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## REVIEW ARTICLE

**Natalia Melka et al., Cerebellum and its role**

**The cerebellum: the ‘little’ brain and its big role**

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### **ABSTRACT**

Reports from recent years provide compelling evidence about the structure and the existence of functional topography in the cerebellum. However, most of them focused on the motor functions of the cerebellum. Recent studies suggest the involvement of the posterior lobe of the cerebellum in the context of neurodegenerative and cognitive disorders. The pathophysiology of these diseases is not sufficiently understood, and recent studies indicate that it could also affect additional subregions of the cerebellum. Anatomical and clinical studies, combined with neuroimaging, provide new ways of thinking about the organization and functioning of the cerebellum. This review summarizes knowledge about the topography and functions of the cerebellum, and focuses on its anatomical and functional contributions to the development of neurological diseases.

**Keywords: cerebellum, anatomical organization, limbic system**

## **INTRODUCTION**

One of the first reports linking the cerebellum to cognitive functions was the work of Vincenzo Malacarne in a book entirely devoted to the cerebellum [64], in which the author correlated an individual's intelligence level with the number and degree of development of cerebellar lamellae. Since then, more and more research has focused on non-motor functions, including cognitive and emotional processes; however, interpretation and reference to the results were hindered by a strongly entrenched view regarding the purely motor role of the cerebellum. A breakthrough occurred after 1997 when patients with damage to the posterior lobe of the cerebellum were observed to have a series of emotional-cognitive symptoms that went beyond the realm of motor dysfunction previously attributed to the cerebellum. Since then, interest in the topic has been rapidly increasing. The results obtained also help in understanding why the cerebellum, accounting for only 10% of the total brain volume, has over 50% of the total number of neurons in the central nervous system [49, 103, 109]. Currently, we know that the cerebellum occupies an important place in the neural circuits underlying cognitive processes, and its numerous connections with the limbic system indicate a strong involvement in emotions [1, 11, 92]. This hypothesis is confirmed by clinical observations conducted in individuals with cerebellar hemisphere injuries, where a characteristic cognitive-emotional syndrome has been identified based on the clinical symptoms observed, also known as Schmahmann syndrome [92]. Concurrent research has shown strong connections between non-motor areas of the cerebral cortex and the cerebellum [16], demonstrating that over half of the cerebellum may be associated with non-motor functions, and the efferent and afferent connections with the limbic system and cerebral cortex are the basis for explaining the cerebellum's involvement in emotional processes and its contribution to motivation [11]. Considering the complex function of the cerebellum, we should treat this structure as a collection of more or less independent centers, distinguishing within it, for example, motor centers if they are connected to the motor system or the limbic one if the connections of these areas of the cerebellum are related to the limbic system. In this approach, within the cerebellum, we can distinguish characteristic regions responsible for processing motor and non-motor information, including those related to emotions. The latter are often called the limbic cerebellum, emphasizing its role in higher-order behavioral functions.

### **Cerebellar anatomy**

Over the years, several proposals for dividing the cerebellum have emerged. The most anatomical division of this structure is based on the existence of two classic fissures present in all organisms possessing this structure. It includes the anterior lobe, separated from the posterior lobe by the primary fissure, and the cerebellar vermis, separated from the posterior lobe by the posterolateral fissure. The second most popular division is based on functional zones localized parallel to the midline, including the vermis zone located medially, the intermediate or paravermal zone, and the lateral (hemispherical) zone located laterally. Additionally, within the cerebellar vermis, 10 lobules have been identified, which can be grouped into transverse zones [4, 5, 73]. A unique combination of Purkinje cell phenotypes characterizes each transverse zone, and different zones have distinct developmental timelines. A simple explanation for the evolutionary development of cerebellar lobules is that it was a way to increase surface area and thus adapt to the increased number of cells, which in turn facilitated the acquisition of more complex functional circuits [73, 113].

Considering the phylogenetic development of the cerebellum, we distinguish three characteristic parts within this structure: archicerebellum, paleocerebellum, and neocerebellum. The phylogenetic division of the cerebellum largely corresponds to the traditional functional division of this structure. The oldest part of the cerebellum, the cerebellar vermis, is connected to the vestibular system and the reticular formation of the brainstem. This system participates in the control of balance, posture, and eye movements. The slightly younger paleocerebellum, also called the spinocerebellum, includes the anterior lobe, the vermis, and the paravermis. Until recently, this part was considered the main region responsible for controlling postural movements of the body; however, modern research has shown that the vermis has many connections with subcortical areas of the brain directly involved in motivation and emotions, and the term “limbic cerebellum” emphasizes these connections. The posterior lobes, considered the youngest evolutionary structures, include the third and last system and are called the neocerebellum.

### **Methods of cerebellar segmentation**

Due to the complex division of the cerebellum, which is also subject to classification changes, manual division and description of the cerebellum is an extremely time-consuming process. To shorten this time, various semi-automatic or automatic methods supporting researchers in describing and identifying individual cerebellar lobules have been developed. One of the first

semi-automatic algorithms is the spatially unbiased infra-tentorial template (SUIT) [32]. However, this method does not allow for the detection of anatomical differences. More recent and accurate methods are fully automatic, such as the Automatic Classification of Cerebellar Lobules Algorithm using Implicit Multi-boundary evolution (ACCLAIM) [14], the method based on multi-atlas segmentation called MAGeT Brain (Multiple Automatically Generated Templates of different Brains) [18], and the Rapid Automatic Segmentation of the human Cerebellum And its Lobules (RASCAL) [112], or the innovative method of cerebellar lobule segmentation called CERES (CEREbellum Segmentation) [84, 85]. Undoubtedly, the implementation of a technique that allows for automatic segmentation in a maximally shortened time offers tremendous potential for working with a large number of patients and helps better understand the anatomy of the cerebellum and the consequences of its disorders.

**Table 1.** Comparison of current cerebellar divisions with a division into lobules

<b>Lobes (based on fissures)</b>	<b>Lobes (based on folia)</b>	<b>Transverse zone</b>
<b>Anterior</b> (Paleocerebellum)	<b>I</b> <b>II</b> <b>III</b> <b>IV</b> <b>V</b>	<b>AZ</b> (anterior zone)
<b>Posterior</b> (Neocerebellum)	<b>VI</b> <b>VII</b>	<b>CZ</b> (central zone)
	<b>VIII</b> <b>IX</b>	<b>PZ</b> (posteriori zone)
<b>Flocculonodular</b> (Archicerebellum)	<b>X</b>	<b>NZ</b> (nodular zone)

### **Cellular structure**

The cerebellum consists of an outer gray matter area, an inner white matter area, and three pairs of deep cerebellar nuclei [27]. The cerebellar cortex has three layers [103]. The outermost layer is the molecular layer containing inhibitory interneurons, the intermediate layer contains Purkinje cells, and the innermost layer is the granular cell layer. Purkinje cells are a unique type of neuron with a specific structure. Due to their massive and highly branched dendritic tree, they can integrate large amounts of information and learn through dendritic remodeling. The Purkinje cell layer integrates excitatory signals from the granular layer with inhibitory information from the molecular layer. Purkinje cells are the only cells that project out of the cerebellum and are essential for motor coordination [7], as well as for other important cognitive functions such as emotions. The ability to characterize each type of cerebellar neuron is crucial for understanding cerebellar pathology [103]. Various cerebellar defects, including developmental dysfunctions, can manifest as motor disorders and be associated with non-motor states such as depression and cognitive deficits [30, 41, 99].

Changes in cerebellar volume and molecular alterations in Purkinje cells have been noted in patients with affective disorders, depression, as well as neurotic traits [1, 68, 93]. Purkinje cell involvement in disorders such as autism is also indicated. Postmortem studies in patients with autism spectrum disorders have shown loss of cerebellar Purkinje cells [105], and it is also suggested that dysregulated GABA production in Purkinje cells may contribute to the clinical features of autism [117]. The availability of cell-specific markers is essential for understanding the role of each type of neuron in the cerebellum. Numerous molecular markers, such as the calcium-binding protein calbindin D28K (CB), can be used for labeling and quantitatively assessing Purkinje cells. Purkinje cells are the only cerebellar cells that express CB. Staining of the cerebellum for calbindin expression reveals regular transverse divisions, with distinct transition regions that divide the vermis into the aforementioned four transverse zones [7]. It is also important to note that CB in Purkinje cells plays a significant role in coordinating motor behaviors [7]. Studies indicate that the selective genetic deletion of calbindin from cerebellar Purkinje cells results in a new mouse phenotype with marked deficits in the precision of motor coordination and the processing of visual information important for coordination.

## **Where do emotions reside in the cerebellum?**

### **Anatomical evidence**

It has long been known that the cerebellum has direct connections with motor centers. However, contemporary research has also shown bidirectional connections of the cerebellum with brain regions involved in emotion regulation. Understanding the physiological significance of these connections has a fundamental impact on explaining the role of the cerebellum in higher cognitive functions [79], as it explains the mechanisms through which these areas mutually influence each other [12, 53, 78]. Extensive connections have also been identified and described between the cerebellum and prefrontal cortical and posterior parietal regions [80, 111]. The posterior lobe, known as the limbic cerebellum, plays a crucial role in these loops, as it has connections with the prefrontal, temporal, cingulate, and posterior parietal cortices. Additionally, connections with the brainstem have been demonstrated, which through neurotransmitters such as norepinephrine, serotonin, and dopamine, influence mood regulation in humans [38, 57, 88].

### **The cerebello-amygdala circuit — a missing link?**

In light of current research findings, the cerebellum is described as an essential structure for affective, cognitive, and memory processing. Functional connections between the cerebellum and the amygdala, a key structure in the limbic system responsible for emotional processes, were identified over four decades ago [48]. Recent anatomical evidence has ruled out the existence of a monosynaptic connection between these structures [53]. Using transneuronal tracing techniques, researchers described a new polysynaptic network of connections between the deep cerebellar nuclei and the basolateral part of the amygdala, passing through the thalamus [53]. Additionally, the latest reports indicate that there is a functional connectivity between the cerebellum and the amygdala which is correlated with anxiety [120]. This discovery marks the beginning of a path towards new knowledge regarding the role of the cerebellum in influencing the emotion-controlling structure in humans.

### **“HippoBellum”**

Years of research yielding convergent results report on the role of the cerebellum in spatial cognition. There is evidence of anatomical and functional connections between the cerebellum and the hippocampus [86, 118]. Evidence of communication between these structures provides the opportunity to delineate new therapeutic pathways for pathologies related to the hippocampus. The therapeutic potential in an increasing number of diverse neuropsychiatric and neurological diseases is provided by experimental cerebellar neurostimulation [67]. Studies report on the potential use of the cerebellum in treating temporal lobe epilepsy [100]. There is growing interest in the clinical aspect of the cerebellum due to its involvement in cognitive functions, including episodic memory. The role of the cerebellum in cognitive deficits is also indicated [52]. Influencing the hippocampus through cerebellar stimulation opens up possibilities in the therapy of hippocampal-dependent memory disorders occurring in neurodegenerative diseases such as Alzheimer's.

**Not only motor support — important collaboration between basal ganglia and cerebellum**



Just like the cerebellum, the basal ganglia were until recently overlooked in the context of emotional functions [75]. Their connections with the cerebellum were not considered at all, and it was thought that these structures modulate cortical activity independently of each other, through separate pathways passing through the thalamus. Similar to the cerebellum, the basal ganglia were attributed only a motor function. Recent reports describe the involvement of these structures not only in motor but also in cognitive functions. Today, it is known that there are direct connections between the cerebellum and the basal ganglia, meaning that they jointly shape and adapt both motor and emotional functions [25, 46, 55, 76, 115]. Their functions are not separate but overlap. The cerebellum precisely adjusts the response to improve the final outcome according to the current physiological state [75]. Such a mechanism of cooperation, consistent with the context of a given situation, allows for the generation of a proportional and situationally appropriate response. Understanding the importance of this collaboration between the cerebellum and basal ganglia is important from the perspective of neurodegenerative diseases associated with aging and the decline in both motor and cognitive functions. References in the literature regarding brain aging have so far mainly referred to the cerebral cortex. Establishing the role of connections between structures that play a crucial role in motor behaviors and affect higher-order mental functions [46, 97, 98], as well as the connections of these structures with motor, prefrontal, and associative cortex [44, 46, 80, 110], is important for a better understanding of the pathomechanisms of diseases such as Parkinson's disease [82, 121], or Huntington's disease [39, 87]. In the case of these diseases, both structural and functional changes in the cerebellum have been noted.

### **Functional neuroimaging studies — what about the cerebellum and its topography?**

The lack of direct monosynaptic connections between the cerebral cortex and the cerebellum poses a significant challenge in studying the organization of the brain-cerebellar network [101]. Centripetal connections pass through the pons, and centrifugal connections lead from the deep cerebellar nuclei through the thalamus [91]. Brain-cerebellar connections cannot be studied using monosynaptic retrograde tracing. A breakthrough was the use of polysynaptic tracing in nonhuman primates, which revealed the fundamental nature of brain-cerebellar connections [54]. The authors described separate brain-cerebellar connections for motor and non-motor functions.

We now know that the spatial organization of motor and nonmotor function representations within the cerebellum is based on polysynaptic connections between the cerebellum and other brain areas. Radiological studies based on functional magnetic resonance imaging (fMRI) techniques indicate the existence of a functional division of the cerebellum. MRI provides a comprehensive view of brain structures, including the entire brain, and importantly, its sensitivity and specificity allow for the study of polysynaptic connections, making them the basis of today's cerebellar functional research. fMRI studies in healthy individuals indicate cerebellar activation during a wide range of activities, from simple motor tasks to higher-order cognitive tasks. Patterns of this activation vary for sensorimotor, affective, and cognitive tasks. These findings are confirmed by electrophysiological experiments and pathway analysis in animal models [54]. Understanding the functional topography is crucial for understanding and interpreting clinical data in the case of cerebellar diseases or injuries. This allows for an understanding of the role of the cerebellum in both motor and higher-order mental functions [97].

Available research findings in healthy individuals indicate that half of the cerebellar cortex is involved in cognitive processes. Non-motor functions have their representation in the posterior lobe of the cerebellum, which includes lobules VI–IX. There is evidence of functionally diverse regions within each lobule, which are associated with distinct functional networks, in various ways supporting affective or cognitive processing [94]. A hypothesis has been put forward about the involvement of the posterior lobe of the cerebellum in intrinsic connectivity networks involved in higher-order mental functions [44]. According to the results of these studies, the neocerebellum participates in 1) executive control networks, 2) the salience network, and 3) the default-mode network [44]. Imaging studies also describe the existence of a functional network between lobules VIIB, VIII, and IX of the cerebellum and the amygdala [13, 43, 58, 89, 97]. Activation of the neocerebellum in healthy adults depends on the nature of the task being performed [97]: emotional processing activated lobules VI, VIIA, and Crus I, executive functions activated VI, VII Crus I, and Crus II, and working memory was associated with the activation of lobules CI, VII, and VIIIA. Social cognitive tasks activated lobules IX and crus I [108]. Interestingly, in the case of motor tasks that required action planning, lobules VI and VII were sometimes activated in addition to anterior lobe activation [90].

### **The cerebellum and depression**

A better and more precise understanding of the cerebellum's involvement in non-motor functions develops our knowledge of the neurobiology of emotions. Cerebellar damage has caused patients to experience impairments in higher mental and executive functions [101], as well as emotional disorders [1]. Conversely, any cerebellar dysfunction is directly associated with emotional impairment, as observed in anxiety [70], post-traumatic stress disorder [69], schizophrenia [20, 36, 71], autism [64], as well as with emotional and cognitive disorders collectively referred to as cerebellar cognitive-affective syndrome [50, 59, 92]. Increasingly, data indicate the involvement of the cerebellum in depression [6, 13, 24]. Many clinical studies point to the coexistence of depression with cerebellar diseases [23, 24, 62].

### **Cerebellar structural and functional abnormalities in depression**

Depression is defined as “cortico-limbic dysregulation”: a disruption of connections between the dorsal cognitive control system and the ventral emotional system [66]. Altered responses have also been noted in the cerebellum [37]. Studies in patients with depression indicate abnormal cerebellar-brain couplings in affective-limbic and cognitive networks. Cerebellar areas including Crus I, Crus II, and lobule VIIa showed significantly decreased connectivity with the ventromedial prefrontal cortex [2, 62], as well as with the dorsolateral prefrontal cortex [2, 62], areas implicated in cognitive functions. A strong correlation between connections and symptom severity indicates the significant role of the cerebellum in both affective and cognitive dysfunction in depression. Habas [44] points to the involvement of the cerebellum in two major neuronal networks involved in depression: the salience network and the default mode network. He also suggests a modulating role of lobules VI in the salience network. In support of the affective role of the cerebellum, the network connecting the amygdala and neocerebellum is mentioned here as well. Abnormalities in posterior cerebellar activity, such as significantly reduced cerebello-cerebral functional connectivity, have been observed in patients with severe depressive disorders [2, 42, 62]. Structural studies of non-motor cerebellar areas in patients with depression [13, 28, 29, 68, 72] have shown significant differences in the volume of these areas compared to the volume in patients in remission and healthy individuals. Cerebellar volume was strongly associated with the severity and duration of the disease. The relationship between the volume of lobules VI and symptom severity is particularly emphasized [13]. Interestingly, in cerebellar areas involved in higher mental functions, increased blood flow has been noted in cases of depressive disorders [31].

## **What about stress?**

Stress and depression may rely on similar mechanisms of neuronal plasticity disruption. Stress leads to physical and behavioral impairment, and stress-related diseases and mental disorders can be disabling and life-threatening. The consequences of stress include not only cardiovascular, autoimmune, or metabolic diseases but also anxiety disorders, mood disorders, depression, or post-traumatic stress disorder. The contribution of the cerebellum to higher mental functions is no longer subject to debate; it is known to have connections with brain structures also associated with stress. Studies indicate changes in the cerebellum, both morphological and functional, due to stress. Individuals who experienced events such as maltreatment and sexual abuse in childhood showed volumetric changes in the cerebellum [3, 61, 109, 116]. Here, as in the case of depression, studies have shown increased blood flow [3]. In individuals who developed obsessive-compulsive disorder as a result of stressful events, significant differences were observed in the cerebellum, with an increase in volume compared to a control group of healthy individuals. [15, 81]. Patients with post-traumatic stress disorder showed reduced volume of the posterior cerebellar lobe [8, 17, 21, 102]. Neuroimaging studies conducted on individuals who experienced episodes of major depression showed reduced functional connectivity [33, 35, 60, 74, 106]. In individuals with post-traumatic stress disorder, numerous reports describe reduced functional connectivity of the posterior cerebellar lobe [19, 22, 34, 45, 47, 51, 70]. Interestingly, in individuals who experienced chronic work-related stress leading to burnout, changes in functional connectivity between the cerebellum and the amygdala were observed [40].

## **The cerebellum and neurodegenerative diseases**

In addition to its involvement in many physiological brain functions, the cerebellum is also implicated in pathological processes, including disorders of higher nervous functions. A detailed delineation of the cerebellum's functions as a whole, as well as further divisions, can be used to better understand its structural changes and to diagnose and monitor the development of many diseases. For example, patients with Alzheimer's disease showed decreased volumes of posterior cerebellar lobes [95, 104]. Differences were also noted in patients with multiple sclerosis [56], Huntington's disease [83, 87], and Parkinson's disease [10, 114]. However, many publications provide ambiguous results regarding the role of the cerebellum in various neurodegenerative disorders regarding cognitive functions. This can be

explained by the fact that accurate segmentation of the cerebellum is quite difficult due to its complex structure [85].

### **At the end — chemical messengers**

The cerebellum plays a significant role in both motor and non-motor functions through a complex interaction of neurotransmitters. Dopamine, serotonin, norepinephrine, and acetylcholine act as neuromodulators influencing cerebellar functions such as motor coordination, cognition, and emotion. Studies indicate that serotonin levels in the cerebellum affect mood regulation, memory, and learning [107]. Dopaminergic projections to the cerebellum are involved in decision-making and reward-based learning [26]. Dopamine receptors located in the cerebellum influence cognitive flexibility and executive functions, with receptor-level changes affecting social behaviors [26]. Norepinephrine impacts focus and the effective processing of sensory information, influencing the cerebellum's role in cognitive functions under stress, emotion regulation, and decision-making [9, 96]. Similarly, acetylcholine affects cerebellar functions related to learning and attention maintenance. Cholinergic signals in the cerebellum influence the accuracy and efficiency of cognitive tasks requiring sustained attention and play a role in encoding new information and memory consolidation processes [119]. Dysregulation of these chemical messengers has been implicated in various neurological and psychiatric disorders, including depression and stress-related conditions. Understanding the roles of these chemical messengers in cerebellar function and dysfunction is critical for developing targeted therapeutic interventions for such disorders.

### **CONCLUSIONS**

The cerebellum, previously considered solely a motor structure, plays a key role in non-motor functions such as cognitive and emotional processes. Since the cerebellum has extensive connections with the cerebral cortex, limbic system, and basal ganglia, it can directly influence emotions, motivation, and cognitive functions. Neuroimaging studies provide evidence of the functional organization of the cerebellum. Activation of the cerebellum has been observed during both simple motor tasks and complex cognitive tasks. Today, it is known that the symptoms of many neurological diseases have unique associations with

different areas of the cerebellum. The posterior lobe of the cerebellum is particularly significant in the context of cognitive and neurodegenerative disorders. Damage to the cerebellum can lead to emotional and cognitive disturbances, such as Schmahmann's syndrome. Changes in the volume and functionality of the cerebellum are observed in cases of depression, autism, PTSD, and other mental disorders. Neurotransmitters also play an important role in regulating cerebellar functions, affecting cognitive processes, motor coordination, and emotional regulation. Better understanding the role of the cerebellum in non-motor functions opens new therapeutic possibilities, especially in treating neurodegenerative diseases, emotional disorders, and cognitive impairments.

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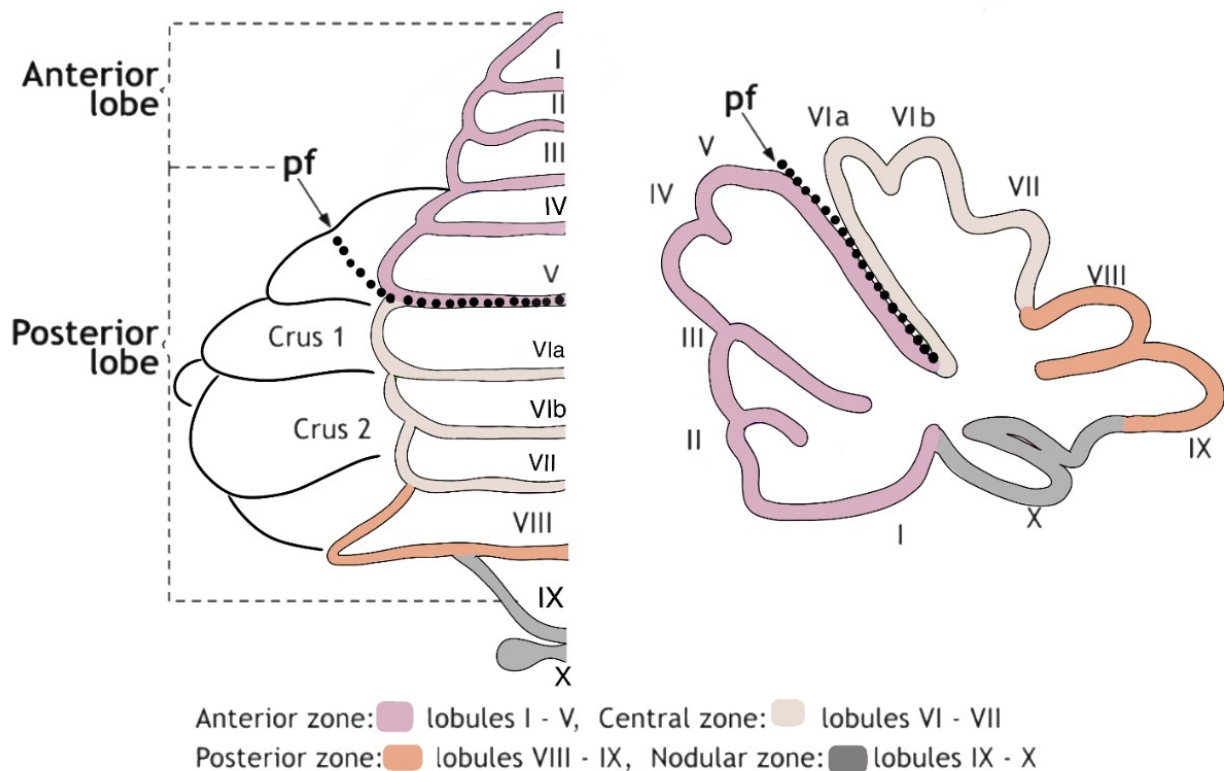
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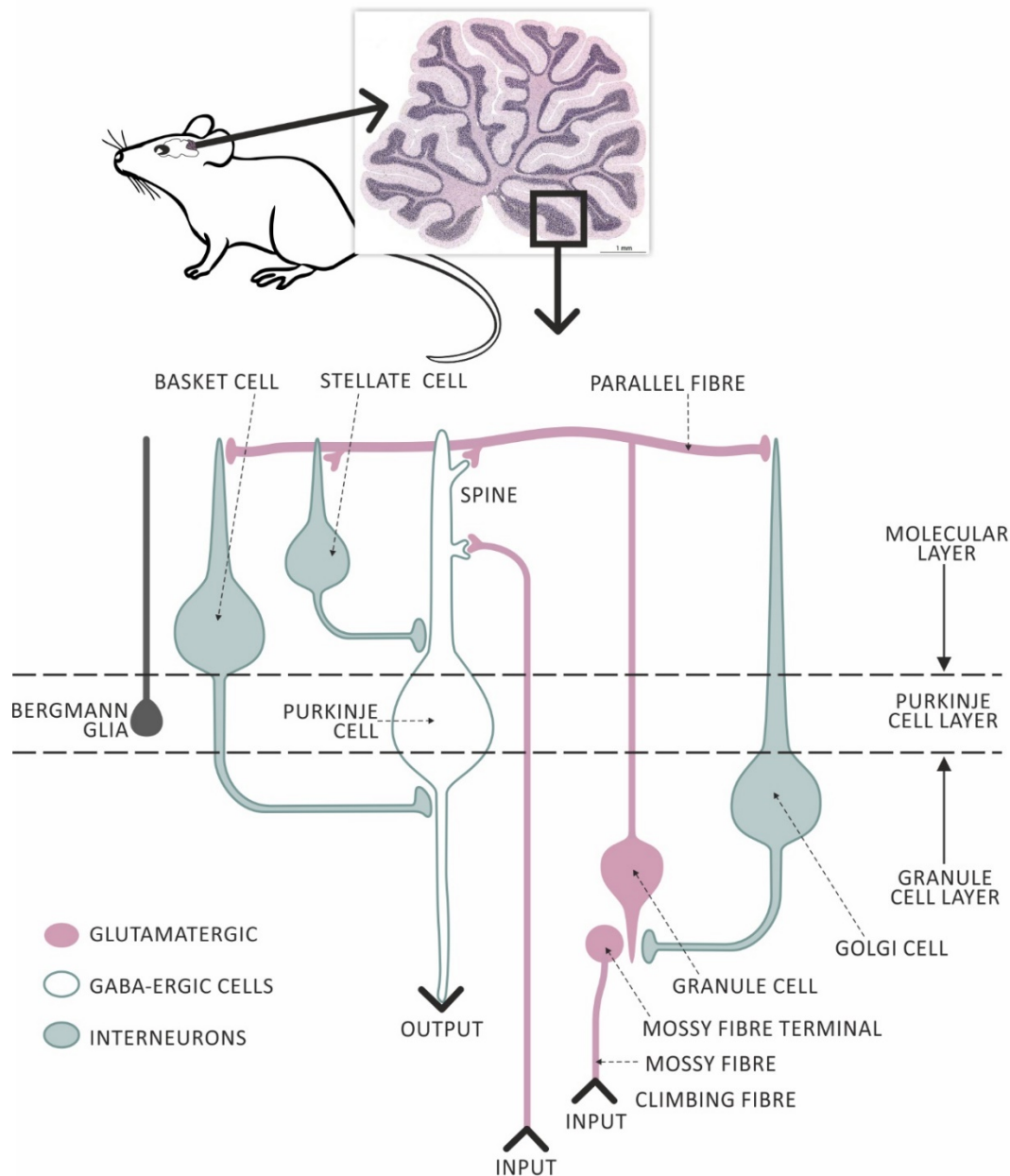
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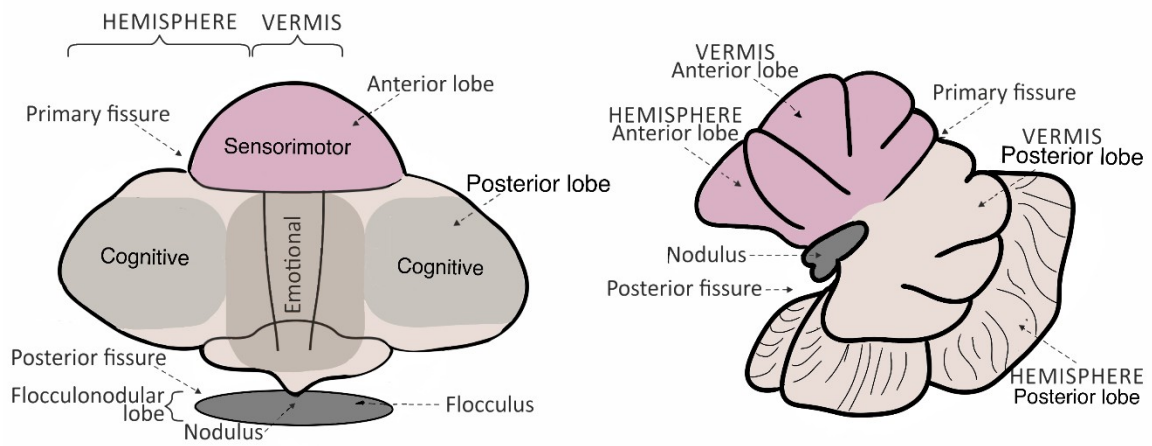
**Figure 1.** Depending on the chosen division, the surface of the cerebellum can be divided into lobes (based on constant fissures) or based on zones parallel to the median line. The latter



division is more functional than anatomical. Considering the phylogenetic aspects due to the time of origin, we can distinguish three characteristic parts within the cerebellum, also reflecting the functional division of this structure. The division of the cerebellum based on the midline includes the vermis, paravermis, and hemispheres. The division of the vermis includes 10 lobules, which combine into functional transverse zones: anterior (AZ), central (CZ), posterior (PZ), and nodular zone (NZ). The anterior zone forms the anterior lobe (AL). The central and posterior zones form the posterior lobe (PL). The nodular zone forms the flocculonodular lobes. The division between the anterior and posterior lobes is demarcated by the primary fissure (pf). The phylogenetic division of the cerebellum includes: Archicerebellum (nodule — X), Paleocerebellum (anterior lobe — I–V), and Neocerebellum (posterior lobe — VI–IX).



**Figure 2.** Cytoarchitecture and neuronal circuitry of the mouse cerebellar cortex: Purkinje cells make synaptic connections with granule cells. Purkinje cells transfer the signals from granule cells and other interneurons and send the final output to the deep cerebellar nuclei. Climbing fibers and mossy fibers are the main afferents from outside the cerebellum [77].



**Figure 3.** The image depicts a macroscopic diagram of the cerebellum and indicates the regions and type of function with which they are mainly associated.