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Autonomic functions of the cerebellum: Anatomical bases and clinical implications

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Abstract. Traditionally, the cerebellum is viewed as a center for integrating vestibular and general proprioceptive sensory, enabling the processing of somatic motor responses essential for maintaining balance and posture. Moreover, the cerebellum regulates higher motor functions of the neocortex, which involve motor planning and coordination of movements, as well as nonmotor functions related to cognition and affectivity. In recent years, several studies have suggested that the cerebellum may play a role in regulating visceral functions. Although the specific neural pathways through which these visceral functions are mediated remain unclear, anatomical evidence to support these functions has been supplied by the detection of a feedback circuit that connects bidirectionally the cerebellum and the hypothalamus, the primary integrative center of the autonomic nervous system. This hypothalamocerebellar circuit strongly supports the idea of the cerebellum as a center of the autonomic nervous system.

Keyword: Cerebellum, Hypothalamus, Hypothalamocerebellar circuit, Autonomic nervous system.

1. BACKGROUND

1.1. The Cerebellum as a Center of the Somatic Nervous System

The publication of the influential work *The Cerebellum as a Neuronal Machine* by John C. Eccles, Masao Ito, and Janos Szentagothai in 1967 established the foundations for understanding the anatomy, physiology, pathophysiology, and clinical aspects of the cerebellum. A series of neuroscience studies conducted in subsequent years have widely validated the findings reported in this pivotal study and have led to the modern views according to which the cerebellum is considered to play a crucial role in integrating vestibular and general proprioceptive sensory and regulating the activity of the motor areas of the neocortex. The cerebellum is functionally divided into three regions: the *vestibulocerebellum*, *spinocerebellum*, and *cerebrocerebellum* (also known as *pontocerebellum*) (Table 1).

This functional subdivision is reflected in the anatomical subdivision of the cerebellum (Figure 1). In fact, the vestibulocerebellum substantially cor-

Table 1. Functional subdivision of the cerebellum: main afferents and efferents.

	Afferents	Efferents
Vestibulocerebellum	· Vestibulocerebellar tract · Olivocerebellar tract	· Cerebellovestibular tract · Cerebelloolivay tract
Spinocerebellum	· Posterior spinocerebellar tract · Anterior spinocerebellar tract · Cuneocerebellar tract · Reticulocerebellar tracts · Trigeminocerebellar tracts · Olivocerebellar tract	· Cerebellotectal tract · Cerebellorubral tract · Cerebelloreticular tracts · Cerebelloolivay tract
Cerebrocerebellum	· Pontocerebellar tracts · Reticulocerebellar tracts · Olivocerebellar tract	· Cerebellothalamic tract · Cerebelloreticular tracts · Cerebelloolivay tract

responds to the *flocculonodular lobe*, the spinocerebellum comprises a significant portion of the *anterior lobe* and a portion vermis in the middle lobe, and the cerebrocerebellum includes most of the *middle* (or *posterior*) *lobe* along with portions of the hemispheres in the anterior lobe (Ito, 1984; Berry et al., 1995; Voogd and Glickstein, 1998; Fitzpatrick, 2004; Brodal, 2016; Unverdi et al., 2024). Interestingly, these functional and anatomical subdivisions also have phylogenetic significance. The vestibulocerebellum is the phylogenetically oldest region, known as the *archicerebellum*; the spinocerebellum occupies an intermediate position from a phylogenetic point of view, referred to as the *paleocerebellum*; and the cerebrocerebellum represents the most recent phylogenetically region, termed the *neocerebellum* (Berry et al., 1995).

The vestibulocerebellum and spinocerebellum, especially through the fastigial nucleus and the globose and emboliform nuclei respectively, control various centers of the somatic motor system, including the vestibular nuclei, midbrain tectum, magnocellular red nucleus, and some neuronal groups in the reticular formation (Table 1). Through these centers, the vestibulocerebellum and spinocerebellum regulate the activity of brainstem and spinal somatic motor neurons, which are directly responsible for the contraction of striated muscle fibers. This regulation is crucial for maintaining muscle tone and executing automatic somatic movements. Consequently, both the vestibulocerebellum and spinocerebellum play an essential role in controlling balance, posture, walking, and gaze (Ito, 1984; Berry et al., 1995; Voogd and Glickstein, 1998; Ghez and Thach, 2000; Hook and Mugnaini, 2003; Fitzpatrick, 2004; Voogd and Ruigrok, 2012; Brodal, 2016).

The cerebrocerebellum is part of the cerebrocerebellar circuit, which is a feedback or loop circuit establishing a two-way connection between the neocortex and

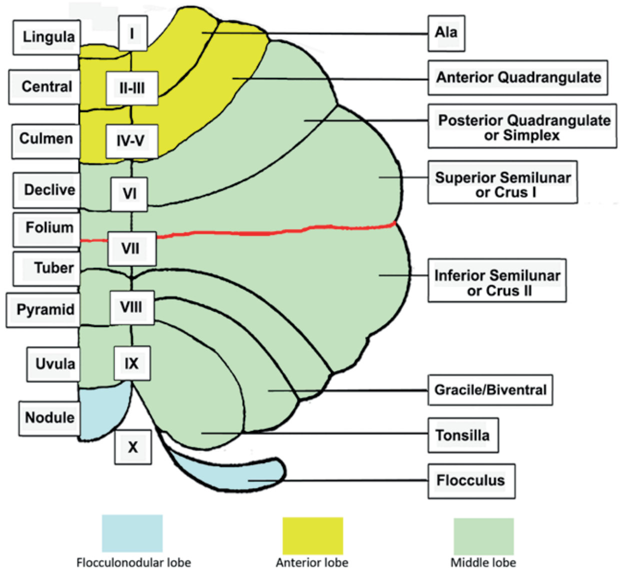

Figure 1. Anatomical subdivisions of the human cerebellum. Diagram showing the lobes and lobules of unfolded cerebellum. The lobules of the vermis and the right hemisphere of the right side are named according to the classic anatomical nomenclature and to the Larsell's nomenclature (Roman numerals from I to X); the horizontal fissure is marked in red. The anatomical of the cerebellum subdivision into three lobes largely corresponds to the functional subdivision of the cerebellum: the vestibulocerebellum relates to the flocculonodular lobe, the spinocerebellum, to the anterior lobe, and the cerebrocerebellum, to the middle lobe.

the cerebrocerebellum. The circuit consists of a descending limb that originates from the neocortex and projects, via the basilar pontine nuclei, onto the cortex of the cerebrocerebellum; and an ascending limb that originates from the cerebrocerebellum, especially from the dentate nucleus, and selectively projects, via the thalamus (ventrolateral nuclear complex), onto the motor areas of the neocortex. This circuit is involved in regulating the activity of neocortical areas responsible for planning complex spatial and temporal sequences of movements as well as executing voluntary movements that require high precision and coordination (Kelly and Strick, 2003; Schmahmann et al., 2004; Fitzpatrick, 2004; Schmahmann and Pandya, 1997a, b; Voogd and Ruigrok, 2012).

Numerous clinical studies have evidenced that cerebellar disorders can be associated with specific clinical symptoms that present a correlation with the anatomical and functional subdivisions of the cerebellum, even if these symptoms may occur in various combinations. In summary, vestibulocerebellar disorders are primarily associated with vestibular symptoms, such as balance defects, dizziness, and nystagmus. Spinocerebellar disorders mainly involve somatic motor symptoms, including disturbances in muscle tone (hypotonia), posture, and gaze issues, as well as difficulties in performing rapid alternating movements (dysdiadochokinesia). Cerebrocerebellar disorders are characterized by motor symptoms resulting from functional deficits in the motor areas of the neocortex. These clinically occur with impairments in executing coordinated and synergistic movements (*motor ataxia*). This provokes disorders of voluntary movements, including walking, praxias, speech articulation, and oculomotion; inability to execute movements that require high precision during their execution, typified by undershooting or overshooting the intended position with the hand, arm, or leg (dysmetria); appearance of tremor during voluntary movements (intention tremor) (Koeppen 2018; Manto et al., 2022; Ataullah et al., 2024).

1.2. The Cerebellum as a Center of the Psychic System

More recent research has shown that the cerebrocerebellum plays a crucial role in regulating functions played by nonmotor areas of the neocortex (Strick et al., 2009; Timman et al., 2010; Grimaldi and Manto, 2012; Benagiano et al., 2018). The anatomical bases for these nonmotor functions of the cerebrocerebellum lie in the organization of the cerebrocerebellar circuit into distinct channels (or subcircuits). Each channel includes a descending limb that originates from a specific nonmotor area of the neocortex and projects onto an anatomically and functionally related region of the cerebrocerebellum; and an ascending limb that starts in the cerebrocerebellum (especially from the dentate nucleus) and projects back onto the same cortical area from which the descending limb originated. Therefore, while the traditional view of the cerebrocerebellar circuit primarily focuses on the motor channel, the new views postulate the existence of nonmotor channels, including the sensory, associative, and limbic channel. These channels establish bidirectional connections between the neocortex of sensory associative and limbic areas and related regions of the cerebrocerebellum (Schmahmann and Pandya, 1991, 1993, 1995, 1997a, b; Clower et al., 2001; Middleton and Strick, 2001; Dum and Strick, 2003; Kelly and Strick, 2003; Ramnani et al., 2006; Akkal et al., 2007; Leergaard and Bjaalie, 2007).

The presence of distinct channels throughout the cerebrocerebellar circuit has been confirmed by studies carried out with diffusion tensor tractography techniques. These studies have revealed that the tracts in the descending limb (neocorticopontine and pontocerebellar tracts) and those in the ascending limb (cerebellothalamic and thalamocortical tracts) are organized into separate, anatomically distinct fascicles. Each of these fascicles connects a specific area of the neocortex with a corresponding region in the cerebrocerebellum (Granziera et al., 2009; Kamali et al., 2010; Kwon et al., 2011; Keser et al., 2015; Palesi et al., 2015).

These observations have provided the anatomical bases for findings from experimental, neuropsychological, and clinical studies, indicating that lesions selectively localized in a specific region of the cerebrocerebellum can disrupt a particular channel and be associated with specific nonmotor disorders. The resulting cerebrocerebellar syndromes can influence cognitive functions, leading to conditions like *cognitive ataxia*, which affects sensory perceptions, learning, memory, language, and ideation (Appollonio et al., 1993; Leiner et al., 1993; Topka et al., 1993; Daum et al., 1993; Akshoomoff and Courchesne, 1994; Silveri and Misciagna, 2000; Gottwald et al., 2004; Schmahmann et al., 2007a, b; Timman and Daum, 2010). Alternatively, the syndromes can impact affective functions, leading to *affective ataxia*, which concerns the adequacy of mood, balance of emotions and feelings, and appropriateness of behavior (Ho et al., 2004; Schmahmann et al., 2007a,b; Tavano et al., 2007; Hoppenbrouwers et al. 2008; Moreno-Lopez et al 2015; Carta et al 2019).

Finally, in cases of neurodevelopmental disorders of the cerebrocerebellum, clinical and behavioral studies have described, in addition to motor ataxia, deficits in learning and concentration classifiable as autism spectrum disorders (Courchesne, 1997; Muratori et al., 2001; Jones et al., 2002; Steinlin, 2008; Bolduc and Limperopolous, 2009; Bolduc et al., 2012; Becker and Stoodley, 2013).

The *Cerebellar Cognitive Affective Syndrome* (CCAS) is a complex clinical syndrome characterized by various symptoms, including disorientation in space and time, difficulty in concentrating (hypoprosexia), challenges in solving logical problems, and deficits in generating, developing, and communicating ideas; patients with CCAS also exhibit inadequate emotional expressions and personality changes. The diverse symptoms associated with CCAS have been linked to dysfunction affecting the different cerebrocerebellar channels (Schmahmann and Sherman, 1998).

Studies using functional magnetic resonance imaging (fMRI) have shown continuous activation of the cerebrocerebellar lobes while performing working memory tasks. This has suggested that the cerebrocerebellum and its connections with various areas of the neocortex play a crucial role in learning and memory processes (Chen and Desmond, 2005; Marvel and Desmond, 2010; von der Gablentz et al., 2015; Peterburs & Desmond, 2016; Brissenden et al., 2021).

1.3. The Cerebellum as a Center of the Autonomic Nervous System

Experimental studies and clinical observations have suggested that the cerebellum plays a role in regulating various visceral functions (Reis and Golanov, 1997; Xu and Frazier, 2000; Colombel et al., 2002; Dietrichs and Haines, 2002; Zhu et al., 2004; Peng et al., 2006; Zhu and Wang, 2008; Cao et al., 2015).

While the idea of the cerebellum acting as a regulatory center for the autonomic nervous system has been proposed for several years, research on the anatomical bases for this function has been surprisingly limited and the available information is scarce and incomplete.

The present review aimed to assess the current understanding of the cerebellum as a regulatory center for visceral functions. Particular attention was paid to exploring whether the somatic, psychic, and autonomic functions of the cerebellum influence one another and what the consequences of these interactions may be.

2. HYPOTHALAMOCEREBELLAR CIRCUIT

The anatomical bases for the role of the cerebellum as a regulatory center of the autonomic nervous system could be supported by the demonstration of the hypothalamocerebellar circuit. This is a feedback circuit that bidirectionally connects the hypothalamus, the main regulatory center of visceral functions, and the cerebellum (Haines et al., 1997; Zhu et al., 2006; Sakakibara, 2018; Rizzi et al., 2020; Urbini et al., 2023).

Similar to the cerebrocerebellar circuit, the hypothalamocerebellar circuit is composed of a descending and an ascending limb. The descending limb includes a direct and an indirect pathway (Figure 2).

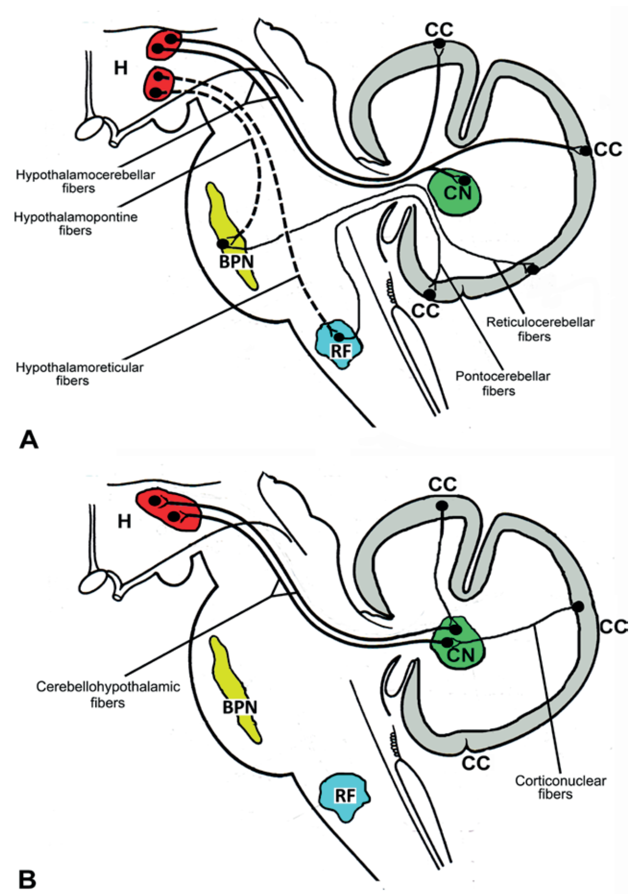

Figure 2. Hypothalamocerebellar circuit: A. descending limb; **B.** ascending limb. The diagram illustrates both the direct and indirect pathways of the circuit. The hypothalamic nuclei putatively at the origin of hypothalamocerebellar, hypothalamoreticular, and hypothalamopontine fibers include the preoptic, ventromedial, dorsomedial, medial mamillary, and tuberomamillary nucleus. **Abbreviations: BPN**: basilar pontine nucleus; **CC**: cerebellar cortex; **CN**: cerebellar nucleus; **H**: hypothalamus; **RF**: reticular formation.

2.1. Direct Hypothalamocerebellar Pathway

The direct hypothalamocerebellar pathway connects the hypothalamus and cerebellum directly and bidirectionally (Benagiano et al., 2018; Rizzi et al., 2020).

Descending limb: hypothalamocerebellar fibers (Figure 2A). Anatomical studies carried out on experimental animals have shown that the descending limb consists of direct hypothalamocerebellar fibers originating from neurons in various hypothalamic nuclei. These nuclei include the preoptic, ventromedial, dorsomedial, medial mamillary, and tuberomamillary nucleus. To a lesser extent, hypothalamocerebellar neurons have also been detected in the suprachiasmatic, posterior, paraventricular, and arcuate nucleus (Dietrichs and Haines, 1984; Haines and Dietrichs, 1984). The hypothalamocerebellar fibers descend to the midbrain tegmentum and prevalently enter the homolateral superior cerebellar peduncle, reaching the central core of the white matter in the cerebellum. Here, they send collaterals to all the cerebellar nuclei and ultimately radiate towards the cortex of *all* the cerebellar lobes (Dietrichs and Haines, 1984; Haines and Dietrichs, 1984; Supple, 1993; Dietrichs et al., 1994; Haas and Panula, 2003; Haas et al., 2008).

Microscopic observations have revealed that the hypothalamocerebellar fibers terminate in all layers of the cerebellar cortex, *multilayered fibers*, possibly synapsing on various types of corticocerebellar neurons (Panula et al., 1993; Li et al., 2014). Consequently, it has been proposed to consider the multilayered fibers as a third type of afferent fibers to the cerebellar cortex, alongside the well-known mossy and climbing fibers (Haines et al., 1997).

Immunocytochemical studies have shown that the terminals of the multilayered fibers are immunoreactive for histamine and use it as a chemical neurotransmitter (Airaksinen et al., 1988; Panula et al., 1993; Li et al., 1999; Rizzi et al., 2019). Accordingly, histamine receptors (H-receptors) have been detected in the cerebellar cortex of various species of mammals, using autoradiographic, immunocytochemical, and *in situ* hybridization techniques. Specifically, H-1 receptors have been found in all the cortical layers, located on the parallel fibers (Rotter and Frostholm, 1986; Traiffort et al., 1994); H-2 receptors have been detected in the Purkinje neuron layer, on the Purkinje neuron bodies and preaxons, and granular layer, on the granule dendrites (Vizuete et al., 1997); H-3 receptors have been detected in the Purkinje neuron layer only (Chazot et al., 2001; Pillot et al., 2002), and have been visualized in the human cerebellum by positron emission tomography (PET) (Ashworth et al., 2010). In vitro studies have shown that histaminergic terminals have excitatory effects on H-1 and H-2 receptors expressed by granules (Li et al., 1999), and on H-2 receptors expressed by Purkinje neurons (Tian et al., 2000).

Histamine-containing neurons have been demonstrated in some hypothalamic nuclei, primarily in the tuberomamillary nucleus, and to a lesser extent, the ventromedial, dorsomedial, and paraventricular nucleus (Brown et al., 2001; Haas & Panula, 2003; Haas et al., 2008). It is noteworthy that these nuclei also contain the neurons at the origin of the hypothalamocerebellar fibers.

Ascending limb: cerebellohypothalamic fibers (Figure 2B). The excitatory signals sent by the histaminergic terminals of the multilayered fibers activate the Purkinje neurons either directly or indirectly. These neurons serve as the source of output from the cerebellar cortex, sending corticonuclear fibers to the neurons located in all the cerebellar nuclei (Ito, 1984; Berry et al., 1995; Voogd and Glickstein, 1998). It is well known that the outputs from Purkinje neurons to the nuclear neurons are inhibitory and use GABA as a neurotransmitter (Benagiano et al., 2000, 2001).

Anatomical studies using anterograde and retrograde tract-tracing techniques, along with physiological studies based on electrophysiology techniques, have identified the *cerebellohypothalamic fibers*. These fibers originate from neurons located in all the cerebellar nuclei, primarily the fastigium and interpositus nucleus. They travel through the superior cerebellar peduncle, midbrain tegmentum, and into the hypothalamus (Dietrichs and Haines, 1984; Haines and Dietrichs, 1984; Wang et al., 1997; Cavdar et al., 2001a, b). Most of the cerebellohypothalamic fibers cross at the decussation of the midbrain tegmentum, and reach the contralateral hypothalamus, differently from the hypothalamocerebellar fibers, which establish homolateral connections (Lemaire et al., 2011). These fibers project onto hypothalamic nuclei that correspond largely to those at the origin of the descending limb, including the ventromedial, dorsomedial, and tuberomamillary nucleus (Wang et al., 1997; Cavdar et al., 2001a, b). The effects of the cerebellohypothalamic fibers on hypothalamic neurons can be of excitatory type, mediated by glutamate (Lu et al., 2012; Cao et al., 2015), or, more rarely, of inhibitory type, mediated by GABA (Wang et al., 2011; Cao et al., 2013; Lu et al., 2015).

2.2. Indirect Hypothalamocerebellar Pathways

In the indirect pathways, the connections between the hypothalamus and cerebellum are established through the involvement of brainstem centers. Briefly, fibers originating in the same hypothalamic nuclei that give rise to the direct hypothalamocerebellar pathway, before reaching the cerebellum, interrupt in brainstem nuclei, such as nuclei of the reticular formation and basilar pontine nuclei.

The indirect pathways include the *hypothalamoreticulocerebellar* and *hypothalamopontocerebellar pathways*. Each of these pathways consists of a proximal segment, either the hypothalamoreticular fibers or the hypothalamopontine fibers, and a distal segment, either the reticulocerebellar fibers or the pontocerebellar fibers. The *hypothalamoreticular fibers* primarily project onto neurons located in the precerebellar lateral reticular nucleus, which is located in the lateral medullary reticular formation (Dietrichs et al., 1985; Mihailoff et al., 1989; Allen and Hopkins, 1990); the *hypothalamopontine fibers* target neurons that are sparse in the rostral medial and dorsal medial basilar pontine nuclei (Aas, 1989; Liu and Mihailoff, 1999). Actually, detailed information on the anatomy, neurochemistry, and physiology of these pathways is lacking in the literature.

3. DISCUSSION

The existence of a hypothalamocerebellar circuit, which connects bidirectionally the hypothalamus and the cerebellum, is now well established (Dietrichs and Haines, 1984; Haines and Dietrichs, 1984; Supple, 1993; Dietrichs et al., 1994). This is a feedback circuit organized similarly to the more widely recognized cerebrocerebellar circuit. It consists of a descending limb that originates from various hypothalamic nuclei, specifically, the ventromedial, dorsomedial, and tuberomamillary nucleus, and terminates in the cerebellar cortex across all cerebellar lobes; and an ascending limb that starts in the cerebellar cortex and projects back onto the same hypothalamic nuclei from which the descending limb originates. It is important to note that the hypothalamocerebellar fibers are distributed throughout all cerebellar lobes. They terminate as multilayered fibers in all cortical layers and express histamine as a chemical neurotransmitter (Li et al., 1999; Haas and Panula, 2003; Haas et al., 2008; Rizzi et al., 2019). All these are characteristics that differentiate the hypothalamocerebellar fibers, which form the hypothalamocerebellar circuit, from the pontocerebellar ones, which form the cerebrocerebellar circuit.

The hypothalamus acts as the primary regulatory center for visceral functions and is an important subcortical component of the limbic system (Onat and Cavdar, 2003; Saper, 2012). It is likely that the signals sent to the cerebellum via the hypothalamocerebellar fibers, which form the descending limb of the hypothalamocerebellar circuit, contain information related to the visceral and limbic systems. These connections suggest that the cerebellum, through the cerebellohypothalamic fibers, ascending limb of the hypothalamocerebellar circuit, plays a regulatory role of hypothalamic nuclei involved in visceral and limbic functions.

The role of the hypothalamic-cerebellar circuit would be comparable to that of the cerebrocerebellar circuit: the cerebellum could influence the activity of the hypothalamic nuclei just as the cerebrocerebellum controls the activity of motor and nonmotor areas of the neocortex. Interestingly, the entire cerebellum would be involved in regulating the hypothalamus, while only the cerebrocerebellum would be involved in regulating the neocortex.

The existence of the hypothalamocerebellar circuit provides anatomical evidence supporting a series of observations that indicate the role of the cerebellum in regulating visceral functions and its involvement in the pathogenesis of visceral disorders. These findings align with experimental studies showing that electrical stimulation or lesions of the cerebellum can trigger visceral changes affecting gastrointestinal, cardiovascular, respiratory, immune, and other visceral functions (Reis and Golanov, 1997; Xu and Frazier, 2000; Colombel et al., 2002; Dietrichs and Haines, 2002; Zhu et al., 2004; Peng et al., 2006; Zhu and Wang, 2007; Cao et al., 2015).

Additionally, the hypothalamus is a center of the limbic system, which is extensively connected to other limbic centers, including the limbic lobe of the neocortex, hippocampus, amygdala, and ventral striatum. This suggests that the hypothalamocerebellar circuit may play a role in regulating psychic functions related to mood, emotions, feelings, and instinctive behaviors (Ho et al., 2004; Schutter and van Honk, 2005; Schmahmann et al., 2007; Tavano et al., 2007; Hoppenbrouwers et al., 2008; Moreno-Lopez et al., 2015; Carta et al., 2019). These functions, influenced by the hypothalamocerebellar circuit, would complement those exerted through the limbic channel of the cerebrocerebellar circuit.

The hypothalamocerebellar fibers connect the hypothalamus with all lobes of the cerebellum. This means they inevitably terminate in regions of the cerebellum that also receive other types of inputs, i.e., vestibular afferents (vestibulocerebellum), general proprioceptive afferents (spinocerebellum), and cerebrocerebellar afferents (cerebrocerebellum). The overlap of these different types of afferents in the same regions of the cerebellar cortex enhances the interaction among the somatic, psychic, and visceral functions regulated by the cerebellum. The integration of the vestibular sensory, played by the vestibulocerebellum, and that of the general proprioceptive sensory, played by the spinocerebellum, would be influenced by visceral sensory information from the hypothalamus, which reach the vestibulocerebellum and the spinocerebellum. In turn, both the vestibulocerebellum and spinocerebellum send back to the hypothalamus signals that would influence its visceral motor responses. On the other hand, the regulatory function of the neocortex, played by the cerebrocerebellum through the cerebrocerebellar circuit, would be influenced by visceral sensory information, leading to complex interactions between the somatic, psychic, and autonomic system.

Finally, the basilar pontine nuclei and some neuronal groups within the reticular formation, which are intercalated in the descending limb of the indirect hypothalamocerebellar pathway and the cerebrocerebellar circuits, could serve as further points of contact between the two main regulatory circuits within the central nervous system.

4. CONCLUSION

The cerebellum can be regarded as a central component of the somatic, psychic, and autonomic systems. It plays a significant role in regulating various areas of the neocortex, through the cerebrocerebellar circuit, as well as different hypothalamic nuclei, through the hypothalamocerebellar circuit.

These new perspectives on the cerebellum functions may help explain the development of visceral disorders, mood disorders, and behavioral disturbances, commonly observed in patients with cerebellar diseases, alongside the symptoms commonly associated with these conditions.

Unfortunately, these insights have not yet gained widespread recognition in clinical settings, where the cerebellum is often viewed solely in terms of its motor functions. It is crucial that further experimental, behavioral, and clinical studies support these new perspectives so that they can be effectively integrated into clinical practice.

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