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Unravelling the cerebellum's role in sleep regulation: Prospects for precision sleep medicine

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ABSTRACT

The cerebellum, traditionally associated with motor coordination, is increasingly recognized as a regulator of non-motor functions—including cognition and emotions. However, its involvement in sleep regulation has been comparatively overlooked, mainly due to the historical exclusion of the cerebellum from electrophysiological and neuroimaging sleep research. Growing evidence now identifies the cerebellum as an active component of sleep mechanisms in both physiological and clinical contexts. Supporting findings include: (1) extensive cerebellar connectivity with major sleep-regulatory circuits; (2) state-dependent cerebellar neuronal activity synchronized with neocortical oscillations during NREM and REM sleep; (3) alterations in sleep patterns following cerebellar electrical stimulation; (4) differential expression of sleep-related genes in the cerebellum; (5) intrinsic cerebellar circadian rhythmicity; (6) structural and functional cerebellar changes in primary sleep disorders; and (7) high prevalence of sleep disturbances in cerebellar pathologies. Collectively, these data suggest that the cerebellum is deeply engaged in key sleep mechanisms, including the generation and modulation of sleep-related brain rhythms—such as sleep spindles—, sleep-dependent memory consolidation, and likely compensatory processes in sleep disruption. Nevertheless, fundamental mechanistic questions remain unresolved, particularly whether the cerebellum performs predictive modeling during sleep to support offline cognitive processing. Elucidating these computational functions and harnessing cerebellar neuroplasticity may advance our understanding of the intricate links between sleep, cognition, and emotion, while inspiring next-generation therapeutic approaches in sleep medicine.

1. Introduction

1.1. Neglect of the cerebellum in sleep research

The cerebellum has long been recognized as the primary neural hub for ensuring movement accuracy, continuously integrating motor intentions (via efference copies) with sensory feedback through predictive modeling and error-driven plasticity [1,2]. However, over the past four decades, extensive clinical, imaging, and electrophysiological evidence has prompted a dramatic paradigm shift in our understanding of this structure [3]. While its role as a motor comparator remains undisputed, converging evidence now underscores its critical involvement in non-motor domains—particularly in regulating cognition [4], emotions [5], and even vegetative functions such as thirst [6] and sleep-wake cycles [7,8].

However, among sleep researchers, the cerebellum has long been overlooked. In fact, the first electrophysiological recordings from the cerebellum of sleeping animals [9] emerged over 32 years after the earliest electrophysiological observations of sleep in animals [10] and 17 years following the discovery of REM sleep [11]. Moreover, bibliometric analyses of PubMed-indexed documents have previously highlighted the notably low co-occurrence of the MeSH terms “sleep” and “cerebellum” compared to other brain regions such as the hippocampus, cerebral cortex, hypothalamus, and brainstem (Fig. 1A). However, emerging research over the past decade indicates a growing interest in exploring the cerebellum's potential role in sleep physiology (Fig. 1B).

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Emerging evidence in conjunction with seminal studies supports the cerebellum's role in sleep regulation through seven key points: (i) the cerebellum is interconnected with sleep-regulating brain regions; (ii) the cerebellar neuronal activity and blood flow vary across sleep states and align with neocortical rhythms; (iii) the cerebellar stimulation induce changes in sleep patterns; (iv) some sleep-related genes are differentially expressed in the cerebellum, influencing sleep duration, chronotype and disorders; (v) the cerebellum acts as a secondary circadian clock with rhythmic gene expression influenced by the suprachiasmatic nucleus; (vi) the cerebellum undergoes structural and functional changes in common sleep disorders unrelated to cerebellar disease; and (vii) cerebellar diseases are often linked to a wide range of sleep disorders.

1.2. Aims and scope of this review

Although previous review articles have appropriately examined the existing evidence supporting the cerebellum's role in sleep regulation [7, 8], this remains an active and rapidly evolving area of research. In the present paper, we aim to revise and update current knowledge by providing a detailed analysis of each of the seven key aspects of cerebellar involvement in sleep outlined above. Additionally, we highlight how this evidence advances our understanding of cerebellar mechanisms and their impact on sleep-related cognitive functions, brain resilience in the context of sleep disorders, and potential therapeutic strategies involving cerebellar modulation.

2. Evidence for cerebellar involvement in sleep regulation

2.1. Cerebellar interconnectedness with sleep-regulation circuits

The cerebellum exhibits widespread connectivity, interacting with diverse cortical and subcortical structures [12]. Particularly, this includes neural circuits controlling sleep-wake cycles (Fig. 2) [13]. Studies in cats have shown that the cerebellum receives strong serotonergic input from the raphe nuclei, particularly targeting lobules VIIA, X, and Crus I, whereas lobule VI and the deep cerebellar nuclei (DCN) receive comparatively weaker projections [14,15]. Stimulation of cerebellar fastigial nuclei alters raphe neuronal firing in cats [16] and rats [17],

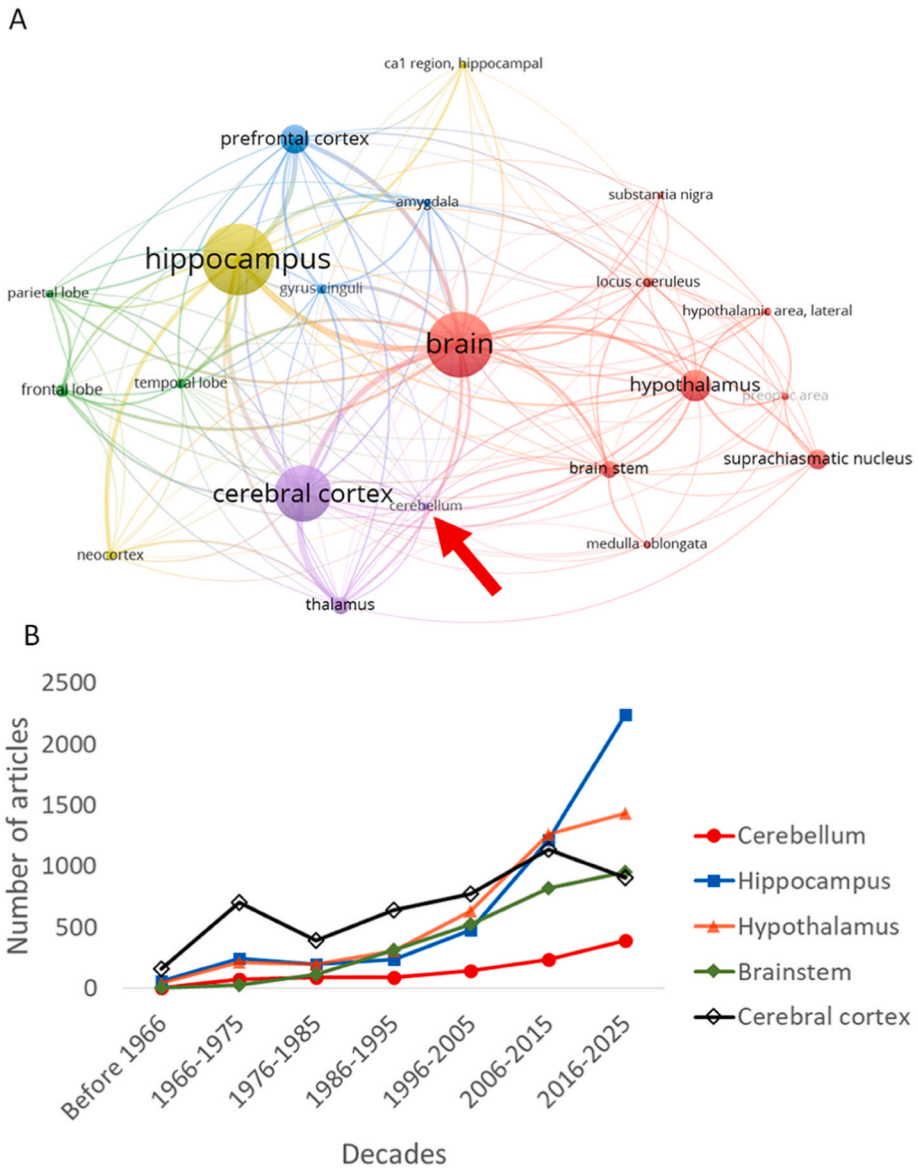

Fig. 1. Bibliometric analysis. A) Comparative Co-occurrence analysis of MeSH terms highlighting the low association between 'sleep' and 'cerebellum' relative to other brain regions in PubMed-Indexed literature. B) Gradual increase in MeSH term Co-occurrence of 'sleep' and 'cerebellum' and other brain regions over time. *Data retrieved on April 21, 2025.*

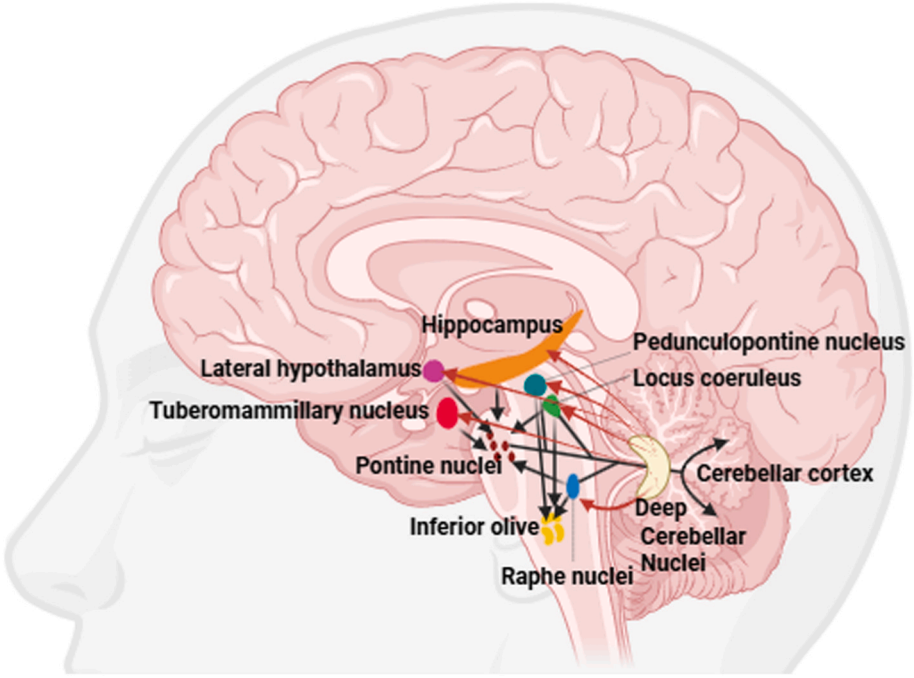

Fig. 2. Key Cerebellar Connections With Sleep-Wake Control Centers. *Not all monosynaptic projections as outlined may be true monosynaptic projections. Although most of the anatomical evidence of cerebellar connectivity with other sleep centers comes from animal models, primarily cats, we extrapolate these findings to the human brain due to the high interspecies homology of the anatomical substrates underlying sleep. Created with BioRender.com.*

highlighting reciprocal interactions in sleep-wake modulation.

The cerebellum also receives noradrenergic input from the *locus coeruleus* (LC) in cats [18] and rats [19]. In the latter models, these inputs modulate, rather than directly convey, information by enhancing climbing fiber activity on Purkinje cell. Reciprocal connections from cerebellum to LC have also been reported [18,20]. Behavioral studies in mice during the dark phase reveal that the noradrenergic LC-cerebellum pathway contributes to fear memory formation [21]. Persistent activity of this pathway during sleep might further suggest cerebellar involvement in sleep-mediated fear memory consolidation.

The pedunculopontine nucleus (PPN) also has reciprocal connections with the cerebellum; PPN stimulation activates neurons in the fastigial, interpositus, and dentate nuclei of the cerebellum in rats [22], while DCN project to the PPN in squirrel monkeys [23]. Additionally, both histaminergic inputs from the tuberomammillary nucleus [24] and orexinergic (hypocretin-1) projections from the hypothalamus [25] to the cerebellum have been documented in cats.

A growing body of evidence demonstrates that the cerebellum is anatomically and physiologically interconnected with the hippocampus, a relationship termed hypobellum [26–28]. These bidirectional interactions underscore the cerebellum's expanding role in non-motor functions, particularly cognition and sleep-related processes. In fact, the cerebellum and hippocampus exhibit coordinated activity patterns across sleep stages [29], as will be detailed in subsequent sections.

It is important to note that most neuroanatomical evidence regarding the cerebellum's interconnectedness with other sleep-regulating centers comes from animal studies but the principal neuronal circuits and transitions between sleep states are homologous between cats, rodents, and humans, supporting the translational value of animal sleep research for understanding human physiology [30].

2.2. Sleep-related cerebellar activity

Neuroimaging and electrophysiological studies have consistently demonstrated that cerebellar neuronal activity is dynamically modulated across sleep-wake states, exhibiting precise synchronization with neocortical oscillations and activity and subcortical structures such as the hippocampus (Fig. 3). These evidences has significantly advanced our understanding of sleep neurobiology and have highlighted the technological potential of cerebellar EEG in automated sleep stage classification [31]. The following section presents evidence of sleep-dependent cerebellar activity across both REM and NREM sleep stages.

2.2.1. Sleep-related cerebellar activity during Non-Rapid Eye Movement (NREM) sleep

Non-Rapid Eye Movement (NREM) Sleep is characterized by slower brain waves (theta and delta). It is divided into three stages: N1, N2, and N3, with N3 being the deepest. During NREM sleep, bodily functions such as breathing and heart rate slow down, and it is crucial for physical and mental restoration, including muscle repair and immune system reinforcement [33,34].

Studies employing positron emission tomography (PET) in healthy subjects have consistently shown that cerebellar activity is significantly reduced during NREM sleep compared to both wakefulness and REM sleep [35,36]. This reduction aligns with the observed decrease in Purkinje cell activity during NREM sleep relative to wakefulness and REM sleep, a pattern evident in both the vermis and cerebellar hemispheres [9,37]. Similarly, reduced activity of mossy and climbing fiber are noticed in NREM sleep [38].

However, functional Magnetic Resonance Imaging (fMRI) studies have revealed cerebellar activations during N2 and N3 stages, which correlate with electroencephalographic (EEG) signatures such as sleep spindles [39], K-complexes [40], and slow waves [41–43]. Simultaneous EEG-fMRI in 73 healthy subjects showed sleep-dependent changes in cerebellar connectivity during NREM sleep. Cerebellar connectivity slightly increased from wakefulness to N2, then sharply declined in N3, with enhanced limbic-cerebellar connectivity during deep sleep correlating with delta power. Neocortico-cerebellar connectivity also showed region-specific changes across NREM stages [44].

An intriguing study explored cerebello-hippocampal synchronization across sleep stages in mice. For NREM sleep, it found significant delta-band synchronization (<4 Hz) between cerebellar lobule VI and hippocampus, influencing cerebellar local field potential (LFP) activity.

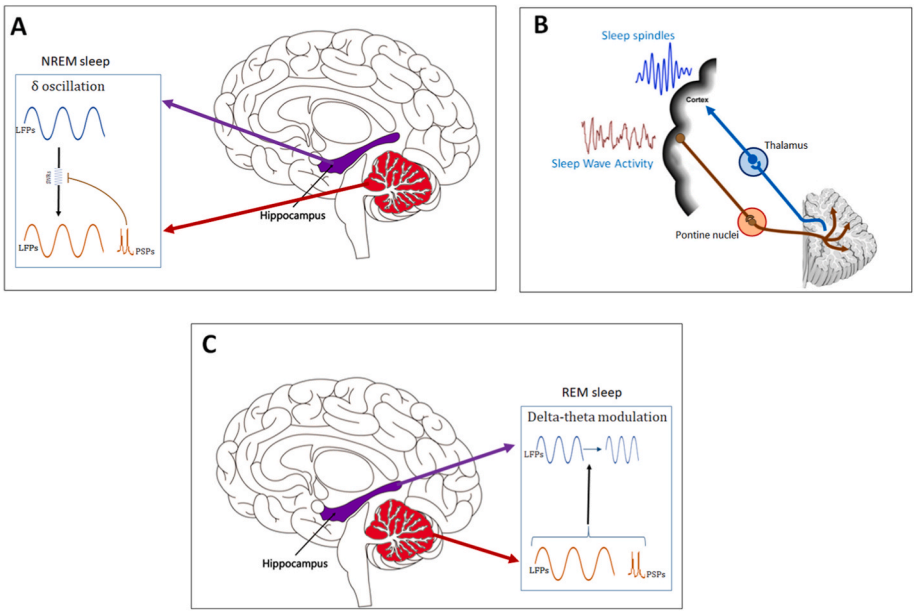

Fig. 3. Sleep-related cerebellar activity. A) Significant delta-band synchronization (<4 Hz) between cerebellar lobule VI and hippocampus during NREM sleep. Hippocampal sharp-wave ripple (SWR) activity induced discrete LFP modulations in cerebellum (Adapted from Torres-Herraez et al., 2022 [29]). B) Proposed pathway of information flow from the cerebellum to the motor cortex via the thalamus during sleep spindles (Adapted from Xu et al., 2021 [32]). C) Hippocampus-cerebellum crosstalk during REM sleep shows widespread delta activity and phasic sharp-wave potentials phase-locked to hippocampal theta rhythms (Adapted from Torres-Herraez et al., 2022 [29]).

Additionally, hippocampal sharp-wave ripple (SWR) activity induced discrete LFP modulations in all recorded cerebellar areas, especially in lobule VI of the dorsal vermis. These modulations were phase-locked to the upstate of cerebellar delta oscillations [29]. Interestingly, the influence of hippocampal SWR activity on the cerebellum mirrors the bidirectional relationship between hippocampal SWRs and neocortical sleep spindles [45–47], suggesting a functional parallel facilitating memory consolidation during sleep by coordinating neural activity across these regions (Fig. 3A).

The cerebellum is crucial in the transition from NREM sleep to wakefulness. Multi-unit recordings in mice show Purkinje cells and cerebellar cortex neurons significantly increase firing just before this transition, while DCN activity decreases. This may seem paradoxical, since DCN inhibition would not directly support wakefulness via the thalamus. However, heightened Purkinje cell activity could specifically inhibit intrinsic DCN inhibitory mechanisms, disinhibiting excitatory thalamic output and potentially contributing to the transition to wakefulness. Notably, this increase in cerebellar cortex cell activity is specific to the NREM-to-wakefulness transition and is not observed during other sleep stage transitions [48].

The following evidence demonstrates the cerebellum's involvement in the generation and/or regulation of the most significant polygraphic elements of NREM sleep: sleep spindles, K-complex and slow waves.

2.2.1.1. Cerebellar involvement in sleep spindles. Sleep spindles are brief bursts of oscillatory brain activity (9–16 Hz) that occur during NREM sleep and are thought to play a dual role in sleep and memory. They help maintaining sleep continuity by filtering out external disturbances, and they contribute to memory consolidation by facilitating synaptic plasticity and strengthening memory traces through interactions between the hippocampus and neocortex [49].

While traditional knowledges attribute sleep spindle generation solely to thalamocortical circuits, recent evidences reveal that the cerebellum plays a surprising role in both the generation and propagation of these oscillations. Particularly, a recent functional connectivity study using both population and single-unit electrophysiological recordings in monkeys uncovered an unexpected pathway of information flow from the cerebellum to the motor cortex via the thalamus during sleep spindles (Fig. 3B) [32]. A subsequent study in mice have noticed too significant directed coherence at spindle frequencies, confirming a causal flow of neural activity from the cerebellum to both the thalamus and motor cortex [50]. These findings suggest that the cerebellum may harbor a previously unrecognized spindle generator, contributing to the generation of these oscillations. Indeed, at least two distinct excitation-inhibition loops within the cerebellum generate reverberating activity at spindle frequencies, resembling the well-characterized thalamocortical circuits responsible for sleep spindle generation. One of these loops consists of a circuit connecting Purkinje cells, DCN, the inferior olive, and back to Purkinje cells, while the second involves interconnected granule cells and Golgi cells [51].

Regarding the functional role of cerebellar spindles, it has been proposed that information flow from the cerebellum to the motor cortex at spindle frequencies may support sleep-dependent memory processes. Specifically, the coupling of cerebellar spindles with neocortical spindles is thought to reflect the offline processing of daytime learning. This process involves the transformation of information stored in cerebellar forward models into refined learned patterns, which are then represented in the neocortex [51]. Indeed, a rat study showed that coherence of LFPs between motor cortex and cerebellum in the spindle band directly correlated with motor task success. This suggests sleep spindles in both regions engage neurons active during waking tasks, supporting motor memory consolidation [52]. In addition, cerebellar sleep spindles have been observed alongside muscle twitches during sleep in mice, potentially reflecting cerebellar-to-cortical communication that contributes to neural plasticity and supports cerebellum-dependent memory processes [50]. Moreover, simultaneous EEG-fMRI recordings during post-training sleep revealed overnight improvements in motor sequence learning performance, associated with spindle-locked reactivation of cerebellar lobule VI within the striato-cerebello-cortical network originally engaged during task acquisition, reflecting the involvement of this sleep-related cerebellar activity in motor learning consolidation [53].

These stronger pieces of evidence supporting the role of the cerebellum in sleep spindle generation were bolstered by two pivotal studies: Firstly, the discharge rate of Purkinje cells trends to increase in

coincidence with cortical spindles in cats [38], while an EEG-fMRI co-registration study, uncover a co-occurrence of sleep spindles and cerebellar activation in healthy young volunteers [39].

2.2.1.2. Cerebellar involvement in K-complexes. K-complexes are distinct EEG patterns observed during NREM sleep that are characterized by a high-amplitude, biphasic wave with an initial sharp upward deflection followed by a slower downward component, lasting about 0.5–1.5 s. These waveforms are thought to play a role in sleep maintenance and sensory processing during sleep [54,55].

To our knowledge, only two human fMRI studies have explored cerebellar activation during K-complexes using simultaneous EEG-fMRI signals, but they have yielded contradictory findings. The first study, involving 37 healthy subjects, detected increased Blood Oxygen Level-Dependent (BOLD) signals in the cerebellum. These activations were accompanied by heightened activity in a broad network of regions, including the thalamus, brainstem, auditory, visual, and sensorimotor cortices, as well as the anterior and midcingulate gyrus, precuneus, prefrontal cortex, and inferior parietal lobule [40]. This extensive neural network suggests that the cerebellum participates in a coordinated response across multiple brain regions during K-complex events.

However, a smaller study involving 7 healthy subjects revealed a distinct pattern of activation. This study detected increased BOLD signals primarily in the thalamus, superior temporal lobes, and medial frontal/occipital regions but did not observe cerebellar involvement [56]. The discrepancy between findings can be attributed to several factors. Sample size variation affects statistical power and reliability, which may contribute to differing results. Moreover, five of seven subjects in the second study had epilepsy, a condition that could alter normal physiology and complicate interpretation of cerebellar function during K-complexes.

The mechanisms underlying cerebellar activation during K-complexes are not well understood, but hypothetical perspectives suggest a modulatory rather than generative role of cerebellar activity on thalamocortical oscillations via the cerebellothalamic pathway. These oscillations act as a pacemaker, regulating the synchronized cortical activity associated with K-complexes. Additionally, studies have demonstrated that brainstem activation precedes K-complexes, indicating a potential pathway for cerebellar involvement [57]. The cerebellum interacts with brainstem nuclei, which could influence the maintenance of K-complexes during sleep stability.

2.2.1.3. Cerebellar involvement in slow-wave activity. Slow waves, or slow-wave activity (SWA), are high-amplitude, low-frequency (0.5–4 Hz) brain waves that dominate Stage 3 of NREM sleep. They are generated by synchronized thalamocortical activity and are thought to be key for physical restoration, memory consolidation, and brain cleanse [58,59].

Utilizing simultaneous EEG-fMRI, researchers have observed that SWA is associated with significant activity in the cerebellum. Notably, a study involving nine healthy subjects revealed that cerebellar activity in lobules III (culmen) and IV (declive) was increased during slow wave sleep (SWS) compared to both wakefulness and the N2 stage [41]. A subsequent study with 14 healthy volunteers showed significant cerebellar activation during slow oscillations, with cerebellar activity directly correlated to high-amplitude slow and delta waves [42].

An additional EEG-fMRI study with 20 healthy adults showed cerebellar activation during SWA, especially in the vermis and superior cerebellar hemispheres. This was linked to stronger connectivity between the cerebellum and the somatomotor network, hinting at a role for the cerebellum in sleep-related motor memory consolidation [43]. Furthermore, in a large study with 73 healthy individuals, a direct correlation between EEG delta power and cerebellar connectivity with the limbic system was observed [44]. In addition, combining EEG sleep recordings with high-resolution structural brain imaging using voxel-based morphometry in 22 subjects revealed a direct correlation between SWA and cerebellar gray matter volume (GMV) [60].

These findings align with a key study of three epilepsy patients with electrodes in the DCN. Patients showed spike discharges synchronized with NREM slow waves and minor sharp potentials during REM sleep [61]. Upon PET imaging, a significant negative correlation was observed between delta wave activity and the regional cerebral blood flow in the bilateral posterior Crus I of the cerebellar hemispheres [62].

Animal studies suggest the cerebellum may contribute to cortical bistability during N3 sleep, where neurons alternate between high and low activity. During this stage, it has been observed that Purkinje cells increase their interspike intervals, likely aligning with the down-state activity that underlies N3 sleep [9,63]. This phenomenon could be mediated by neocortical influence on climbing fibers via the inferior olive [64], along with interneurons in the cerebellar cortex [65]. The neocortical origin of slow waves was recently confirmed using single-unit and population recordings in rhesus macaques in which the functional connectivity from the motor cortex to the cerebellum was particularly observed during slow waves but in the contrary direction during sleep spindles [32].

Another rat study under ketamine-xylazine anesthesia revealed the cerebellum's role in sensorimotor integration during SWA. It showed that Purkinje cell activation, not ponto-cerebellar fibers, mediates feedforward communication between the primary somatosensory cortex and DCN [66]. These findings suggest the cerebellum fine-tunes sensorimotor integration by regulating cortical slow wave activity and coherence, important for motor memory consolidation. Indeed, increased cerebellar-somatomotor connectivity has been observed in healthy individuals during slow wave activity [43].

2.2.2. Sleep-related cerebellar activity during rapid eye movements (REM) sleep

REM sleep is a distinct physiological state marked by rapid eye movements, heightened cerebral activity, vivid dreaming, and skeletal muscle atonia (temporary paralysis). This phase typically initiates approximately 90 min after sleep onset and recurs cyclically throughout the night, accounting for 20–25 % of total sleep duration in healthy adults. Functionally, REM sleep is critical in memory consolidation, emotional regulation, and neurodevelopment [67,68].

In general, cerebellar activity during REM sleep is significantly higher compared to both NREM sleep and wakefulness. This increased activation has been consistently observed in human neuroimaging studies using PET [35] and fMRI [69] particularly in the cerebellar hemispheres and the vermis. Notably, the vermis exhibits an even more pronounced increase in activity during REM sleep compared to other cerebellar regions, suggesting its potential role in modulating specific REM-related processes, such as eye movements, due to cerebellar vermis is the main target of vestibular system [69].

Seminal studies in monkeys and cats during physiological REM sleep revealed a significant increase in Purkinje cell activity compared to waking [9,37]. This was characterized by higher consistency in simple spike activity, which is linked to the activation of mossy fiber–parallel fiber pathways [9]. These findings suggest a cerebellar role in REM sleep, potentially related to internal processing and motor learning consolidation. Notably, complex spike activity was also observed to increase in cats, likely reflecting cerebellar involvement in eye movement control [37].

A key study in monkeys during natural REM sleep found that simple-spike activity (from mossy fiber–parallel fiber pathways) increased notably compared to wakefulness and NREM sleep, while complex-spike activity (from climbing fiber pathways) was lowest during REM [9]. These findings were partially supported in studies involving cats, where mossy fiber activity was observed to be higher during rapid eye movements in REM sleep compared to NREM sleep. Conversely, the activity of climbing fibers during REM sleep was phasically reduced and only increased when rapid eye movements were absent [38]. Thus, the

preponderance of activation of mossy rather climbing fibers in REM sleep suggest that the cerebellum's role during REM sleep is primarily associated with internal processing and motor learning consolidation rather than external sensory processing, which is consistent with the broader roles of REM sleep in cognitive and motor function development [67,68].

In cats, activity within the interpositus and fastigial nuclei was significantly elevated during REM sleep compared to both NREM sleep and wakefulness. This paradoxical increase occurred despite heightened Purkinje cell activity, which typically exerts inhibitory effects on these nuclei [70]. The findings suggest a dominance of excitatory inputs to the DCN, likely originating from pontine regions such as the pontine reticular formation, which may override Purkinje-mediated inhibition during REM sleep.

Evidence on hippocampus-cerebellum crosstalk during REM sleep reveals widespread delta activity accompanied by discrete phasic sharp-wave potentials across cerebellar regions, which are phase-locked to hippocampal theta rhythms (Fig. 3C). This interaction may regulate the network dynamics underlying sleep-dependent cognitive processes [29].

The following evidence demonstrates the cerebellum's involvement in the generation and/or regulation of the most significant polygraphic elements of REM sleep: rapid eye movements and sleep atonia.

2.2.2.1. Cerebellar involvement in the rapid eye movements during REM sleep. Rapid eye movements (REMs) during REM sleep are characterized by quick, unpredictable bursts of eye movements that likely reflect shifts in gaze within dreams. These movements are closely associated with bursts of electrical activity known as ponto-geniculo-occipital (PGO) waves, which originate in the brainstem and stimulate the visual cortex, enhancing the vividness of dream imagery and experiences. While the brainstem, particularly the pons and caudal midbrain, is the primary generator of rapid eye movements during REM sleep, the cerebellum modulates these movements through functional parallels to its role in wakefulness, albeit with distinct neural mechanisms [71].

A seminal study investigated oculomotor control during REM sleep by implanting electrodes in the lateral rectus muscles (responsible for eye abduction) and sleep-regulatory brain areas of cats. Post-cerebellectomy, researchers observed a 76 % increase in amplitude of phasic muscle activity during REM sleep compared to pre-surgery baselines, demonstrating the cerebellum's inhibitory role in regulating burst intensity [72]. Supporting these findings, further research in cerebellectomized cats revealed a significant increase in PGO wave amplitudes post-surgery. In contrast, removal of the frontal lobe modified the pattern of PGO wave discharges rather than altering their amplitude, underscoring distinct regulatory roles of these brain regions in REM sleep dynamics [73].

A study coregistering rapid eye movements from video recordings and rapid event-related fMRI in eleven healthy participants identified significant activation of the cerebellar vermis and both cerebellar hemispheres in association with REMs [69].This finding supports that the cerebellum plays an active role in the modulation of rapid eye movements during REM sleep, highlighting its involvement in oculomotor control during REM sleep.

2.2.2.2. Cerebellar involvement in sleep atonia. Sleep atonia during REM sleep is a natural state of temporary muscle paralysis that prevents the sleeper from acting out their dreams. It primarily affects skeletal muscles while sparing essential functions like breathing and eye movements. This mechanism is driven by the inhibition of motor neurons through signals from the brainstem, particularly involving the sublaterodorsal nucleus (SLD) [74].

To our knowledge, the cerebellum's role in directly controlling sleep atonia during REM sleep has not been explicitly addressed in the literature. However, mechanisms similar to those involved in the modulation of phasic muscle activity during REM sleep may also play a role in the regulation of sleep atonia [72]. Specifically, the cerebellum's inhibitory influence on motor activity and its interactions with brainstem circuits responsible for generating REM sleep could indirectly contribute to the maintenance of muscle atonia. Further research is needed to elucidate the precise involvement of the cerebellum in this process. The cerebellum might exert modulatory influence over the SLD and other brainstem structures directly responsible for generating REM atonia through its projections to various brainstem regions.

2.3. Cerebellar stimulation approaches induce changes in sleep patterns

While most experimental studies linking the cerebellum to sleep rely on electrophysiological recordings of cerebellar activity during sleep, few have explored the effects of deep cerebellar electrical stimulation on sleep. Nevertheless, evidence from cerebellar electrical stimulation actually emerged prior to intracerebral electrophysiological recordings. In seminal studies, probably the first ones reporting linking between sleep and cerebellum Simkina y Orbelli noticed that the electrical stimulation of the cerebellum was able to awaken sleeping animals and induce sleep in awake ones [75]. When a stimulus was applied to the vermian region for extended periods, the animal remained asleep for the duration of the stimulation [76]. In another two pivotal studies, the cerebellar deep stimulation in rabbits induced frontal cortical spindle-like activity [77], while the repeated electrical stimulation of the anterior cerebellar cortex consistently elicited sleep stages in cats [78].

Recently, the deep brain stimulation targeting the fastigial-interposed nuclear fiber tracts in two genetic mouse model resembling dystonia with cerebellum malfunction alleviated sleep architecture abnormalities [79]. In humans, prefronto-cerebellar transcranial direct current stimulation (tDCS) has been shown to improve sleep symptoms in adults with euthymic bipolar disorder [80] and in children with autism [81]. However, repetitive transcranial magnetic stimulation (rTMS) proved ineffective for improving sleep quality in Alzheimer's disease, though it enhanced multi-domain cognitive functions [82].

Thus, this evidence supports the role attributed to the cerebellum in sleep regulation, as stimulation of the cerebellum may functionally modulate sleep-related networks under both physiological and pathological conditions. This highlights the potential of cerebellar stimulation as a therapeutic option for sleep disorders, whether or not they are associated with cerebellar diseases. However, this promising area warrants further systematic research.

2.4. Genetic signatures of sleep regulation in the cerebellum

To better understand the cerebellum's role in sleep regulation, we must study gene expression patterns for sleep-wake and circadian rhythm genes in this region. While research is limited, emerging Genome-Wide Association Study (GWAS) studies emphasize the importance of genetics in clarifying the cerebellum's sleep-related contributions.

Tissue-specific gene-set analyses from a large GWAS on insomnia (N = 1,331,010) identified the cerebellar hemisphere as one of five brain regions with significant enrichment of genetic signals in expressed genes, particularly in *RBFOX1, PTPRD, NOL4L, RBM5*, and *SNCA* [83]. Two large studies of sleep duration (N = 446,118) [84] and chronotype (N = 697,828) [85] identified the cerebellum as having the highest enrichment of significant genes related to both sleep health traits among 51 specific tissue types examined. In line with these findings, a recent GWAS of composite sleep health scores in 413,904 UK Biobank participants identified several genes—*ANKFY1, WDR73,* and *ZNF592*—that are highly expressed in the cerebellum and closely associated with longer sleep duration and reduced insomnia, suggesting a role for the cerebellum in regulating sleep maintenance and efficiency. Additionally, *KSR2*, another gene with high cerebellar expression, was linked to sleepiness. In this study, tissue enrichment analyses revealed that the

cerebellum displayed the strongest enrichment for genes related to longer sleep duration, followed by the hypothalamus and frontal cortex. For morningness chronotype, the cerebellum also showed high enrichment, second only to the frontal cortex [86].

In accordance with those results, a transcriptome-wide association study (TWAS) examining the impact of gene expression across 13 brain regions on sleep health found the greatest enrichment of significant genes in the cerebellum, compared to other brain regions, including the basal ganglia, the amygdala and frontal cortex. In particular, the genes that most significantly contributed to longer sleep duration (*EIF3KP1*) and greater sleep efficiency (*GNL3*) were found to be highly expressed in the cerebellum [87]. These findings underscore the cerebellum's potential role in the genetic regulation of sleep duration and circadian rhythms, offering insights into the biological mechanisms underlying sleep health.

Other GWAS study revealed that risk variants for REM Sleep Behavior Disorder (RBD) at the *SCARB2* and the *SNCA-AS1* loci were dysregulated in the cerebellum leading to increased expression of the encoded lysosomal integral membrane protein-2 (LIMP-2) and decreased expression of a *SNCA* gene-related long non-coding RNA, respectively. This finding suggests that cerebellar involvement in the pathophysiology of RBD may be mediated by impaired lysosomal function and abnormal synaptic plasticity [88].

In animal models, a study utilizing high-density microarrays in awake and sleeping rats identified 106 sleep-related transcripts in the cerebellum. Notably, these transcripts exhibited a significant overlap with sleep-related transcripts expressed in the cerebral cortex, suggesting shared molecular mechanisms between these brain regions in regulating sleep [89].

Furthermore, studies on mice with a knockout of the *BTBD9* gene—known to be involved in Restless Legs Syndrome (RLS) [90] and sleep disruption [91]—have revealed reduced cerebellar neural activity and altered Purkinje cell function, characterized by increased excitability and non-tonic firing. Notably, Purkinje cell-specific *Btbd9* knockout mice displayed motor restlessness and disrupted sleep during rest phases. These findings suggest that cerebellar dysfunction contributes to RLS-like behaviors, underscoring the cerebellum's significant role in sleep-wake regulation [92].

Overall, these findings underscore the cerebellum not only as a motor coordination center but also as a critical brain region influencing sleep traits identified in GWAS. This is supported by strong genetic signals from genes highly expressed in the cerebellum, paving the way for mechanistic research aimed at deepening our understanding of how the cerebellum contributes to sleep regulation.

2.5. The circadian cerebellum

The cerebellum exhibits oscillations in gene and protein expression related to circadian rhythms, suggesting it has its own molecular circadian oscillator. Indeed, it is considered as a secondary oscillator that complements the primary circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The cerebellar oscillator is primarily located in Purkinje cells, where specific clock genes, such as *PER1* and *PER2*, exhibit rhythmic expression throughout the day, peaking during specific times (e.g., higher at ZT 10 compared to ZT 19). Nevertheless, the expression of cerebellar clock genes is partially regulated by the master clock in the SCN and modulated by neuroendocrine signals such as corticosterone [93], triiodothyronine and melatonin [94].

A particularly intriguing study demonstrated that cerebellar *CLOCK* gene expression was completely abolished in rats with a lesioned SCN. However, the daily rhythm of *CLOCK* gene expression was remarkably restored following the exogenous administration of corticosterone [93]. Regarding the influence of triiodothyronine (T3) on cerebellar *CLOCK* gene profiles, both in vitro experiments using granule cells and in vivo studies revealed a significant impact only during early postnatal stages. This suggests that T3 plays a role in cerebellar developmental processes, likely through its interaction with circadian clock components in the neonatal cerebellum. These findings highlight the importance of T3 in shaping circadian mechanisms during critical periods of cerebellar maturation [94].

While the functional role of cerebellar gene expression oscillations is still unclear, recent researches indicate the cerebellum helps regulate mealtime anticipation via circadian responses to feeding cues. In food-restricted rats, cerebellar glucose metabolism decreased during meal anticipation [95]. In mice, timed feeding altered cerebellar *CLOCK* gene rhythms, and food-anticipatory activity dropped after Purkinje cell depletion or genetic cerebellar disruption [96]. An fMRI study in patients with evening hyperphagia also identified the cerebellum as key in circadian feeding disorders [97]. However, in vitro, cerebellar *CLOCK* gene oscillations only modestly affected neuronal activity, suggesting other circadian network components are more influential in these processes [98].

Although strong evidence is currently lacking, it is plausible that the circadian cerebellum also contributes to the regulation of motor and cognitive functions, both of which are known to be modulated by circadian timing. Exploring this possibility represents an important avenue for future research.

2.6. Cerebellar involvement in common sleep disorders

Numerous structural and functional neuroimaging studies have identified significant alterations in the cerebellum of patients with common sleep disorders, including insomnia, sleep apnea, REM sleep behavior disorder (RBD), and restless legs syndrome (RLS). While no definitive pattern of changes has emerged, most studies report a reduction in cerebellar GMV, accompanied by marked disruptions in functional connectivity both within the cerebellum and between the cerebellum and other central nervous system (CNS) regions indicating extensive network-level alterations (Fig. 4A). Although sleep and its disorders have not been mapped in the cerebellar cortex as extensively as motor and cognitive functions, several available neuroimaging studies have shown lobule-specific changes in the cerebellar cortex, providing an approximation of the cerebellum's role in sleep disorders. These findings indicate that most changes occur in the posterior cerebellum, involving both the vermis and the hemispheres, without a clear unilateral distinction (Fig. 4B). The following presents the evidence of the cerebellum's involvement in the most common sleep disorders.

2.6.1. Insomnia

Insomnia significantly impacts the cerebellum, causing functional and structural changes. Studies show it is associated with reduced cerebral blood flow (CBF) correlating with the severity of insomnia and related depressive symptoms [99]. In general, fMRI studies have revealed reductions of the functional connectivity in the cerebellum [100], being it directly associated with the insomnia severity [101] and more consistently in the anterior lobes [102] particularly in lingula (vermis I-II) and culmen (vermis IV-V) [103].

In addition, patients often show decreased GMV in specific cerebellar regions including vermal lobules VIIb and VIII, left lobule VIII, and right Crus I [104,105]. Individual morphological network analysis based on regional GMV from 102 chronic insomnia patients revealed decreased nodal efficiency in hemispheric lobule VIII and increased efficiency in vermis VIIb [106]. The former is congruent with the atrophy of this region [105] and its reduced functional connectivity with the middle left cingulate gyrus (MCC) and the left medial superior frontal gyrus (mSFG) [105]. Both lobule VIII GMV and its prefrontal connectivity are inversely correlated with insomnia severity, reflecting neural mechanisms that link insomnia to movement disorders during sleep. This convergent structure-function pattern illustrates how lobular atrophy predicts prefrontal hypo-coupling and symptom severity, highlighting a testable axis warranting longitudinal validation.

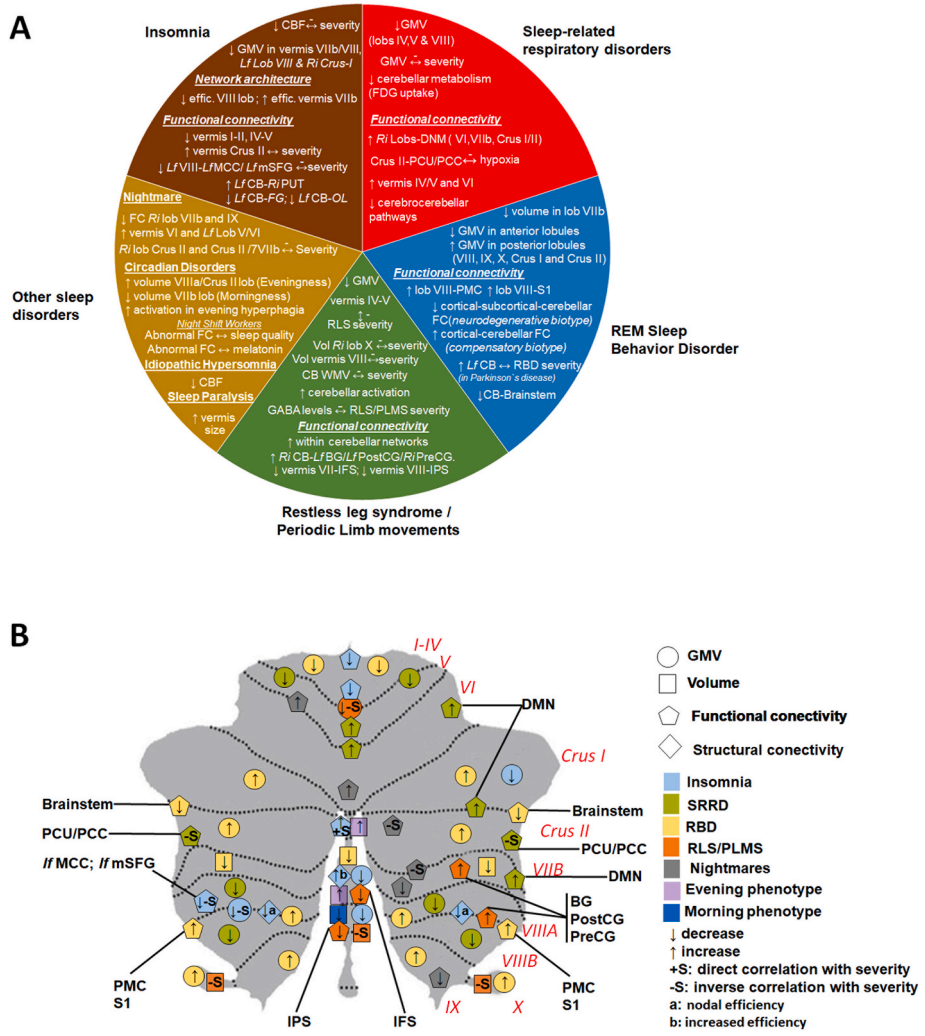

Fig. 4. Cerebellar involvement in common sleep disorders. A) Overview of main findings showing the structural and functional changes of cerebellum in subjects with common sleep disorders. B) Lobe-specific changes in the cerebellar cortex observed in patients with sleep disorders. *BG: Basal Ganglia; CBF: Cerebellar Blood Flow; CB: Cerebellum; DMN: Default Mode Network; effic: efficiency; FC: Functional Connectivity; FDG: Fluorodeoxyglucose; FG: Fusiform Gyrus; GABA: gamma-aminobutyric acid; GMV: Gray Matter Volume; IFS: inferior frontal sulcus; IPS: intraparietal sulcus; Lf: left; lob: lobule; MCC: middle cingulate gyrus; mSFG: medial superior frontal gyrus; OL: Occipital Lobe; PCG: Precentral Gyrus; PCU/PCC: Precuneus/Posterior cingulate; PLMS: Periodic Limb Movements disorder; PMC: Premotor Cortex; PostCG: Postcentral Gyrus; PUT: Putamen; RBD: REM sleep behavior disorder; Ri: right; RLS: Restless Leg Syndrome; S1: Primary Somatosensory Cortex; SRRD: Sleep-related respiratory disorders; WMV: White Matter Volume; increase; ↓: decrease; ↔: direct correlation; -: when the minus sign is above the ↔ reflects inverse correlation.*

Interestingly, increased structural connectivity in the vermis VIIb [106] appears to mismatch the reduced GMV characterized in this region [104]. This paradoxical structure-function coupling reflects surviving neurons upregulating connectivity and efficiency—increasing nodal efficiency or hyperconnectivity—to recruit distant networks indicating compensatory overdrive to maintain biopsychosocial regulation despite volume loss.

Complementing this pattern, functional connectivity analysis demonstrated vermis Crus II hyperconnectivity, correlating with insomnia severity and poor sleep quality. This may reflect a hyperactive cerebellar state contributing to heightened arousal and maladaptive responses to insomnia-related emotional and cognitive changes [107]. Therefore, this lobule VIIb structural → vermis Crus II functional axis suggests consistent posterior lobule structure-function coupling predicting severity.

Additionally, enhanced connectivity between the left cerebellum and right putamen in insomnia with comorbid depression is linked to insomnia severity, likely compensating for cognitive and language changes; meanwhile, cerebellar connectivity with the fusiform gyrus and occipital lobe is reduced [99].

Finally, a study of insomniac adolescents found that cerebellar regional GMV was directly linked to executive functioning. It also showed an inverse correlation between GMV in the right flocculonodular lobe and insomnia severity, a pattern seen only in boys. These findings highlight the cerebellum's role in cognition, brain development, and insomnia [108].

Some fMRI studies report inconsistencies in insomnia's impact on cerebellar functional connectivity, likely stemming from variations in study design, sample size, and connectivity assessment methods. Thus, the precise nature of these alterations and their implications for sleep, cognition, and emotion remain active areas of research and debate.

2.6.2. *Sleep-related respiratory disturbances (SRRD)*

The cerebellum has been recognized for its role in respiration, particularly during challenging conditions such as hypoxia or hypercapnia, which induce a heightened need for air. Its involvement in these respiratory challenges is based on its extensive connectivity with both the forebrain and brainstem respiratory centers [109–111], thus it is not surprising that Obstructive sleep apnea (OSA) promotes significant changes in the cerebellum, which can have significant implications for

cognitive and motor functions.

Patients with OSA show significant reductions in cerebellar GMV, particularly lobules IV/V and VIII [112–116]. One study found an inverse correlation between cerebellar GMV and OSA severity, indicating that greater severity is linked to more pronounced gray matter loss [115]. Additionally, reduced cerebellar metabolism has been observed in these patients, as assessed by FDG-PET imaging [117].

In terms of functional connectivity, OSA patients exhibit impairments in the functional connectivity of the cerebellum. A study involving 60 male OSA patients found increased functional connectivity between specific right cerebellar lobules (VI, VIIb, and Crus I/II) and regions of the default mode network involved in the regulation of emotions, cognition, and language, suggesting a potential adaptive cerebellar compensation for impaired emotional, cognitive and language functioning caused by OSAs. Interestingly, functional connectivity within the Crus II-Precuneus/Posterior cingulate (PCU/PCC) showed a negative correlation with hypoxia severity, indicating that reduced oxygen saturation may impact this neural circuit in the early stages of the disorder [118]. Enhanced local connectivity in the vermal lobules IV/V (culmen) and VI (declive)—documented via regional homogeneity (ReHo) analysis in 25 male severe OSA patients—appears protective, compensating for sleep fragmentation by preserving restorative N3 sleep despite concurrent GMV loss [119].

In contrast, recent research highlighted reduced functional connectivity in cerebrocerebellar connections, along with lower clustering coefficients and network efficiency within the left cerebellum [120].

2.6.3. REM sleep behavior disorder (RBD)

The impact of REM Sleep Behavior Disorder (RBD) on the cerebellum has been highlighted in various studies, indicating structural and functional changes associated with this condition that support a key role of the cerebellum in the RBD physiopathology.

Research has shown that patients with isolated RBD have decreased total cerebellar volumes compared to healthy controls. Notably, significant reductions were observed in specific subdivisions of the cerebellum, particularly in lobule VIIb [121]. Additionally, a decrease in GMV has been reported in the anterior lobules of both the left and right cerebellum [122]. However, findings on posterior cerebellum revealed increase of cerebellar GMV, particularly in the bilateral cerebellar lobules VIII, IX, X, Crus I and Crus II [123–125], which probably reflect compensatory hypertrophy countering anterior atrophy and REM sleep motor dysregulation. Consistent with this, lobule VIII exhibits enhanced functional connectivity to premotor/primary somatosensory cortices in iRBD patients with mild motor impairment compared to those without, supporting cerebellar compensation for early nigrostriatal dopaminergic deficits [126]. In fact, in Parkinson's disease patients with RBD, increased local neuronal activity and connectivity in the left cerebellum correlate with RBD severity [127]. These cerebellar compensatory mechanisms for motor function in iRBD appear not to extend to dysautonomic or cognitive–emotional impairments, as connectivity with the brainstem is reduced [128]. Moreover, decreased functional connectivity between cerebellar posterior lobule and limbic striatum is associated with hypersexuality behavior in idiopathic RBD patients [129].

Differences in cerebellar functional connectivity patterns between some studies with RBD patients may reflect underlying phenotypic heterogeneity. A study integrating MRI and clinical assessments identified two distinct biotypes. Biotype 1 exhibits widespread cortical-subcortical-cerebellar hypoconnectivity with limited cerebellar-sensorimotor hyperconnectivity, suggesting neurodegenerative disruption, while Biotype 2 shows predominant cortical-cerebellar hyperconnectivity with minimal hypoconnectivity, possibly indicating compensatory strategies. [130]. These findings highlight subtype-specific progression patterns, and pave avenues for personalized neuromodulation: excitatory protocols for hypoconnected circuits (Biotype 1) and inhibitory approaches for hyperconnected phenotypes (Biotype 2), underscoring the need for biotype stratification in future research and clinical management of RBD.

2.6.4. Restless leg syndrome/periodic limb movements

Recent studies have highlighted the cerebellum's involvement in Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS), revealing both structural and functional changes. A voxel-based morphometry (VBM) study of 46 RLS patients revealed significant cerebellar GMV reduction, with cerebellar vermis IV/V (culmen) volume inversely correlating with RLS symptom severity [131]. In contrast, a more recent study that included 69 RLS patients did not observe similar lobule-specific cerebellar atrophy when compared to healthy controls. Instead, this latter study identified inverse correlations between the volume of the right lobule X and RLS severity as well as between the volume of vermis VIII and insomnia severity [132]. Recently, a study involving 44 RLS patients from Turkey found no decrease in cerebellar GMV. However, a significant bilateral reduction in white matter volume was observed, which correlated closely with higher RLS severity and increased psychiatric symptoms [133].

Functional imaging studies show increased cerebellar activity in RLS patients. A seminal fMRI study of 19 cases found significant bilateral cerebellar activation during sensory discomfort and periodic leg movements, suggesting the cerebellum is primarily involved in generating sensory symptoms rather than controlling limb movements [134]. This highlights the cerebellum's role in processing sensory experiences in RLS, linking its activation more to discomfort than to motor aspects of the disorder.

Further studies reported higher connectivity within cerebellar networks itself in RLS patients compared to healthy individuals [132,135], but reduced connectivity between vermis VII-inferior frontal sulcus and vermis VIII-intraparietal sulcus hypoconnectivity have been reported. The latter pattern only occurs in untreated RLS patients reflecting impaired sensory processing contributing to RLS symptom generation [135]. This functional disruption aligns with the reported correlation between vermis VIII volume and insomnia severity [132], underscoring a critical structure–function relationship underlying the RLS sleep phenotype.

In addition, RLS patients show increased right cerebellar functional connectivity to left basal ganglia, left postcentral gyrus, and right precentral gyrus, implicating disrupted cerebellum-basal ganglia-sensorimotor circuits in RLS pathophysiology [136].

An interesting research indicates that the cerebellar hyperactivity exhibited by RLS patients is thought to be linked to lower levels of GABA, due to cerebellar GABA levels are negatively correlated with PLMS indices and the severity of RLS symptoms [137].

In summary, these observations underscore the cerebellum's critical role in the pathophysiology of RLS, suggesting that it may actively participate in modulating neural circuits involved in sensory discomfort, highlighting its potential as a target for therapeutic interventions.

2.6.5. Other sleep disorders

Individuals experiencing nightmares demonstrate abnormal functional connectivity within the cerebellum which is closely linked to the frequency of nightmares [138–140]. The functional connectivity pattern is characterized by decreased ReHo in right lobules VIIb and IX, increased ReHo in vermis VI and left V/VI, and inverse correlations between right superior Crus II/right Crus II-VIIb and disturbed dreaming severity. These patterns indicate hypofunctional emotional regulation in the right posterior cerebellum with compensatory vermis/left hyperactivity, consistent with the cerebellum's established role in fear memory processing [141]. These findings identify right Crus II/VIIb as primary excitatory neuromodulation targets to restore fear memory suppression and reduce nightmare generation.

A pilot study involving 10 patients with recurrent isolated sleep paralysis (RISP) revealed a significant enlargement of the cerebellar vermis, which is likely a consequence of compensatory mechanisms

responding to impaired networks that regulate REM sleep and the transition between REM sleep and wakefulness [142] two process in which the cerebellum is known to play a crucial role [48].

A study using single photon emission computed tomography (SPECT) found that patients with idiopathic hypersomnia exhibited decreased regional cerebral blood flow in the cerebellum but it was not related with the daytime sleepiness severity [143].

Additionally, abnormal functional connectivity within the cerebellum has been observed in individuals who work night shifts, correlating with sleep quality scores and melatonin levels with suggests the cerebellar involvement in circadian rhythm disorders [144].

A recent study involving 123 young participants found no significant differences in cerebellar volume between individuals with early chronotype and those with late chronotype. However, a significant gender effect was observed for both the cerebellum and vermis volumes [145]. However, a recent large-scale neuroimaging study of 27,030 UK Biobank participants revealed distinct chronotype-related volumetric differences in cerebellar vermis sub-regions. The analysis showed a directional divergence: eveningness chronotype demonstrated a positive association with vermis VIIIa and Crus II volumes while morningness preference correlated with reduced vermis VIIb volume [146]. Discrepancies between the two studies may stem from differences in sample sizes and the distinct methodologies used to classify chronotypes.

In addition, a significant cerebellar activation was observed in an fMRI study involving obese adults exhibiting evening hyperphagia, a core criterion of night eating syndrome [97]. This condition is associated with a delayed circadian pattern of food intake, further confirming the cerebellum's potential role in regulating circadian-related eating behaviors [147].

Across these rare sleep disorders, the paucity of concurrent structural (GMV) and functional (Functional connectivity/ReHo) findings limits unified structure-function frameworks of their cerebellar physiopathology, warranting further studies.

2.7. Sleep pathology in cerebellar diseases

Cerebellar diseases comprise a diverse group of disorders with both genetic and non-genetic origins, all characterized by cerebellar dysfunction that leads to impaired coordination and balance [148]. These conditions are often accompanied by additional non-ataxia features, among which sleep disorders are notably prevalent [149,150].

2.7.1. Evidences from animal models of cerebellar dysfunctions

Research in animal models of cerebellar dysfunction has significantly advanced our understanding of how the cerebellum regulates sleep patterns, particularly in conditions such as ataxia and dystonia. In homozygous transgenic Spinocerebellar Ataxia type 3 (SCA3) mice, sleep architecture and circadian rhythms are significantly altered. These mice show increased REM sleep duration and greater fragmentation across all sleep states, along with elevated beta power oscillations during both REM and NREM sleep, indicating heightened cortical arousal or neural dysregulation [151].

Recent research found that both homozygous and hemizygous SCA3 mice show disrupted core body temperature rhythms, reflecting impaired circadian function. This disruption is linked to reduced levels of neuropeptides in the SCN, as well as decreased expression of clock genes in the cerebellum, highlighting widespread circadian dysfunction in this model [152].

Mutant AAV vectors of SCA3 were stereotaxically delivered into the cerebellum of monkeys, which were subsequently monitored for eight weeks. Post-injection, the animals exhibited altered sleep architecture, marked by increased wakefulness and transitional sleep phases [153]. These alterations may reflect RBD-like manifestations commonly observed in SCA3 patients [154–156]. Notably, early sleep disturbances emerged in the absence of overt ataxic symptoms, aligning with observations in affected individuals [157].

In Spinocerebellar Ataxia type 2 (SCA2), an *ATXN2* knockout mouse exhibited unstable locomotor activity rhythms under both entrained and free-running conditions, yet PER1 and PER2 levels in the SCN were normal compared to wild-type mice [158]. This suggests that *ATXN2* deficiency disrupts circadian behavior without directly affecting the core SCN molecular clock, implicating downstream or extra-SCN mechanisms in these circadian disturbances.

Moreover, a mouse model of ataxia with silenced Purkinje cell neurotransmission (L7Cre; Vgatfx/fx) shows disrupted sleep patterns similar to human cerebellar ataxia. These mice have decreased REM sleep, increased NREM sleep, and longer REM sleep latency. EEG analysis reveals reduced α, β, θ, and γ power in parietal regions and increased δ power in the frontal lobe, highlighting the role of Purkinje cell dysfunction in altering sleep architecture and cortical oscillations [159].

The Ptf1a cKO mouse, lacking the cerebellar cortex, shows reduced REM sleep during the light phase and increased NREM delta power after sleep deprivation, alongside diminished slow-wave activity across all states. Despite the absence of cerebellar structures, wakefulness and NREM sleep duration remain normal compared to controls [160]. These findings suggest that while the cerebellum may play a modulatory role in specific aspects of sleep regulation, it is not essential for maintaining baseline wakefulness and NREM sleep.

In the case of neurological conditions with cerebellar involvement, animal models have been also useful to understand the cerebellar role in sleep regulation. Two genetic mouse models of dystonia (Ptf1aCre; Vglut2fx/fx and Pdx1Cre; Vglut2fx/fx), disrupt cerebellar circuit wiring by blocking excitatory climbing fiber to Purkinje cell neurotransmission, resulting in significant sleep architecture changes. These mice have increased wakefulness, reduced REM duration, increased REM latency and altered NREM sleep patterns [161]. These findings indicate that cerebellar circuitry dysfunction's role in dystonia extends beyond motor impairments, potentially contributing to abnormal sleep patterns.

Deep brain stimulation targeting the fastigial-interposed nuclear fiber tracts in these models of dystonia alleviated both motor and sleep deficits. This approach specifically reduced total wake time, increased REM/NREM sleep duration, and shortened REM sleep latency. Notably, stimulation confined to the interposed nuclei alone failed to produce sleep improvements [79]. These findings establish proof of concept for the therapeutic potential of cerebellar stimulation in sleep regulation, warranting further investigation.

2.7.2. Evidences from patients with hereditary ataxias

The majority of clinical and polysomnographic researches on sleep disturbances in cerebellar patients have focused on primary genetic ataxias, especially autosomal dominant cerebellar ataxias, also termed spinocerebellar ataxias (SCAs) and autosomal recessive cerebellar ataxias (ARCAs). The most common sleep disorders in hereditary ataxias include RBD, RLS, PLMS, sleep apneas and insomnia, with prevalence varying by conditions [149,150]. The ataxia subtypes that show the highest number of concurrent sleep disorders are SCA2, SCA3, SCA6, Friedreich's ataxia (FA), and Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia (CANVAS) Syndrome (Fig. 5A).

RBD is particularly common in patients with SCA3, with prevalence rates typically just above 50 % [154–156,162–165], and can often be identified years before the onset of ataxia symptoms [157]. In contrast, RBD is much less frequent in SCA10 [166], SCA2 [167–169], SCA6 [170], SCA12 [171], and SCA36 [172], while only isolated cases have been reported in SCA8 [173], and SCA31 [174].

In SCA2, while RBD is uncommon, REM sleep without atonia (RWA)-a subclinical precursor to RBD-is highly prevalent, affecting 31–80 % of patients [167–169]. This electrophysiological marker frequently emerges in early disease stages [167] and strongly associates with longer mutation size (expanded CAG triplet repeats) and accelerated clinical progression, suggesting RWA may serve as a biomarker of polyglutamine burden and disease severity in SCA2 [168].

RLS demonstrates subtype-specific prevalence in SCAs, with

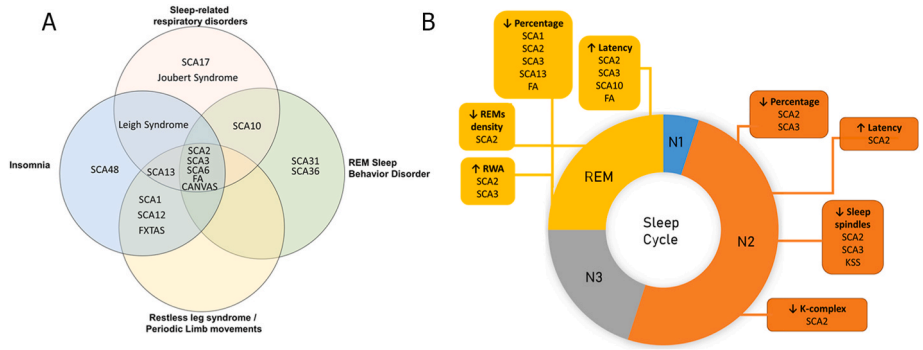

Fig. 5. Overview of the main sleep disorders and polysomnographic features in Hereditary Ataxias. *SCA: Spinocerebellar Ataxia; FA: Friedreich Ataxia, CANVAS: Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome; FXTAS: Fragile X-associated tremor/ataxia syndrome; KSS: Kearns-Sayre syndrome; REM: Rapid eye movement sleep; REMs: Rapid eye movements; N1: noREM sleep stage 1; N2: noREM sleep stage 2; N3: noREM sleep stage 3; RWA: REM sleep without atonia.*

particularly high rates in SCA3 (22–54 %) [154,164,165,175], SCA6 (40 %) [176], SCA2 (18–27 %) [168,177], and SCA1 (23 %) [177,178]. Among recessive ataxias, RLS is particularly frequent in CANVAS Syndrome, occurring in approximately 69 % of cases [179]. This is followed by Friedreich ataxia, where RLS is observed in 30–50 % of patients [180–182]. In Fragile X-associated tremor/ataxia syndrome (FXTAS), carriers of the *FMR1* gene pre-mutation are nearly twice as likely to develop RLS compared to healthy controls, which significantly contributes to reduced sleep quality [183].

PLMS are most prominent in SCA6 (80 %) [176], SCA2 (38–80 %) [168,169], and SCA3 (55–77 %) [154,162,184], but are rarely observed in SCA13 [185]. In SCA2, the severity of PLMS shows a strong correlation with longer disease duration and greater clinical severity [168]. In Friedreich ataxia cases, PLMS are observed in approximately 44 % of patients with concomitant RLS [182], whereas in CANVAS syndrome, PLMS occurs in about 62 % of cases [179].

Sleep-related respiratory disturbances, particularly OSAs, are common in SCA6 (40 %) [170,176] and SCA3 (22–34 %) [164,186]. However, in SCA2, the prevalence and relative predominance of obstructive versus central apneas vary across studies: obstructive apneas are more common in a Brazilian cohort [187], whereas central apneas predominate in a Cuban cohort [168]. In SCA10, higher severity of sleep-related respiratory disturbances-as measured by the respiratory disturbance index (RDI)-is associated with less ataxia severity [166]. Case reports have also documented OSA in rarer subtypes such as SCA13 [185] and SCA17 [188].

Obstructive sleep apnea is frequently observed in CANVAS patients, affecting approximately 92 % of cases [179], whereas it is less common in Friedreich ataxia, with a prevalence of 16–21 % [182]. In these patients, the likelihood of respiratory disturbances during sleep is significantly associated with longer disease duration and genetic factors, specifically the smaller GAA repeat length in the Frataxin gene [180,189]. In Ataxia-telangiectasia (AT), another autosomal recessive ataxia, the low rates of airway obstruction are unexpected given that these patients exhibit severe bulbar weakness; nevertheless, polysomnography studies reveal poor sleep efficiency [190]. A recent epidemiological study reported that children with AT are six times more likely to experience sleep problems compared to healthy children [191].

Abnormal breathing patterns are also reported in patients with Joubert syndrome, a rare genetic disorder characterized by brainstem malformation and cerebellar vermis hypoplasia [192]. These patients exhibit episodic tachypnea in 35 %, apnea in 20 %, mixed tachypnea-apnea in 15 %, and snoring in 50 % of cases, likely due to brainstem dysfunction [193–195]. Additionally, paroxysmal motor events during sleep, including dystonic movements triggered by respiratory arousals, have been documented [196]. In Leigh syndrome, a mitochondrial disorder associated with ataxia [197], the patients commonly present with both obstructive and central sleep apnea, along with increased wakefulness, although their overall sleep architecture remains normal [198,199].

Insomnia is a frequent complaint among patients with SCA3 (38–55 %) [164,175], and SCA2 (22 %) [168], with case reports also describing insomnia in SCA12 [200], SCA13 [185], and SCA48 [201]. Additionally, excessive daytime sleepiness (EDS) is observed in SCA2 (18 %) [187], SCA3 (30–47 %) [155,165,202], and SCA6 [203], while in SCA1, EDS is typically associated with underlying fatigue [204,205]. In Friedreich Ataxia, insomnia occurs in slightly more than one-third of cases, though this finding has not been consistently replicated across all studies [180,182]. In CANVAS syndrome, poor sleep quality is observed in 62 % of patients, insomnia in 54 %, and excessive daytime sleepiness in 15 % cases [179].

Other sleep complaints include painful nocturnal cramps in SCA2 [168,187] and Friedreich Ataxia [182]; reduced dream recall in SCA2 [168], as well as nightmares [175,184], hypnagogic/hypnopompic hallucinations [164], and circadian dysfunction in SCA3. In this last case, the circadian function index was inversely correlated with ataxia severity [152]. In addition, hypersomnia has been reported in Kearns-Sayre syndrome [206], a rare mitochondrial ataxia [207].

Abnormalities in sleep architecture and microstructure are common features of hereditary ataxias (Fig. 5B). They are prominently marked by reduced or absent REM sleep, a consistent feature observed in SCA1 [208], SCA2 [167–169,187,208,209], SCA3 [155,162,208], and Friedreich's ataxia [210], with isolated cases also reported in SCA13 [185]. In general, the percentage of REM sleep in patients with SCA1, SCA2, and SCA3 (analyzed as a mixed cohort) was closely associated with ataxia severity and oculomotor disturbances during wakefulness. These findings highlight the challenges in accurately scoring REM sleep in these patients [208].

Notably, in SCA2 diminished REM sleep percentage and reduced rapid eye movement (REM) density are detectable during prodromal stages [211] and directly correlate with ataxia severity [168], underscoring their role as early biomarkers of disease progression. Moreover, prolonged REM sleep latency has been observed in SCA2 [187], SCA3 [155], SCA10 [166], and Friedreich's ataxia [210], with studies showing a strong correlation between increased latency and longer disease duration in SCA10 [166]. In addition, REM sleep without atonia have been reported in SCA2 [167–169], and SCA3 cases [155].

Regarding Non-REM sleep, reduced N2 stage duration has been observed in SCA2 [167–169] and SCA3 [155], with prolonged latency to N2 stage specifically documented in SCA2 [168]. Furthermore, K-complex activity is diminished in SCA2 patients and correlates with greater ataxia severity [212]. Studies have reported a significant reduction in sleep spindle density in SCA2 and SCA3 [209,212], and a complete absence of spindles in a case of Kearns-Sayre syndrome (KSS) [206].

Notably, in SCA2, sleep spindle deficits precede ataxia onset and are linked to impaired memory performance, serving as a mediator between

cerebellar atrophy and cognitive dysfunction [212,213]. These findings provide the first clinical evidence of the cerebellum's role in regulating sleep architecture and sleep-dependent cognitive processes.

3. Concluding remarks

The historical neglect of the cerebellum in basic and translational neuroscience has constrained our comprehension of brain function and dysfunctions [214]. Sleep science, too, reflects this oversight. However, emerging research over the past two decades has highlighting the cerebellum as an active participant in sleep regulation, not merely a passive motor structure [7,8].

Recent advances in understanding the cerebellum's role in sleep have significantly impacted sleep neurobiology by revealing its active participation in shaping sleep architecture and neural oscillations. Specifically, the cerebellum interacts dynamically with the neocortex and thalamus, influencing sleep stage transitions [48] and contributing to sleep spindle generation [32]. This spindle-generating function, combined with bidirectional cerebellum-hippocampus interactions during sleep [29], has important implications for understanding sleep-dependent memory consolidation, particularly for motor and procedural learning, as the cerebellum helps coordinate offline neural processing. In fact, these findings expand our understanding of how the cerebellum regulates cognitive abilities and emotions, two skills highly dependent on healthy sleep [215]. This phenomenon may underlie sleep-spindle dysfunction in cerebellar patients such as those with SCA2, where sleep spindles appear to mediate the link between cerebellar atrophy and memory deficits [213].

In addition, the cerebellar-driven spindles play a critical role beyond motor learning, influencing early cortical development. Disruptions in cerebellar development—sometimes termed developmental dyschisis—may impair the specialization of distant cortical regions involved in language and social interaction [216]. In disorders such as autism and schizophrenia, overlapping abnormalities in sleep spindles [217] and cerebellar structure [218] suggest that cerebellar dysfunction during sleep could also contribute to cognitive and socio-affective deficits.

However, whether additional specific mechanisms within the sleeping cerebellum contribute to learning and memory, or if its offline sleep processes operate through forward predictive models, remains an unresolved enigma. This critical gap underscores the need for further research to elucidate the precise neural computations and pathways by which the cerebellum supports sleep-dependent cognitive functions.

Moreover, improving our knowledge about the role of the cerebellum during healthy sleep also provides valuable insight into its function in sleep disorders, where it may facilitate adaptive responses to disrupted sleep processes and associated brain dysfunctions, as seen in conditions like chronic insomnia, OSAs and RBD. This “compensatory” role is not surprising given the well-established neuroplasticity of cerebellar circuits [219]. Nevertheless, the specific neuroplastic mechanisms underlying this function and the dynamics of these adaptations across time remain open questions that warrant further investigation. Anyway, it appears that maintaining a healthy cerebellum may serve as a valuable ally in protecting motor, cognitive, and emotional functions against the effects of sleep disturbances. But what happens when the cerebellum is impaired? Several studies have documented a wide spectrum of sleep disturbances in patients with cerebellar dysfunction [150], which likely result from the loss of the cerebellum's proposed “offline operator” and compensatory roles. Therefore, targeting cerebellar circuits could offer promising new therapeutic strategies for sleep disorders, mainly in conditions involving cerebellar pathology.

3.1. Potential cerebellum-targeted next-generation sleep therapies

To our knowledge, only three short studies have tested the efficacy of cerebellum-targeted neuromodulation approaches on sleep dysfunction, reporting significant improvements in euthymic bipolar disorder [80] and autism [81], but not in Alzheimer's disease [82], and none in primary sleep disorders or cerebellar ataxias. However, the plethora of cerebellar alterations associated with sleep disorders supports future disorder-specific strategies that map neural patterns onto tailored treatments, paving the way for precision sleep medicine (Fig. 6).

In such hypothetical framework, biomarkers of cerebellar activity—including MRI-based measures (VBM, fMRI), electrophysiological approaches (cerebellar EEG, polysomnography), and biochemical markers from magnetic resonance spectroscopy—could stratify patients into discrete subtypes, such as insomnia with Crus II hyperconnectivity, distinct RBD biotypes, or phenotypes with reduced spindle activity, thereby guiding personalized neuromodulation and/or pharmacological treatments to ameliorate the severity of sleep disorders (Fig. 6).

Table 1 summarizes proposed neuromodulation and pharmacological approaches designed to target abnormal lobule-specific cerebellar circuits underlying distinct sleep disorders and conditions with reduced sleep spindle activity.

For insomnia, maladaptive Crus II hyperconnectivity could be targeted with inhibitory neuromodulation protocols such as low-frequency rTMS, continuous theta-burst stimulation (cTBS), or cathodal transcranial direct current stimulation (tDCS). Moreover, adaptive lobule VIIb hyperconnectivity could be enhanced with excitatory TMS protocols such as high-frequency rTMS or intermittent theta-burst stimulation (iTBS) to sustain sensorimotor biopsychosocial regulation. Excitatory TMS to the atrophied, frontally hypoconnected lobule VIII could additionally restore network balance in insomnia patients.

For OSA, excitatory TMS could enhance adaptive hyperconnectivity of the right posterior cerebellum (lobules VI, VIIb, and Crus I/II) with the default mode network, supporting emotion, cognition, and language processing. RBD patients could benefit from tailored excitatory TMS protocols to preserve the adaptative lobule VIII-sensorimotor hyperconnectivity (Biotype 2) or to restore widespread cortical-subcortical-cerebellar hypoconnectivity in cases with typical neurodegeneration patterns (Biotype 1) [130].

In RLS, the maladaptive hyperconnectivity from right cerebellum (VIIb/VIII) to basal ganglia and sensorimotor cortices could respond to inhibitory TMS protocols, potentially reducing symptom severity. Finally, nightmares could be addressed with excitatory TMS-based protocols targeting right Crus II/VIIb hypofunction to restore fear memory suppression.

Additionally, excitatory neuromodulation techniques, such as iTBS targeting lobules VI-IX (primarily lobule VII, Crus I/II), can strengthen cerebellar drive to sleep spindles. This approach holds potential for ameliorating cognitive and socio-affective deficits in cerebellar ataxias and neuropsychiatric disorders like autism and schizophrenia, as well as for improve motor learning impairments in neurodegenerative diseases [220] and motor recovery post-stroke [221].

These neuromodulation approaches face significant challenges: targeting specific cerebellar sub-regions may differentially influence sleep outcomes, necessitating highly refined and precise therapeutic strategies; the benefits of cerebellar neuromodulation could be most pronounced in disorders with established cerebellar involvement whereas idiopathic sleep disorders may require combined cerebellar-cortical interventions; and while deep brain stimulation of the cerebellum for sleep applications remains experimental in humans, non-invasive brain stimulation offers a promising, lower-risk alternative-highlighting the importance of individualized and evidence-based approaches in the development of cerebellar neuromodulation therapies for sleep disorders.

Regarding pharmacological treatments, lobule-specific involvement presents a major challenge alongside distinct neural patterns across sleep disorders, hindering precise drug delivery to targeted regions and confirming neuromodulation as the standard for lobule-targeted cerebellar sleep therapies. However, cerebellum-specific GABAergic agents appear more plausible for RLS, where hyperactivity is reliably diffuse

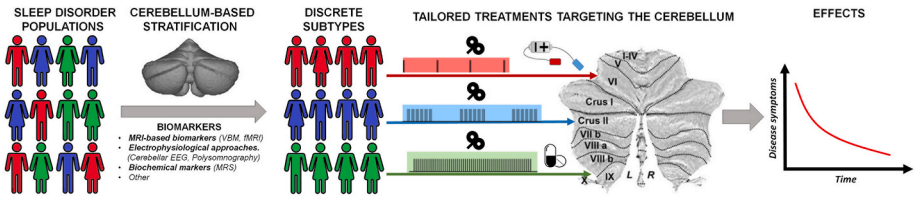

Fig. 6. Hypothetical framework for Precision Sleep Medicine Targeting Cerebellar Circuits. *MRI: Magnetic Resonance Imaging; EEG: Electroencephalography; MRS: Magnetic Resonance Spectroscopy.*

Table 1
Cerebellar phenotypes, targets, and therapeutical strategies in sleep disorders.

Sleep disorder	Main neural pattern	Tailored cerebelar target	Therapeutical approach	Expected impact
Insomnia	Maladaptative vermis Crus II hyperconnectivity correlated with severity	Vermis Crus II	Low-frequency rTMS, cTBS or cathodal tDCS	Dampen hyperactive cerebellar outputs contributing to arousal.
	Adaptative lobule VIIb hyperconnectivity	Lobule VIIb	High-frequency rTMS or iTBS	Reinforce adaptive hyperconnectivity to maintain biopsychosocial regulation.
	Lobule VIII atrophy with hypoconnectivity with frontal cortex inversely related to severity	Lobule VIII	High-frequency rTMS or iTBS	Restore hypofunctional circuit related to more insomnia severity.
OSA	Adaptative hyperconnectivity of lobules VI, VIIb, and Crus I/II with the default mode network	Lobules VI, VIIb, and Crus I/II	High-frequency rTMS or iTBS	Reinforce adaptive circuit maintaining emotions, cognition, and language
RBD	Adaptative lobule VIII –sensorimotor network hyperconnectivity	Lobule VIII	High-frequency rTMS or iTBS	Reinforce adaptive circuit maintaining motor homeostasis
	Widespread cortical-subcortical-cerebellar hypoconnectivity *(for RBD biotype 1)*	Posterior lobe	High-frequency rTMS or iTBS	Restore hypofunctional (atrophied) circuits
RLS	Widespread increase of cerebellar activity. Hyperconnectivity of right cerebellum with basal ganglia and sensorimotor cortices	Right posterior cerebellum (Lobule VIIb/VIII)	Low-frequency rTMS, cTBS or cathodal tDCS Cerebellum-specific GABAergic agents	Dampen hyperactive cerebellum-basal ganglia-sensorimotor circuit contributing to RLS
Nightmares	Inverse correlation between lobules Crus II/VIIb and nightmare severity	Lobules Crus II/VIIb	High-frequency rTMS or iTBS	Restore fear memory suppression and reduce nightmare generation.
Phenotypes with cognitive, socio-affective, and motor learning deficits	Reduced cortical and/or cerebellar-driven sleep spindles	Cerebellar posterior lobe	High-frequency rTMS or iTBS	Enhance cerebellar-driven sleep spindles to ameliorate cognitive, socio-affective, and motor learning deficits.

rTMS: repetitive transcranial magnetic stimulation; TMS: transcranial magnetic stimulation; cTBS: continuous theta-burst stimulation; iTBS: intermittent theta-burst stimulation; tDCS: transcranial direct current stimulation.

and low GABA levels is associated with symptom severity, serving as proof-of-concept [137].

In patients with cerebellar ataxias, characterized by significant cerebellar atrophy, personalized neuromodulation for treating comorbid sleep disorders presents the primary challenge that the cerebellar pathology is diffuse, often involving both motor and non-motor regions [148]. Therefore, any neuromodulation strategy must prioritize preserving or enhancing motor function. A promising approach involves sequential neuromodulation: first targeting ataxia-related circuits—primarily Crus II/VIIb/VIII hemispheres and vermis VIIb/VIII—to stabilize motor control [222], followed by modulation of the sleep-related circuits delineated here. This sequential strategy is physiologically grounded. It prioritizes motor integrity before targeting sleep networks, thereby minimizing the potential exacerbation of motor symptoms while harnessing the brain's residual cerebellar plasticity. This concept was satisfactorily demonstrated in SCA3 patients using rTMS across three distinct cerebellar targets, though focused solely on motor features [223].

Hence, the cerebellum constitutes an unexplored frontier for innovative next-generation sleep interventions. By charting the complex neural signatures of its varied subregions and harnessing its function as a broad-scale network regulator, precision sleep medicine can advance toward biologically anchored, clinically potent strategies.

3.2. Conclusions

In conclusion, the cerebellum emerges not as a passive motor coordinator but as a dynamic network modulator that fine-tunes sleep architecture and offline neural processing—essential for memory consolidation, cognition, and socio-affective functions. Its bidirectional interactions with thalamic, neocortical, and hippocampal networks underscore a pivotal role in both healthy and pathological sleep, offering a promising yet largely unexplored therapeutic landscape for next-generation precision sleep medicine.

CRediT authorship contribution statement

Roberto Rodríguez-Labrada: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Luis Velázquez-Pérez:** Writing – review & editing, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Perplexity.ai to assist with grammar and language editing, as they are not native English speakers, and to help synthesize the complex and extensive body of literature included in the review. After using this tool, the authors carefully reviewed and revised all content as necessary and take full

responsibility for the final version of the published article.

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Declaration of competing interest

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Data availability

This is a review article. All data discussed herein are available from the sources cited in the references.

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