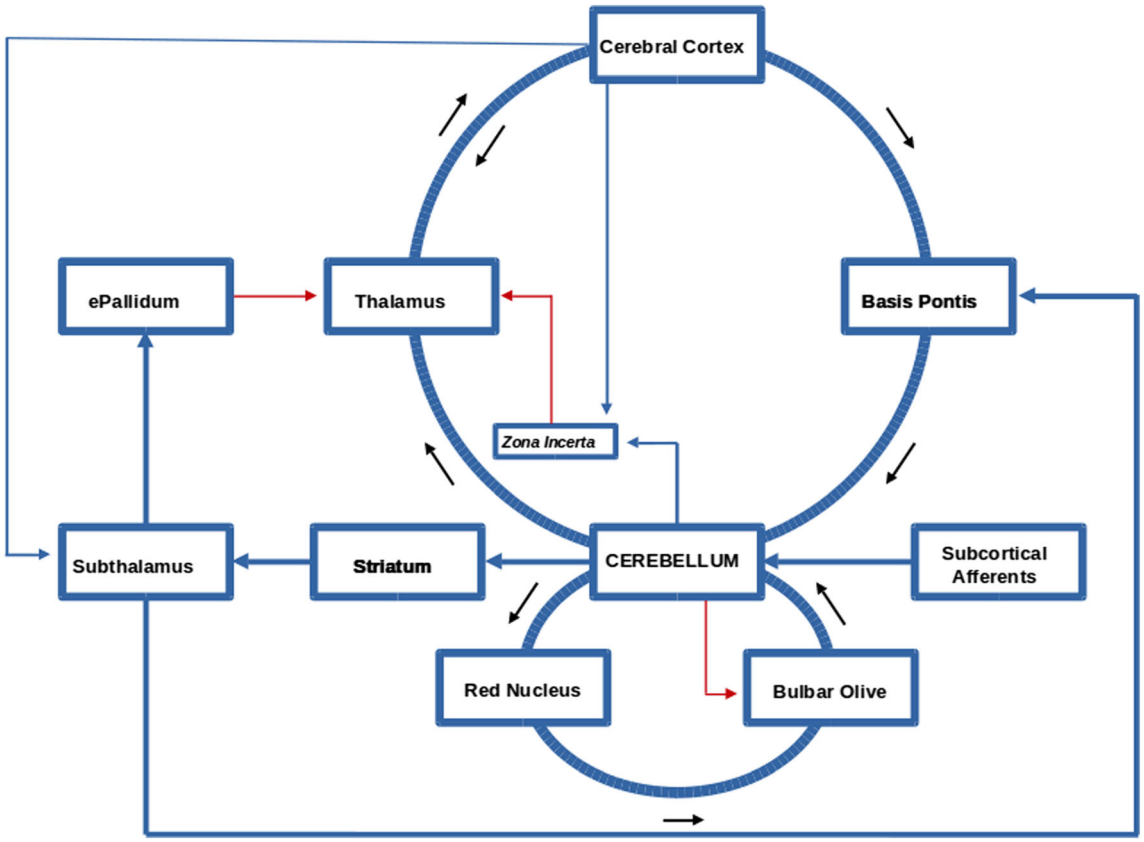

Fig. 4 Schematic diagram illustrating the cerebello-cortical and associated rubro-olivary closed loops and connections with the striatal system

established in mouse that interposed nuclei connect to middle spiny neurons and choline acetyltransferase-positive interneurons in the dorsal striatum through centromedian and parafascicular intralaminar nuclei and that silencing DCN induces impairment of a reward-driven performance [77]. It is noteworthy that at least in the mouse visual cortex, layer 6 pyramidal neurons can recruit within all underlying layers fast-spiking interneurons through recurrent collaterals arising from their axon sent to the thalamus [78].

Cerebellothalamic inputs are regarded as a "driver" pathway in contrast to the striatum regarded as a "modulatory" pathway [4]. These afferents to thalamus can convey (1) directly activating inputs such as (tonic) spikes or rebound burst; (2) indirectly, inhibitory inputs via the zona incerta (in rat [79]; especially to dorsal thalamic and intralaminar nuclei [80]); or (3) no input during pauses of DCN activity. Therefore, cerebellothalamic pathway represents a dual direct "driver" and a polysynaptic "modulatory-like" pathway potentially capable of transferring information and/or of modulating the level of membrane depolarization/hyperpolarization of the relay neurons. It can be hypothesized that cerebellum contributes to select one thalamic response mode useful for its putative general purpose of optimizing and automating mental processes based on computation of internal forward models in the realm of motor activities and cognition [81]. Moreover, updates of cerebellar internal models might depend on the rubro-olivary-climbing fiber system. It has been recently suggested [82] that different cerebrocerebellar subsystems underlie several and successive or concomitant stages of learning processes: model-free exploratory unsupervised learning (attentional and executive networks), reward-based reinforced learning (limbic network), and error-based supervised learning (for example, lobules IV–VI and VIII for on-line motor control). For instance, the motor cerebellum is supposed to implement an inverse model of the motor apparatus allowing to transform a corollary discharge arising from the motor cortex into the corresponding sensory consequences, which can then be compared with sensory feed-backs in order (1) to contribute to mental model of the (covert) movement, during motor imagery; (2) to correct the current overt movement; or (3) to adjust the up-coming one. The result of the cerebellar computation is then conveyed to the cerebral cortex or to the striatum through specific thalamic subnuclei [83]. Cerebellar selection of the thalamic response mode, reflecting the forward model, would contribute to the tuning of the final cortical response. In monkey cerebellar motor thalamus, neurons exhibit "deep sensory field related to a single muscle, a group of synergists, or a single joint" and "fire in relation with the duration of perturbations applied to the intended movement" [84]. Thalamic neurons discharge after the motor cortex but

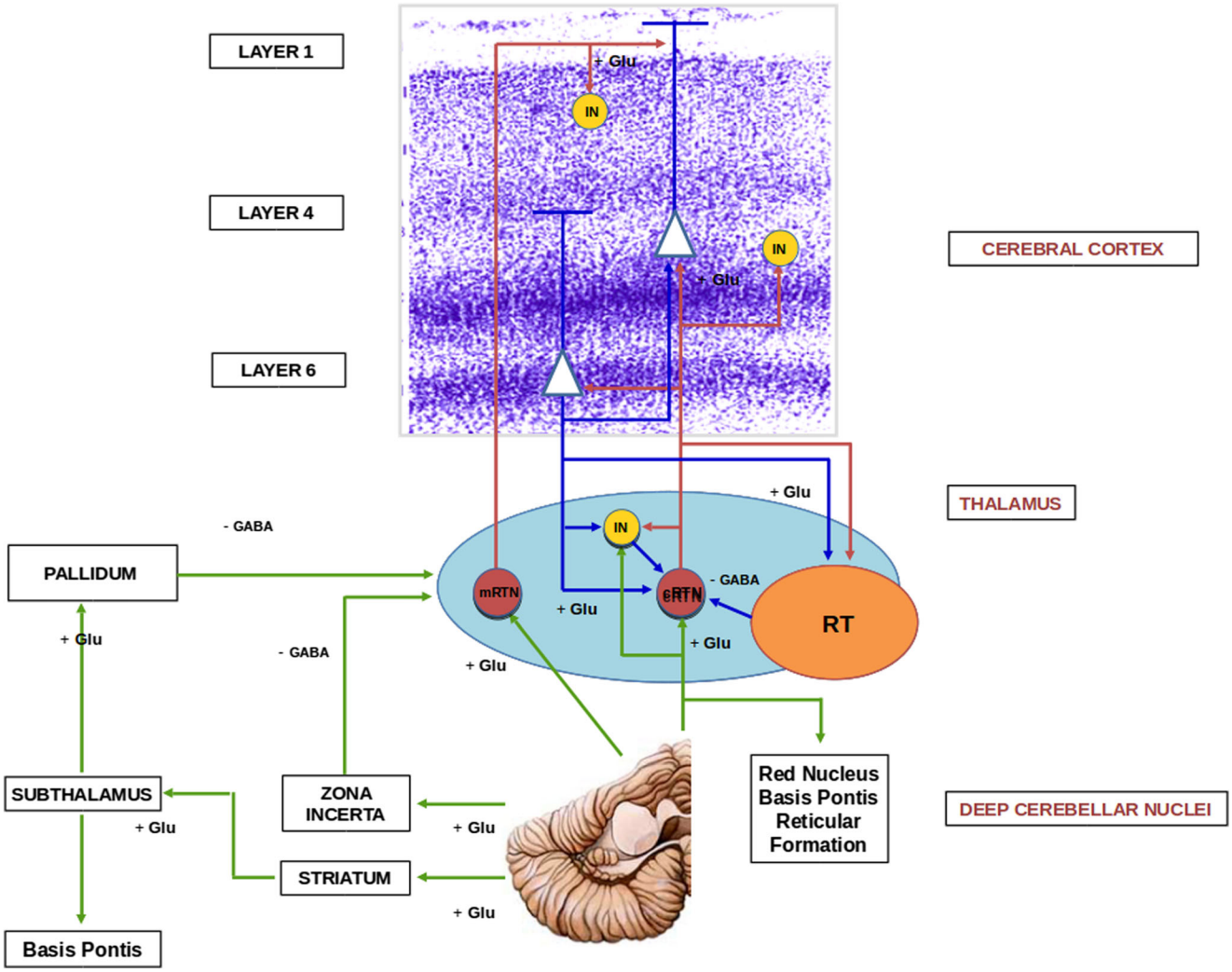

Fig. 5 Schematic diagram illustrating the cerebello-recipient dorsal and reticular thalamus, including core thalamic relay neurons (cTRN), modulatory thalamic relay neurons (mTRN), and GABAergic local interneurons (IN), receiving also afferents from the striatal system and back-projections from the cerebral cortex. TRN send axons to specific layers of the cerebral cortex

before movement onset. During ballistic skilled movements, these neurons fire phasically in relation with the duration of the movement and seem to control the magnitude and duration of the late phasic part of the phasic-tonic cortical neuronal discharge [85]. Therefore, thalamic neurons do not encode kinematical nor dynamical parameters of movement but rather precise timing of complex movement and adjustments of motor response to perturbations [86], which is compatible with forward models. Their coding also integrate contextual cues, since lesions of area X impair preferentially initiation of visually-triggered movements with an increased time reaction and movement amplitude variability [87], i.e., cue-dependent motor planning, whereas VPLo lesion induces transient contralateral deficit in movement production [88]. Bursts in thalamic neurons (in VL) have been recorded in mice after optogenetic stimulation of Purkinje cells (lobule VII). They are likely due of dentate rebound activation, a mechanism used by the cerebellar circuit to sculpture patterns of discharges [89]. However, the role of in vivo rebound activation is still matter of debate [90]. It has been suggested that rebound activation should occur specifically during (motor) learning. It is noteworthy that a strong activation of cerebellothalamocortical circuit is observed during exercise training in rat [91]. So, does learning specifically recruit the thalamus in response to rebound activity in DCN? Interestingly, in rat [92] and in monkey [93], stimulation of DN or IN causes specific thalamocortical activation: area X/VL and VA/VL, which in turn activate the deep (layer 4) and supragranular superficial neurons (premotor and motor cortices), respectively. The cortical response due to fastigial stimulation remained confined to deep layer of the cereberal cortex. It is likely that projections to superficial cortical layers may emanate from the matrix neurons, especially in associative subnuclei. Furthermore, two recent studies in rodent contribute to shed light on the role of the motor "cerebellar" thalamus. Tanaka et al. [94] revealed, in mice, a differential

activation of the striatal and cerebellar thalamocortical projections to the motor cortex during learning of a self-initiated lever-pull task. The successful performance was associated with a reward (water) delivery by a licking-bout. Basal ganglia (substantia nigra, pars reticulata) intervened early during learning, determined the temporal sequence of movement and their kinematical parameters, and influenced mainly the cortical layer 1. The cerebellar action, through cerebellar thalamocortical projections ending in cortical layer 3, controlled timing of movement onset as well as of the reward-based licking-bout and was strongly correlated with success rate. However, both DCN- and basal ganglia-lesioned induced motor sequence impairments in layers 1 and 3. Therefore, despite specific striatal and cerebellar involvement in the motor task, the two systems collaborated either by the direct striato-cerebellar connections or at the cortical columnar level, and cerebellar thalamo-cortical afferents seemed to play an optimizing role in initiating, timing, and coordinating the whole motor performance, including the final reward consumption. In the rat motor thalamus, during a two-alternative forced-choice motor task, one neuronal group ("initiation units") was activated prior to the movement onset and correlated with the reaction time, whereas a second group ("execution units") was locked to movement initiation and correlated to the movement direction [95]. Therefore, the cerebellothalamocortical pathway could transmit a phasic nonspecific signal necessary for the motor cortex to switch from a preparatory state to an execution state, while the basal gangliathalamocortical pathway might control specific action selection and invigoration. Proville et al. [89] also showed that cerebellar inactivation yields to suppression of the synchronization of M1 and S1 in the gamma band, probably impairing sensorimotor coordination in sensory (whisker)-guided exploratory movements used to recognize objects in the environment. These data agree with demonstration of focused gamma coherence between, DN, VL, and M1 after DN stimulation in cat [96]. The cerebellar thalamus participates in functional coordination through coherent rhythmic activity. In human, coherent high-frequency oscillatory activity (8–27 Hz) has observed in contralateral muscles, cerebellar thalamus (ventralis intermedius), and sensorimotor cortex during tremor [97]. The cerebellar thalamus (VL) and supplementary motor area display coherence in the β-band during self-generated movement preparation [98]. β-Coherence was also observed between cerebellum and temporal cortex during auditory-motor (tapping) rhythm learning [99] and α-coherence during reading [100]. Functional neuroimaging studies have shown a covariation of dentate and thalamic activity with the complexity of rhythmic finger movements [101], and low frequency pacing (6–9 Hz) generated in the cerebello-thalamo-M1 system to chunk discrete micromovements into a slow continuous finger movement [102]. It has been postulated that such dynamical synchronization may underlie interareal functional binding and/or temporal tuning of (up-coming) movement. In addition, DCN activation can suppress thalamocortical oscillations during generalized spike-and-wave discharges (absence seizures) [103, 104]. Altogether, these data support the general idea that the cerebellum implements multimodal (forward) internal models [105], calculating consequences of cortical commands (efference copy) using feed-back errors and behaving as a state-estimator/predictor. The cerebellum provides adjusting output to the thalamus in charge of temporally reshaping and coordinating cortical/striatal activities by selecting and instantiating appropriate thalamic mode response and especially cortico-thalamo-cortical oscillations. Although most of the available data regarding the cerebellar thalamus concern the motor system, a recent fMRI study has shown that a cerebellum (tonsilla)-mediodorsal thalamus-supplementary motor area circuit mediates error and posterror processing and controls the ventrolateral prefrontal activation during a stop-signal paradigm [106]. Indeed, thalamic and prefrontal activations are strongly and positively correlated during the posterror slowing. Consequently, error-based cerebello-thalamic control of cerebral activity can be extended from motor to association cortex. Finally and speculatively, we have mentioned that the corticothalamo-cortical and most widespread cerebellothalamocortical loops display oscillatory rhythms. Thalamocortical and several cortical areas may behave as nonlinear dynamical systems [107], such as weakly coupled oscillators [108] displaying attractor-based or metastable dynamics [109]. In this case, cerebellothalamic inputs could serve as order parameters determining the interareal coherence (or coordination), as well as the attractor landscape of the (thalamo-)cortical activity specifying the cortical command. So, it is no longer sufficient to establish anatomofunctionnal correlations between thalamus and for instance, motor parameters, but it is also important to highlight and to model how cerebellothalamic inputs influence dynamic states of the brain. In this vein, numerous studies were devoted to self-organized coordination dynamics comparing brain activation patterns during rate-related transition from unstable motor syncopation to more stable motor synchronization (reviewed in [110]). For example, the experimental task used finger flexion/extension movements performed in phase with or in antiphase with a metronome beat of increasing frequency. For our purpose, two important results were obtained. First, α- and β-coherence and their power spectrum of the motor brain areas vary in function of the stability of the motor task: in particular, β-coherence relies on the complexity of the tasks. Second, although ipsilateral cerebellar activation was common in both tasks, supplementary motor area, lateral premotor cortex, thalamus, and contralateral cerebellum were more strongly activated during overt and covert (mental imagery) syncopation in comparison with synchronization. Cerebellar activation was correlated to both movement rate and coordination pattern. Therefore, the cerebellum through

cerebellothalamocortical (lateral and medial area 6) may participate not only in coordinating cortical activity during motor learning and performance [111] but also in stabilizing automatically complex motor patterns based upon its learned motor repertory. Moreover, the bilateral putamen in relation with supplementary motor area seems to be implicated in intentional switching from a more to a less stable motor pattern [112] and, consequently, to activate desired pattern and to inhibit the undesired one. In a nutshell, cerebellum and striatum are involved in monitoring automatically and intentionally stability of (complex) motor patterns, respectively, by integrating large-scale cortical network and reflecting underlying attractor dynamics, respectively.

Clinical Data

Nuclei of the dorsal thalamus can be considered as a processing station of ascending projections towards the neocortex, which is a key-stage to prepare sensory signals in order to generate genuine sensations at the cortical level. With the exception of olfaction, all the sensory systems project to the thalamus. The thalamus is also a key-player for cognitive tasks, awareness, and arousal. Clinical observations support these notions. Thalamic lesions produce a thalamic syndrome. Lesions of the ventral posterior portion cause a reduction in somatic perception contralaterally, without a full anesthesia. Patients may experience dysesthesias or express severe pain (thalamic pain). Patients may also exhibit dyskinesias. Indeed, clinical observations clearly point towards a role of the cerebellum and cerebellothalamocortical pathways in major motor symptoms, such as tremor [113]. Contralateral and ipsilateral thalamic volumes and ipsilateral superior cerebellar peduncle area are correlated inversely with higher unilateral tremor severity scores. Both cerebellar lesions and thalamic lesions induce a kinetic tremor. Functional surgery of the Vim is associated with a significant reduction of tremor in disorders, such as essential tremor [114]. Vim van also reduce tremor in spinocerebellar ataxias [115]. The Vim is the homolog of the VPLo in primates, which receives not only cerebellar, spinothalamic, and corticothalamic projections but also disynaptic inhibition from the motor cortex via the thalamic reticular nucleus and thalamic interneurons [116]. It has been proposed that changes in Vim neuronal discharge in ataxic patients mainly reflect changes in the activities of DCN [115]. The thalamic ataxia syndrome delineated by Solomon et al. is characterized by contralateral ataxia and hemisensory loss following unilateral thalamic lesions [117]. Hemiparesis was transient, by contrast to ataxia, dysmetria, dysdiadochokinesia, rebound, and hemisensory loss. No patient showed mutism, aphasia, or astasia. All patients presented lesions in the mid to posterior thalamus, consistent with a lesion of the dentatorubrothalamic and ascending sensory pathways to thalamic nuclei.

The role of the cerebellum in higher functions is now well established. A major anatomical pathway involved in these functions if the cerebellothalamocortical pathway. A typical example is autism and autism spectrum disorders (ASD). A cerebellocortical "disconnection" has been proposed as a possible neurobiological basis of autistic dysfunctions [118]. Resting-state studies demonstrate impaired functional connectivity between the dentate nucleus and the cerebral cortex in ASD patients. A reduced connectivity has been uncovered between the left DN and cerebral regions involved in specific networks, such as the default mode network, which are involved in specific aspects of mentalizing, social cognition processing, and higher order emotional processes [118]. Evidence of abnormal functional and structural cerebellar network development in adolescents at very high risk for the development of psychosis has also been provided [119]. Interestingly, the cerebellothalamocortical network development and connectivity at baseline are associated with positive symptoms, opening the door for cerebellar networks as biomarkers of psychiatric diseases. A third field with clinical implications is Parkinson's disease. Impaired dopaminergic projections to the cerebello-thalamo-cortical circuit have a critical role in Parkinson's tremor [120]. Dopamine directly enhances self-inhibition of the VIM, rather than indirectly influencing the cerebellothalamocortical circuit via the basal ganglia. It is now obvious that both the striatal thalamocortical circuit and cerebellothalamocortical circuit are involved in the pathogenesis of motor deficits in Parkinson's disease [121]. A mild cortical impairment has been observed in patients with normal dopaminergic scans (SWEDD) as shown by cerebellum-brain inhibition studies [122].

General Summary

Cerebellar excitatory glutamatergic afferents "drive" first TRN belonging to the core system. These TRN are included in cortico-thalamo-cortical loops encompassing feed-forward thalamo-cortical (mainly layers 3–4) and feed-back modulatory activity-dependent corticothalamic (layer 6) projections. Potential connections may exist between layers 5 and 6 pyramidal cells, through axonal collaterals [23] or interneurons [78], thus coupling the modulatory layer 6 and driver layer 5 cortical systems. Moreover, electrophysiological and histological data suggest that the cerebellar thalamus also encompasses matrix thalamic neurons connected with superficial cortical layer 1, so that it can exert both a focused and a more diffuse influence on cortical columns. The cerebellum also projects to the striatum, zona incerta (in relation with the cereberal cortex) and, inconstantly and scarcely, reticular thalamus. Therefore, cerebellum may concur to a direct driving and indirect modulating activity in the thalamus and could potentially coordinate its computation with the striatal system. Cerebellum, as driver, causes tonic and/or burst thalamic

spiking. This spiking response exhibits very few correlations with movement parameters (mostly movement duration), lags motor cortex activation, and precedes EMG activity. Furthermore, rhythmic cerebellothalamocortical activities in several frequency bands have been detected in normal and pathologic cases, such as β-coherence during movement preparation/initiation. Moreover, DN cooling yields spatiotemporal agonist-antagonist muscular pattern disorganization. Although DN can also dispatch information directly to several brainstem structures, it can be suggested that the major cerebello-thalamo-cortical pathway plays a major role in precisely selecting, timing, and thus coordinating cortical areas that contribute to a same motor or nonmotor function. For instance, frequency coherence should bind together cortical areas, while phase differences should determine accurately their temporal sequencing. It could be also postulated that cerebello-thalamo-cortical oscillations might drive fine temporal parameters such as movement frequency. This fits with the correlation sometimes observed between anterior cerebellar (and thalamus) activation and frequency and spatiotemporal complexity of rhythmic movements [123] and between the posterior lobe activation and unstructured sequential movements in relation with the prefrontal cortex [124]. The cerebellum may be involved in maintaining automatically stability of brain patterns in the realm of motor or cognitive domains acting through thalamocortical modules/loops, thalamocortical divergent projections, and specific thalamic mode responses.

Conclusion

We have emphasized the central role of the "cerebellar thalamus," which must no longer be assimilated to a simple relay and should deserve more anatomo-functional, physiological, and biophysical considerations. Outstanding queries remain. Which differences exist in cerebello-thalamic afferents between primates and humans? Do some cerebellar afferents terminate upon matrix neurons in motor and especially associative thalamic nuclei? Do convergent driver input converge upon TRN? Do some cerebellar afferents reach the reticular thalamus? How do cerebellar projections to zona incerta and striatum modulate the thalamus? May these latter projections be regarded as indirect cerebellar modulatory inputs? Are there internuclear links/loops between cerebellar thalamus subnuclei? How does feed-back layer 6 afferents modulate efficacy of cerebello-thalamic inputs? Do DCN transmit specific information to the thalamus (and cortex), or do they contribute to organize and coordinate cross-areal cortical activity? In this vein, how does the cerebello-thalamic input modulate or to organize cortical rhythms in the framework of cerebellar models, considering the cerebellar system not only as computational optimal system but also as a dynamical system? Do thalamic subnuclei subserve different modality-specific processing? The growing interest of the community in cerebellum-basal ganglia interactions opens also key-questions in terms of thalamic activities during the initial stage or the progression of basal ganglia disorders, such as Parkinson's disease. The field of noninvasive cerebellar stimulation (NICS) is quickly evolving, including in the attempt to modulate symptoms, which were initially attributed to basal ganglia disorders. It remains to be determined whether NICS affects the patterns of discharges in thalamic nuclei.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

Ethical Approval Not applicable.

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