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Review

The Sleeping Cerebellum

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We sleep almost one-third of our lives and sleep plays an important role in critical brain functions like memory formation and consolidation. The role of sleep in cerebellar processing, however, constitutes an enigma in the field of neuroscience; we know little about cerebellar sleep-physiology, cerebro–cerebellar interactions during sleep, or the contributions of sleep to cerebellum-dependent memory consolidation. Likewise, we do not understand why cerebellar malfunction can lead to changes in the sleep–wake cycle and sleep disorders. In this review, we evaluate how sleep and cerebellar processing may influence one another and highlight which scientific routes and technical approaches could be taken to uncover the mechanisms underlying these interactions.

The Cerebellum Is Still an 'Uncharted Land' in Sleep Research

Sleep is an important brain function that supports cognitive processes such as memory retrieval, learning, attention, language processing, decision making, and even creativity [1,2]. As a consequence, the neuronal circuitries and cellular mechanisms that underlie the transitions between wakefulness and sleep or between various sleep stages have been investigated thoroughly and have led to models about how such state transitions occur [3,4]. To date, based on **polysomnographic** (see Glossary) measurements, sleep can be subdivided into **rapid eye movement** (**REM**) and **nonrapid eye movement stages** 1–3 (**NREM**1–3; Figure 1A) [5].

Up to this point, sleep research has mainly focused on how these states correlate across the neocortical and subcortical structures, whereas cerebellar activity has been largely ignored. This neglect is intriguing, because malfunction of the cerebellum does not only impair motor control and motor memory formation [6–8], but it may also lead to changes in the sleep–wake cycle [9,10] and even cause sleep disorders [11]. Furthermore, decades of behavioral and physiological research has shown the positive impact of sleep on episodic memory formation. To what extent sleep is also critical for cerebellum-dependent **procedural memory** formation and motor control, however, is still under fervent debate. The cerebellum is well connected with the cerebrum and the neuronal circuitry underlying sleep–wake regulation (Box 1). In addition, many cerebellar neurons express clock genes associated with control of the circadian rhythm (Box 2). Nevertheless, a marked dearth of data exists on the relation between cerebellar processing and various sleep stages. It remains unclear whether the cerebellum enters sleep, and if so, whether cerebellar activity continues to change in line with the REM and NREM sleep stages and whether cerebellar activity may itself affect the process of sleep. Here, we review and evaluate studies of the neuronal activity of the cerebellum as well as its interactions with the cerebral cortex during sleep, address the question of how malfunctioning of the cerebellum may affect sleep, and, finally, ask to what extent sleep may affect cerebellum-dependent memory formation and **memory consolidation**.

Trends

Sleep supports cognitive processes and sleep disturbances are associated with neuropsychiatric syndromes as well as memory impairments.

To what extent the cerebellum sleeps and to what extent sleep is critical for the cerebellum-dependent memory formation and consolidation remain to be elucidated.

The cerebellum shows sleep stage–dependent activity and its malfunctions can lead to changes in the sleep–wake cycle, leading to sleep disorders.

The cerebral cortex and cerebellum strongly interact during both the awake state and sleep, and such interactions during sleep also contribute to consolidation of memories.

Given the sleep stage–dependent character of cerebellar activity and of the neocortical–cerebellar interactions, the role of this activity and these interactions for memory consolidation might strongly depend on the precise sleep stage and sleep architecture.

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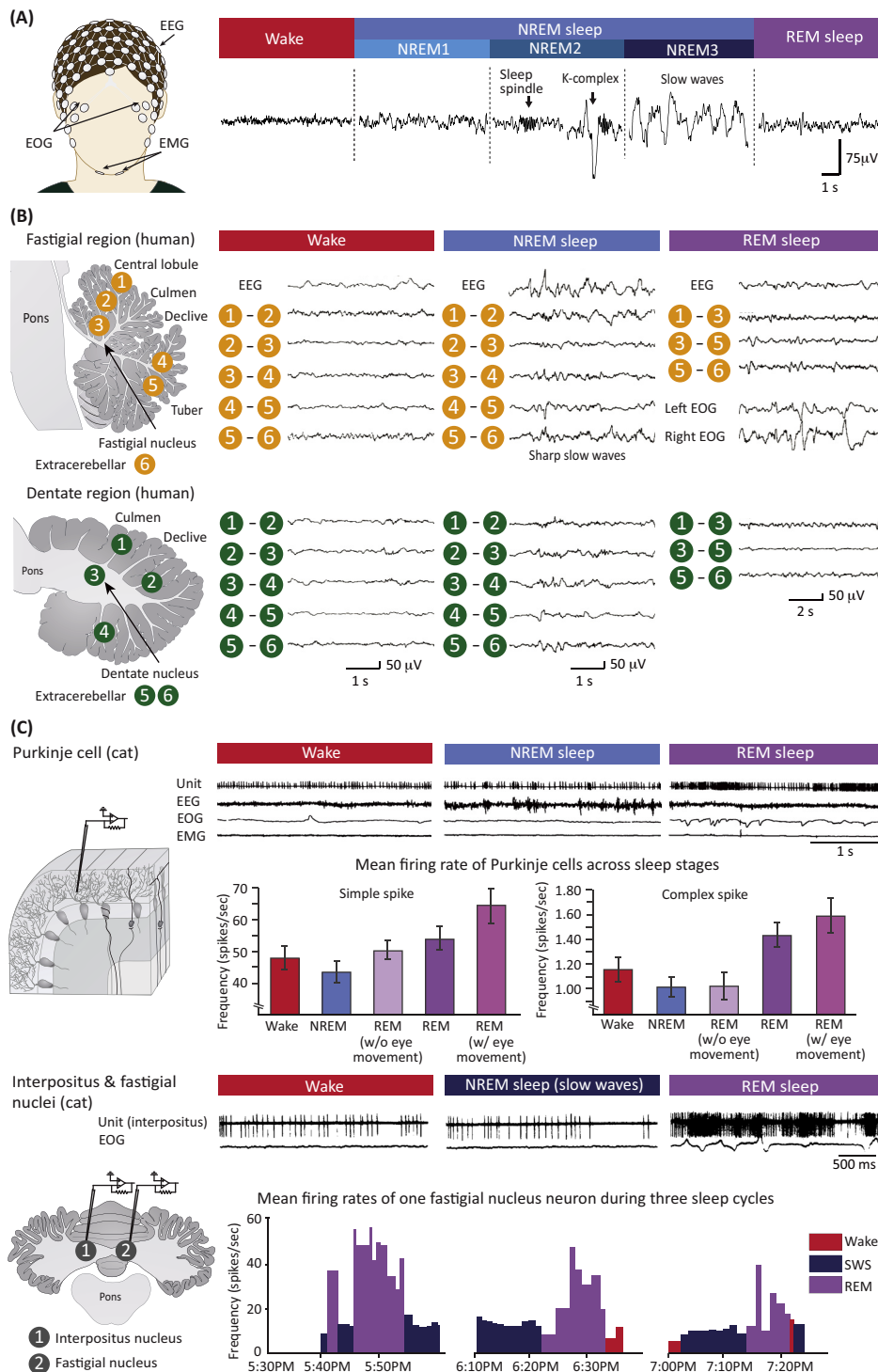c.canto@nin.knaw.nl (C.B. Canto).

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Glossary

Bistability: the phenomenon that a neuron can reside either in an active depolarized up-state or an inactive hyperpolarized down-state.

Cerebellar nuclei neuron (CNN): CNNs integrate information from the Purkinje cells as well as from the mossy fiber and climbing fiber collaterals, and they form the output neurons of the cerebellum as a whole.

Electroencephalography (EEG): a method to record electrical activity of the human brain from electrodes on a scalp surface.

Functional magnetic resonance imaging (fMRI): an imaging technique to measure the local changes of the magnetic resonance signal caused by the blood flow that is associated with neural activity.

Local field potential (LFP): averaged neural signal recorded from a local population of neurons with an extracellular microelectrode.

Memory consolidation: a neuronal process to stabilize newly acquired memories.

Nonrapid eye movement sleep (NREM sleep, stage NREM): NREM comprises three stages. K-complexes are single slow waves occurring typically in NREM2, while more continuous slow waves occur in what is considered deep sleep or stage 3 NREM sleep. They have a peak frequency of less than 1 Hz and together they are the highest-amplitude waves a healthy human brain can produce. They are caused by large groups of neurons simultaneously alternating between a hyperpolarized down state in which the neurons are inactive, and a depolarized up-state with irregular neuronal firing that may resemble the waking state. These slow waves appear to be a cortically generated phenomenon, as isolated cerebral cortex still produces slow waves. They can occur in separate cortical areas but may also involve multiple cortical regions simultaneously.

Polysomnography: the method to record human sleep states, combining the EEG and the electrical activity of the submental muscles, eye movements, and the heat rate.

Positron emission tomography (PET): an imaging technique to measure blood flow or oxygen metabolism reflecting neural activity

Figure 1. Human Scalp Electroencephalographic (EEG) Activity, Intracranial Recordings, and Extracellular Recordings of the Human and Cat Cerebellum during Different Sleep Stages. Neurophysiology of wake (red and left traces), nonrapid eye movement (NREM; blue and middle traces), and rapid eye movement (REM; right and purple traces) sleep. (A) Human scalp EEG recordings during waking, NREM1–3, and REM sleep. During waking the EEG is characterized by low-amplitude and high-frequency EEG. NREM sleep can be subdivided into lighter sleep stages

Sleep-Stage-dependent Cerebellar Activity

Classically, sleep has been characterized by identifying distinct phenomena at the level of the cerebral cortex. As such, sleep has been subdivided into two core sleep stages, (REM) (NREM) sleep, which cyclically alternate throughout the night. The characteristic sleep phenomena include K-complexes, spindles and slow waves in the various phases of NREM sleep, and theta waves during REM sleep [1,12]. Cerebellar activity during sleep was first detailed in the early 1970s. This activity was found to not only reflect the intrinsic activity of cerebellar neurons but also the activity of their afferents [7,13,14]. In addition to sparsely distributed monoaminergic inputs [15] (Box 1), the cerebellum receives two major afferents, the climbing fibers, originating from the inferior olive, and the mossy fibers, originating from a wide variety of sources in the brain stem [7] (see Figure IC in Box 1). The climbing fibers and mossy fiber–parallel fiber system converge on **Purkinje cells** and **cerebellar nuclei neurons**, which form the output of the cerebellar cortex and cerebellum as a whole, respectively. Whereas activity in climbing fibers elicits so-called complex spikes in Purkinje cells, that of mossy fibers and parallel fibers modulates Purkinje cells' simple spike activity (for review, see [7]). In cats, both climbing fibers and mossy fibers show relatively low and high levels of activity during NREM and REM, respectively [13,14], revealing the existence of sleep-stage-dependent cerebellar activity.

NREM-dependent Cerebellar Activity

In the cerebral cortex, NREM sleep can be subdivided into lighter sleep stages NREM1–2 and deep slow-wave sleep (SWS). K-complexes are single slow waves occurring typically in NREM stage 2, while more continuous slow waves occur in what is considered deep sleep or stage 3 NREM sleep [12]. They have a peak frequency of less than 1 Hz and together they are the highest-amplitude waves a healthy human brain can produce, caused by large groups of neurons simultaneously alternating between a hyperpolarized down state in which the neurons are inactive, and a depolarized up-state with irregular neuronal firing that may resemble the waking state [16]. These slow waves appear to be a cortically generated phenomenon, as isolated cerebral cortex preparations still produce slow waves [17–19]. Slow waves can occur

through the detection of gamma rays emitted from radionuclides.

Procedural memory: long-term unconscious (implicit) memory of skills.

Purkinje cells (PCs): the sole output neurons of the cerebellar cortex. PCs are GABAergic and intrinsically active, with a simple spike firing frequency ranging from approximately 30 to approximately 120 Hz dependent on the inputs from the parallel fibers and molecular layer interneurons. PCs also receive sensorimotor information from the climbing fibers, which generate complex spikes at a frequency of about 0.5 to 5 Hz.

Rapid eye movement sleep (REM sleep, stage REM): theta activity characterizes REM sleep, although not continuously. Particularly in animal experimental studies, striking so-called ponto-geniculo-occipital waves occur, coinciding with the eye movements.

Voxel-based morphometry: an analysis method to assess the volume of the cerebrospinal fluid, gray matter, and white matter of the brain.

NREM1–2 and deep slow-wave sleep (SWS). K-complexes are single slow waves occurring typically in NREM2. Spindles are short bursts of activity at a frequency of 10–15 Hz [20]. More continuous slow waves occur in what is considered deep sleep, NREM3, or SWS [12]. Slow waves are caused by large groups of neurons simultaneously alternating between a hyperpolarized down-state in which the neurons are inactive, and a depolarized up-state with irregular neuronal firing that may resemble the waking state [16]. Theta activity characterizes REM sleep, although not continuously. Particularly in animal experimental studies, striking so-called ponto-geniculo-occipital waves occur, coinciding with the eye movements. Human scalp EEG data were obtained from Eus J.W. van Someren (personal communication). (B) Human cerebellar nuclei show sleep activity during both NREM and REM sleep. (Top traces) Scalp EEG traces recorded during waking and sleep. (Lower traces) Human cerebellar local field potential recordings with the anatomical location of the recording sites drawn left. During NREM sleep, the fastigial trees show sharp slow wave-like activities, whereas the dentate trees show minor sharp slow waves. During REM sleep, the fastigial nucleus shows sharp slow waves, while the dentate nucleus shows less sharp slow waves. For the recordings of both the fastigial and dentate regions, each number denotes the location of the electrodes. Fastigial region: 1, rostral portion of central lobulus; 2, caudal (lower) portion of central lobulus; 3, culmen (5.5 mm dorsal to fastigial nucleus); 4, medullary substance between declive and tuber; 5, tuber; and 6, extracerebellar territory. Dentate region: 1, culmen; 2, declive; 3, dentate nucleus; 4, paramedian portion of biventer; 5 and 6, extra-cerebellar adjacent regions. The locations of the circles represent the locations of electrodes; as the authors did not specify the exact location or hemisphere of recording, this is an approximate location. The scales of the intracranial EEG used in the dentate region follow those in the fastigial region. Scalp EEG and intracranial recording images were adapted with permission from [21] (C). Cat Purkinje cell and cerebellar nuclei neuron activity during waking and sleep. (Left) The recording locations. (Upper graphs) Cat Purkinje cell activity. To classify waking and sleep stages, the EEG, electro-oculogram (EOG), and electromyogram (EMG) are displayed together with the unit activity of simple and complex spikes of an extracellularly recorded Purkinje cell [48]. Below the traces, the histograms of the mean (± standard error of the mean) simple and complex spike firing rates of cat Purkinje cells (N = 39) under five behavioral conditions are presented (wake, NREM, REM without (w/o) eye movement, REM, and REM with (w/) eye movement). Spike frequency decreases slightly during NREM, while it increases during REM sleep. (Bottom traces and histograms) In addition, cat cerebellar nuclei neurons [interpositus (upper traces) and fastigial nuclei (bottom histograms)] show an increase in firing frequency during REM sleep. Each histogram bin represents the time of occurrence of successive groups of 500 interspike intervals. The image of the cat cerebellum and the extracellular recording results were adapted with permission from [48,49,154].

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in separate cortical areas but may also involve multiple cortical regions simultaneously. Spindles, which typically present as short bursts of activity at a frequency of 10–15 Hz, probably originate in the thalamus from an interaction between the intrinsic GABAergic cells of the reticular nucleus and the glutamatergic thalamocortical cells [20]. At the level of the cortex, the end result is a characteristic waxing and waning spindle-like morphology.

In the cerebellum, **local field potentials** (**LFPs**) have been recorded during NREM sleep in humans since the 1970s. The fastigial and dentate nuclei of naïve epileptic patients implanted with electrodes in their cerebellar nuclei regions showed synchronous spike discharges during NREM and minor sharp potentials during REM activity [21] (Figure 1B). NREM sleep-related synchronized slow waves in the fastigial nucleus turned out to be sharper than those in the dentate nucleus, suggesting region-specific sleep-related cerebellar activity [22]. Initially, clean **electroencephalographic** (**EEG**) measurements of the cerebellum could only be obtained with such invasive recordings during and/or after neurosurgery [23–25], because external EEG recordings were often contaminated with signals from the visual cortex and/or neck muscles [26]. Moreover, identifying cerebellar signaling on the basis of external EEG and magnetic encephalographic data in humans was also complicated by the central location of the cerebellum and the difficulties in solving the inverse problem for estimating the current source of the EEG/magnetic encephalographic signals [27]. New approaches involving combinations of techniques, such as combined analyses of EEG and **functional magnetic resonance imaging** (**fMRI**) or **positron emission tomography** (**PET**) imaging data, partly resolved these issues. A combination of fMRI and EEG recordings indicated that cerebellar signals during NREM1 are lower compared with those during wakefulness [28,29]. Since cerebellar fMRI signals largely reflect mossy and parallel fiber activity [28,29], these fMRI studies support the notion that mossy fibers derived from the pons also contribute to cerebellar NREM sleep stages by decreasing their excitatory drive. The results of PET studies combined with EEG recordings also pointed toward decreased cerebellar activity during the transition from pre-sleep wakefulness to SWS [30–34]. During NREM2, cerebellar fMRI signals co-occurred with K-complexes [35] and sleep spindles [36] as measured with EEG from the neocortex, whereas during NREM3, cerebellar fMRI signals co-occurred with slow waves at the neocortex [29] (Figure 1A and [37]). The level of slow wave density associated with fMRI bold signals in the cerebellum was positively correlated with its gray matter volume as measured with **voxel-based morphometry** [37,38], providing possible explanations for intersubject variability of sleep EEG features as well as for interlobular differences within the cerebellum of individuals. Indeed, in both fMRI and PET studies, the reported changes in cerebellar activation have been mainly localized in the larger lobules IV, V, VI, and VII [29–32,34,36,37] (Figure 2).

Despite the advances in human imaging technologies, invasive animal studies, allowing simultaneous recordings of LFPs and activity of single neurons at a high spatiotemporal resolution, are essential to help us to better understand sleep-stage-dependent cerebellar

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Box 1. Neuromodulators Influencing the Wake–Sleep Network

Distinct neuronal networks and related afferent pathways with specific monoaminergic neurotransmitters are involved in regulation of wake–sleep stages. Many of these neurotransmitters influence cerebellar activity (Figure I), but their role in regulation of cerebellar processing during sleep has been neglected. Cell populations known to project to the cerebellum and to alter the state of arousal include the cholinergic, noradrenergic, serotonergic, histaminergic, orexinergic, and dopaminergic inputs. Injections of such monoamines or agonists of their receptors into the cerebellum can facilitate wakefulness and/or consolidation of various tasks, further supporting a role for neuromodulators during sleep-related cerebellum-dependent consolidation [102–105]. Most, if not all, of the monoaminergic systems also have widespread impact on other parts of the brain involved in sleep control. For example, the noradrenergic, serotonergic, and histaminergic neurons control the GABAergic galanin-containing neurons of the ventrolateral and median preoptic nucleus that become active during NREM [3], while orexinergic neurons can stabilize the switch between the wake–sleep-promoting networks [3,10].
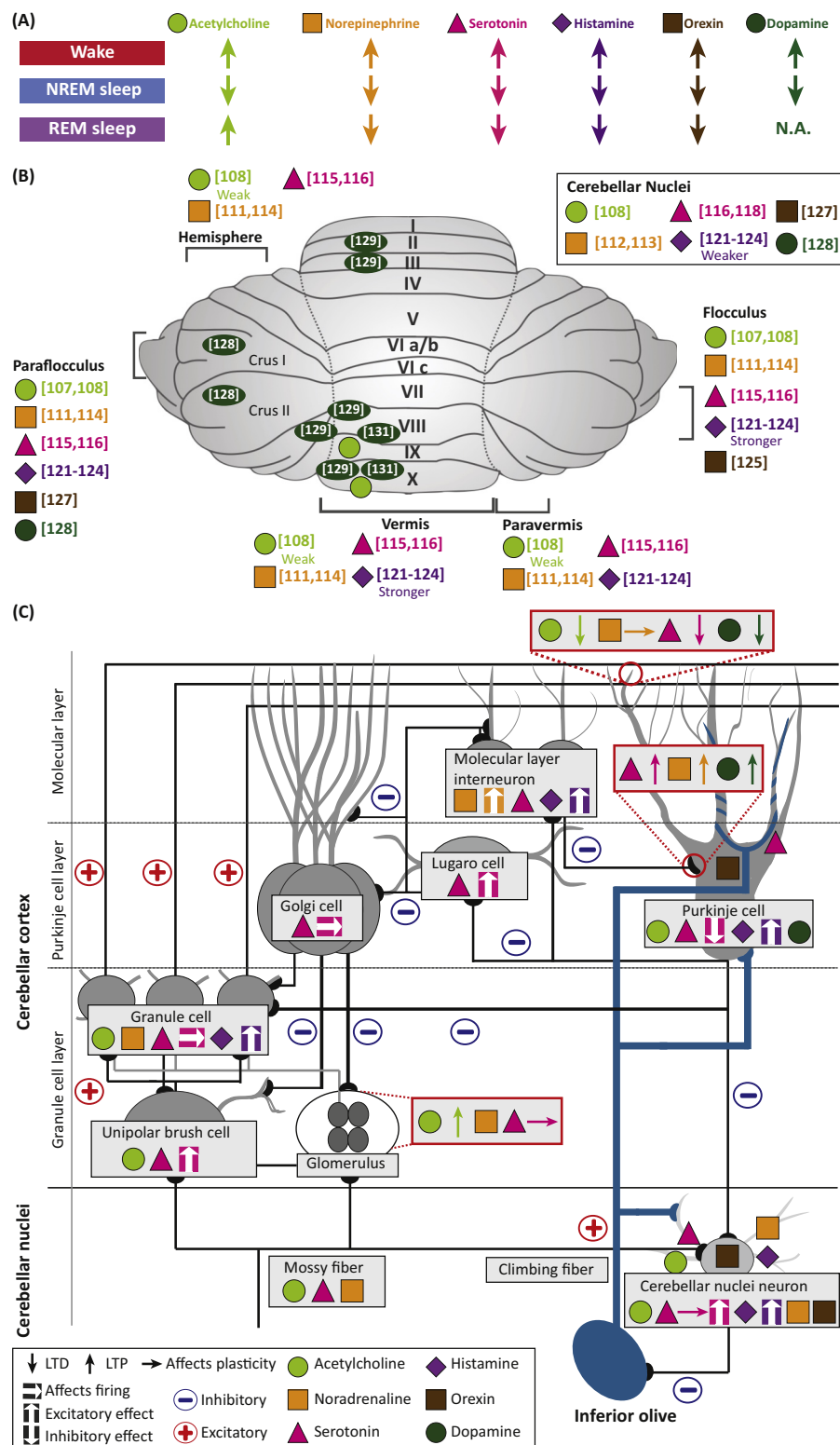
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Figure I. Cerebellar Inputs of Monoaminergic Neuromodulator Systems That Influence the Wake–Sleep Network. (A) Neuromodulator activity during sleep–wake cycles. In general, monoaminergic transmitters and Orexin

(Figure legend continued on the bottom of the next page.)

activity. Cerebellar signs of **bistability**, which is distinct for NREM3, have been studied in animals since the second half of the previous century [39]. Extracellular electrophysiological recordings of individual neurons in the cerebellar cortex and nuclei have been mainly performed in naturally sleeping macaques and cats. The firing frequencies of Purkinje cells as well as interpositus and fastigial cerebellar nuclei neurons do not show a difference in firing frequency between wakefulness and superficial NREM (Figure 1C) [40]. During deep NREM3 however, the percentage of short interspike intervals (<10 ms) of Purkinje cells decreases at the cost of that of longer intervals (>50 ms) [39,41]. Given that baseline simple spike activity of Purkinje cells is determined by intrinsic properties [22], the presence of long interspike intervals during deep NREM is consistent with activity observed during prevailing down- states following application of anesthetics [40]. The activity of climbing fibers and/or that of downstream interneurons may promote the alternation between up-states and down-states in Purkinje cells [42,43]. Because the inferior olive, in turn, may well be modulated by neocortical up-states and down-states [44], the cerebral cortex might impose its NREM state upon the cerebellum, at least in part, via the olive. However, general level setting systems, like the monoaminergic inputs to the cerebellum (Box 1), are also likely to contribute.

REM-dependent Cerebellar Activity

Although not continuous, REM sleep can be characterized by activity in the theta range. In addition, the REM sleep state shows the so-called ponto-geniculo-occipital waves, which can even coincide with the phase of the eye movements during REM [45]. In humans, both the hemispheres and vermis of the cerebellum show increased activity with PET [30] or fMRI [46,47] during REM, highlighting an increase in activity in their mossy fiber–parallel fiber pathways during this sleep stage. Likewise, in naturally sleeping cats and macaques, the activity of Purkinje cells and that of the cerebellar nuclei neurons both increase during REM, with the neurons in the fastigial nucleus showing the strongest trends [39,41,48,49]. Such a unidirectional effect on the firing frequency of cells that normally show an antiphasic behavior (see Figure IC in Box 1) can only be explained by common afferent inputs from a level setting system. Moreover, chronic recordings of the cerebellar nuclei of cats also show large-amplitude ponto-geniculo-occipital waves during REM [50]. Given the increased oculomotor activity during REM, it is not surprising that the simple spike firing frequency of Purkinje cells can increase during this sleep stage [48]. However, not all neurons, neither in the cerebellar cortex nor in the nuclei, show eye movement-related activity and not all changes in neuronal or field activity are purely motor related ([49,50] and Figure 1C). Interestingly, in their first 2 postnatal weeks, rats show myoclonic twitch activity during active sleep, a form of REM sleep, and the activity of their Purkinje cells and cerebellar nuclei neurons correlate with these movements. The rhythmicity of this activity diminishes after postnatal day 8 [51], highlighting the possibility that myoclonic twitches during active sleep support synapse maturation in the cerebellum during early postnatal development [51,52]. Taken together, the current data indicate that, in contrast

reduce their activity during NREM and are silent during REM. Cholinergic modulation is not only active during waking, but also during REM sleep. Ventral tegmental area (VTA) dopaminergic neurons are necessary for arousal and show reduced activity during NREM compared with waking [106] (adapted from [45]). (B) Distribution of modulators and corresponding receptors on a dorsal view of the rat cerebellar cortex, with numbers indicating the reference (see general list). Most modulators and receptors have a ubiquitous distribution across the cerebellum with weaker and stronger expressions dependent on the area. Its cholinergic inputs (light green) originate in pedunculopontine and laterodorsal tegmental nuclei [107,108]; its noradrenergic inputs (orange) originate in locus coeruleus [109–114]; its serotonergic inputs (pink) originate in dorsal raphe and pontine raphe nucleus [115–118]; its histaminergic inputs (purple) originate in tuberomammillary nucleus [119–124]; its orexinergic inputs (brown) originate in the lateral hypothalamic area [125–127]; its dopaminergic inputs (green) originate in the VTA and substantia nigra pars compacta [128–131]. (C) Overview presenting cerebellar layers and cell-type-specific distribution of neuromodulators together with the excitatory (+) or inhibitory (−) nature and their impact on plasticity (adapted from [15]) [14,107–131]. LTP and LTD indicate long-term potentiation and long-term depression, respectively. Soma and dendrites are color coded in gray, the axons in black. See legends in the Figure I for meanings of signals.

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to during NREM, cerebellar activity increases during REM, and that one or more level setting systems are likely to control the activity of the cerebellar cortex and cerebellar nuclei in a concerted action (Figure 1 and Box 1).

Sleep-Stage-dependent Cortico–Cerebellar Connectivity

The cerebellum is strongly and reciprocally connected with the cerebral cortex via the thalamus, pons, mesodiencephalic junction, and inferior olive, and the reverberating activity in this loop is heavily subject to the sleep–wake state [53–55]. At the onset of natural sleep, cerebellar nuclei neurons in cats show irregular, long bursts of spikes that are coherent with slow waves in the ventral lateral nuclei of the thalamus [56,57]. In addition, during anesthesia the inferior olive and crus II in the cerebellar cortex of rats contain LFPs and multiunit activity that are coherent with slow oscillations in the somatosensory neocortex. Similarly, cerebellar up-states and down-states in rats have been associated with an increase and decrease in multiunit activity in the cerebral cortex, respectively [44]. Connectivity studies in humans reveal that the functional connectivity within the cortico–cerebellar network remains intact during sleep, but differs between NREM sleep stages. Whereas the functional connectivity between cerebellum and cerebrum can be either increased or decreased during NREM2, during NREM3 it is generally decreased [58]. This relation does not only hold for various parts of the neocortex, including somatosensory cortex, motor cortex, insular cortex, supramarginal gyrus, and frontal and parietal lobes, but also for the thalamus [59,60]. During REM sleep, the left cerebellum lobule VI shows a negative correlation with the posterior cingulate cortex, while the right lobules IV and V show a positive correlation with the thalamus [60], highlighting that cortico–cerebellar connectivity remains functionally intact during sleep but that its relevance depends on the sleep stage and brain region involved.

Direct pharmacological and optogenetic manipulations of the activity of cerebellar nuclei neurons in awake mice modify oscillatory activity in the cerebral cortex under both physiological and pathological circumstances [24]. Coherence between oscillations and interactions between cerebellum and cerebrum also exist during natural spontaneous behavior and/or sensorimotor tasks in awake mice, rats, monkeys, and humans [44,55,61,62]. Still, it remains to be elucidated which parts of the cortico–cerebellar loop provide the most dominant impact on reverberating activity in the awake state as well as during various sleeping stages. Lesion studies in anesthetized rats suggest that the cerebral cortex has a larger role than the cerebellar cortex in that abolishment of neocortical oscillations causes a cessation in cerebellar slow oscillations, whereas bilateral removal of the cerebellar cortex does not significantly alter LFP or multiunit activity in the neocortex [44]. Moreover, connectivity analysis with the use of directed transfer functions in anesthetized rats indicates that the main flow of information during slow oscillations occurs from the neocortex to the cerebellum, with the somatosensory cortex having the strongest influence on cerebellar nuclei activity [63]. These data are in line with the fact that neocortical up-states can inhibit cerebellar nuclei neurons through activation of granule cells and Purkinje cells [63].
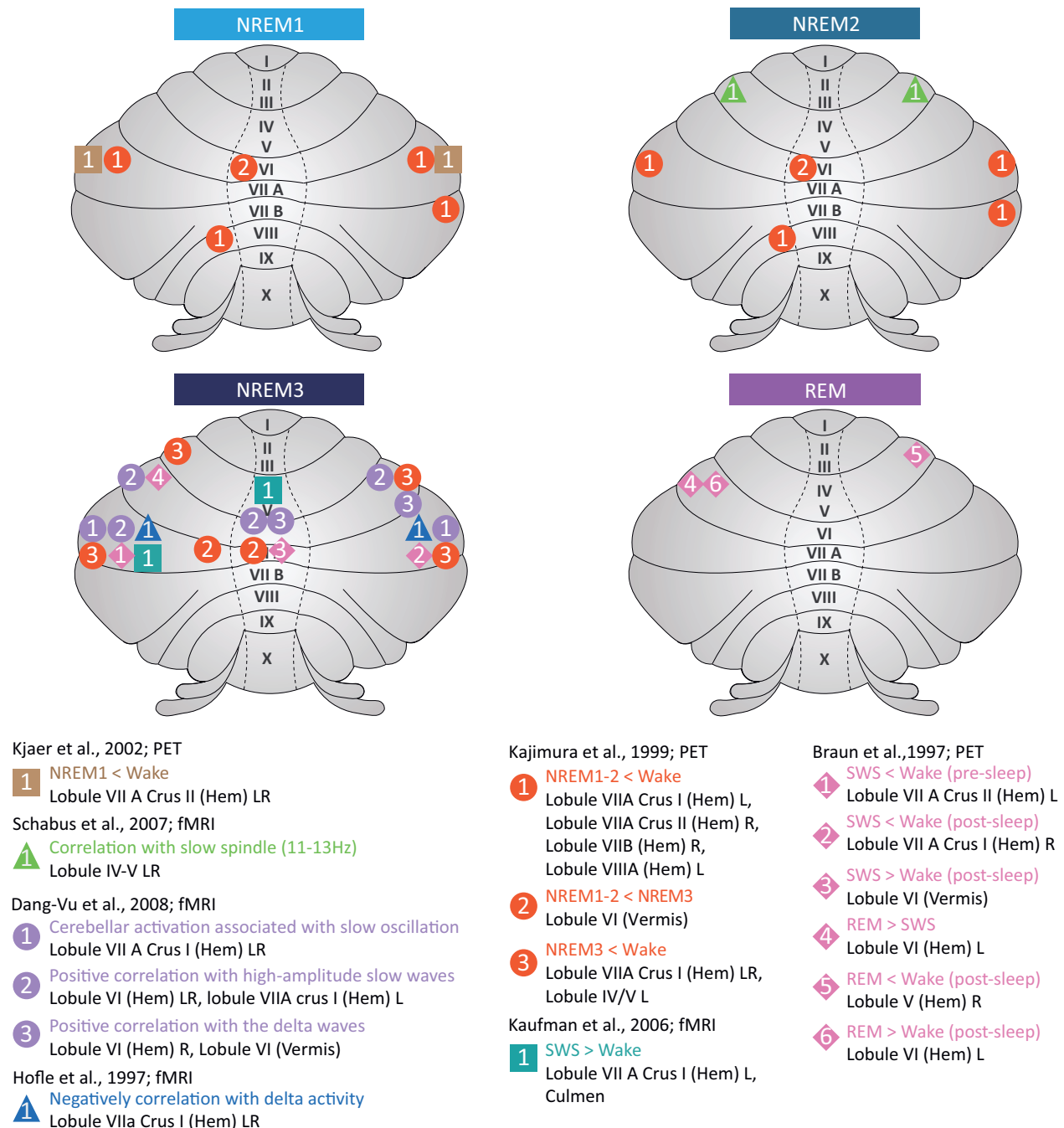
Figure 2. Human Cerebellar Activation Map during Various Sleep Stages Based on EEG–PET and EEG–fMRI Studies. Changes in cerebellar activation during NREM1 (light blue), NREM2 (blue), NREM3 (dark blue), and REM (purple). Changes in cerebellar activation have been mainly localized in the larger lobules IV, V, VI, and VII. The cerebellar label is redefined by a probabilistic atlas of the human cerebellum [155], referring to either Montreal Neurological Institute (MNI) or Talairach coordinates reported in [29–32,34,36,37]. Neither MNI nor Talairach coordinates in cerebellar regions are available in [33,35]. For display purposes, the locations of the circle labels do not correspond to the reported MNI or Talairach coordinates. If the awake period before and after sleep periods was analyzed and reported separately in an article, the additional labels, 'pre-sleep' and 'post-sleep', are mentioned after the term 'wake'. The recording modality (fMRI and PET) is mentioned after the reference. EEG, electroencephalographic; fMRI, functional magnetic resonance imaging; Hem, hemisphere; L, left hemisphere; NREM, nonrapid eye movement; PET, positron emission tomography; R, right hemisphere; REM, rapid eye movement.

Together, the findings obtained in animals and humans suggest that the neocortex entrains the cerebellum during slow oscillations, and conversely that the cerebellum may fine-tune neocortical forms of synchrony. Further pathophysiological studies, multivariate analysis, and machine learning techniques will help to elucidate cerebro–cerebellar connectivity during the various sleep stages [58,64].
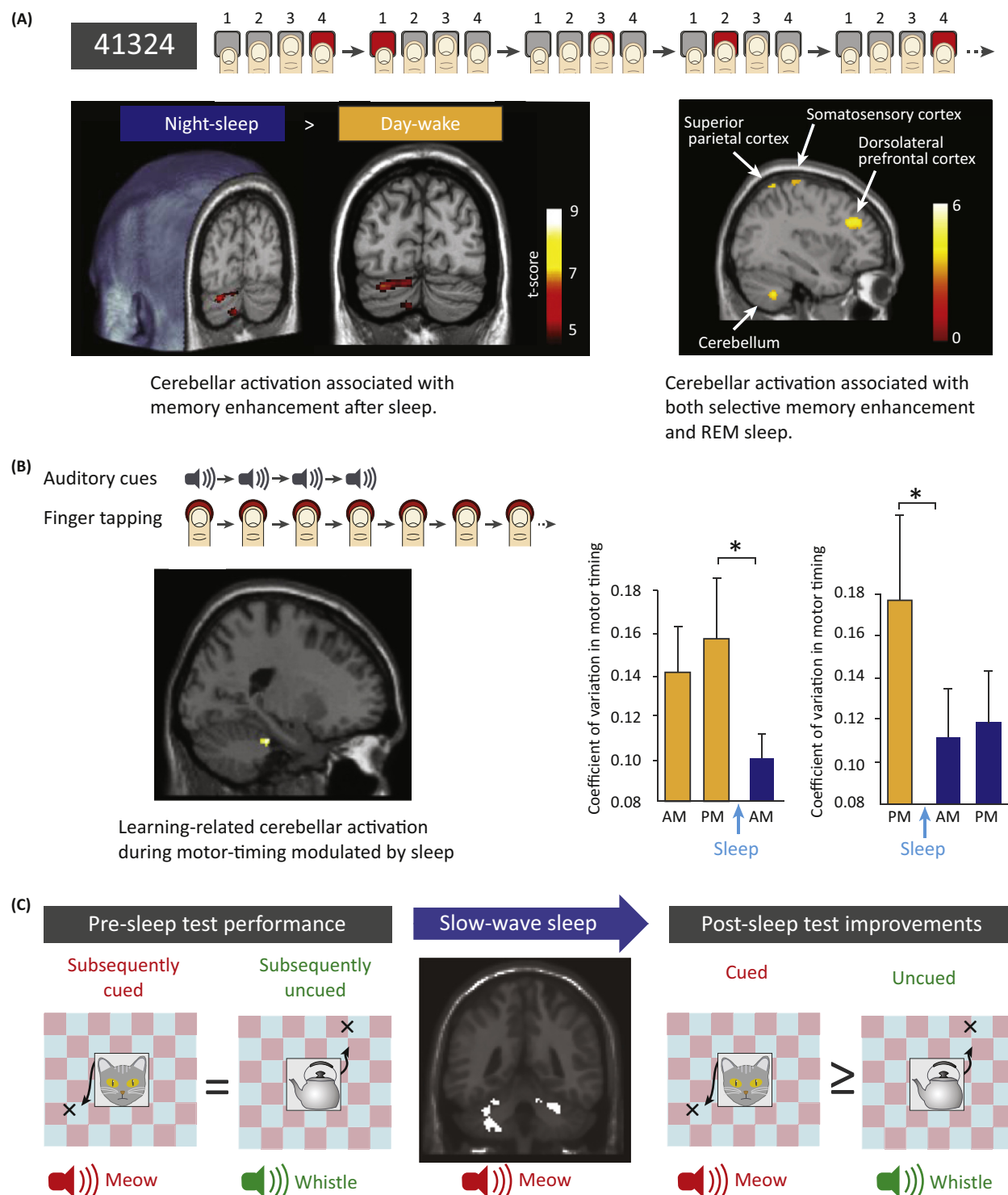
Sleep Disorders Can Lead to Cerebellar Malfunction and Vice Versa

Patients suffering from primary sleep disorders such as chronic insomnia, fatal familial insomnia, or obstructive sleep apnea accompanied by daytime sleepiness [65] show a decreased cerebellar volume [11,66]. Likewise, patients with REM sleep behavior disorder, which generates dream-enacting motor activity during REM, show a volumetric decrement in the anterior lobes of the cerebellar cortex and cerebellar nuclei [67,68]. Vice versa, patients suffering from primary malfunctions of the cerebellum can show a variety of sleep disorders (for a detailed review, see [11,69–73]). For example, patients with spinocerebellar ataxias [69,70,74,75], which are characterized by degeneration of the cerebellum and its afferent and efferent connections, can show increased daytime somnolence as well as NREM- and REM-related parasomnias. These data underline that the cerebellum fine-tunes neocortical forms of sleep-related activity. Along the same line, lesions of the cerebellar vermis and hemispheres in cats increase the mean duration of NREM and the total duration of REM periods, while decreasing the mean number of sleep periods throughout the sleep–wake cycle [10,76]. Moreover, lesions of the superior peduncle in cats, the sole output pathway of the cerebellum [7], result in a reduced mean duration and total time of NREM and REM sleep, respectively [9]. Thus, sleep disorders and cerebellar pathology are intricately involved with each other, and presumably due to the strong reciprocal projections between the cerebellum and cerebral cortex, they coexist relatively often.

Role of Sleep in Cerebellar Learning and Consolidation

Learning-dependent timing, procedural memory formation, and spatiotemporal predictions of motor actions, which are known to be controlled at least in part by the cerebellum [1,77–82], are facilitated by sleep [83] (Figure 3). Sleep improves the speed of tapping by 10–20% in sleep-dependent sequence learning tasks, such as the sequence finger-tapping task and serial reaction time task (Figure 3A) [78], and the subsequent level of post-sleep activity in the cerebellar cortex is correlated with the consolidation of the learned rhythmic motor activity [84] (Figure 3B). The gain in performance of the finger-to-thumb opposition task is correlated with the amplitude of sleep spindles and depth of REM sleep [85], while a reduction in sleep spindle duration, as occurs during aging, cannot only be associated with a decrease in gray matter volume of the cerebellum, but also with deficits in consolidation of motor memories [86]. The parts of the cerebellum that are activated during the execution of a serial reaction time task during wakefulness are significantly more active during REM sleep in subjects previously trained on the task than in nontrained subjects [87–89]. Sleep deprivation affects not only the acquisition of classical eyeblink conditioning, which is known to depend on an intact cerebellum [90], but also the functional connectivity between the lateral cerebellar nuclei and the neocortical superior temporal sulcus following learning of pursuit and rotation tracking tasks [91].

The data presented above support the hypothesis that memory traces for both sequence and trajectory learning are partly processed and consolidated during sleep in humans. How sleep promotes consolidation of cerebellum-dependent memories remains a topic for further research. One of the interesting options is that new collaterals from mossy fibers, climbing fibers, and/or nucleocortical afferents sprout in the cerebellar nuclei and cortex overnight and form massive new connections following procedural learning [6,92,93]. This could also explain why cerebellar learning may at first largely depend on rapid plasticity in the cerebellar cortex, and subsequently, as the memory stabilizes, on more gradual plasticity in the cerebellar and

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(A)

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Night-sleep > Day-wake

Cerebellar activation associated with memory enhancement after sleep.

Superior parietal cortex
Somatosensory cortex
Dorsolateral prefrontal cortex
Cerebellum

Cerebellar activation associated with both selective memory enhancement and REM sleep.

(B)

Auditory cues

Finger tapping

Learning-related cerebellar activation during motor-timing modulated by sleep

Coefficient of variation in motor timing

AM   PM   AM
Sleep

PM   AM   PM
Sleep

(C)

Pre-sleep test performance

Subsequently cued   Subsequently uncued

Meow   Whistle

Slow-wave sleep

Meow

Post-sleep test improvements

Cued   Uncued

Meow   Whistle

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Figure 3. Cerebellum-Related Memory Consolidation during Sleep. (A) Motor sequence learning. In a serial reaction time task (top), human subjects are tested on how fast and accurate they press a predefined sequence before and after waking or sleeping. The result (left) shows an increased activation during the task of left cerebellar lobules VI and VII, from before to after sleep [156]. In a task requiring the subject to associate motor sequences with sounds, the cerebellar activations corresponding to the selective enhancement of the specific motor sequence correlated with REM sleep duration (right) [87]. (B) Temporal learning. In a motor timing task

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Box 3. Theoretical Models Explaining Sleep-dependent Memory Consolidation

Although the underlying neural mechanisms for memory consolidation during sleep are still under debate, there are two dominant explanatory models: the reactivation and synaptic homeostasis model. The reactivation model proposes that the reactivation of learning-related neural patterns in sleep strengthens the neural network of acquired memory prior to sleep [138,139]. Both hippocampal place cells and primary visual cortex cells in rodents reactivate a sequential pattern of the learned route of a maze during NREM [140,141]. This pattern, which is especially prominent during SWS, is temporally compressed and accompanied by sharp-wave ripples.

Such reactivations during NREM may even induce the formation of postsynaptic dendritic spines in pyramidal cells, highlighting structural phenomena that may provide a substrate for consolidation [142]. Importantly, although [142] shows reduced synapse formation after sleep disturbance, the data do not exclude the possibility that improvement was driven by sleep facilitating intrasession learning or offline consolidation [143]: spine formation may also be related to bouts of waking. Nagai and colleagues [143] used the same task and showed that improvement followed both sleep and sleep deprivation.

The synaptic homeostasis model states that the synaptic strengths saturated during cognitive processing are 'sheared off' during sleep, especially SWS, leaving task-relevant synaptic connections intact and freeing up capacity for subsequent learning [144–146]. Reports in rodents and *Drosophila* support the possibility that net synaptic strength is increased during waking and decreased during SWS [147,148]. For example, the expression level of synaptic proteins is high in the awake state and low during sleep [149].

Theoretical models developed to explain cerebellum-dependent learning have largely focused on the 'internal model' [150,151]. This model describes a neural process estimating the future states of the motor system through the interpretation of the external sensory inputs at present (forward model), and allows this estimate in turn to be used to provide the commands to the motor system to shift the present state to the objected state (inverse model).

Although sleep researchers have inferred that the underlying mechanism of sleep might help the development of an internal model [79,152], there is little direct evidence to support it. Recently, a theoretical model that integrates the reactivation model with cerebellar internal, forward and inverse, models has been proposed to optimize consolidation during sleep [153]. A future challenge lies in further combining theoretical models describing sleep-dependent memory consolidation with concepts of realistic cerebellar electrophysiological and neuroanatomical phenomena, such as bistability, intrinsic plasticity, and overnight sprouting, to obtain a deeper understanding of the role of sleep in cerebellum-dependent memory formation and consolidation.

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vestibular nuclei, downstream [94–98]. The role of sleep in consolidation of cerebellar memory formation is also supported by the precise sequence of changes that occur over the course of long-term skill learning. For example, Fogel and colleagues [99] showed that on the night that human subjects are first exposed to a procedural task, the density of fast spindles increases significantly during both NREM2 and SWS, whereas on the night that the subjects become experts, they show increased REM sleep duration while the spindles become larger in terms of amplitude and duration during SWS. Re-exposure to the task 1 week later results in increased NREM sleep duration, and again, increased spindle density of fast spindles during SWS and NREM2, which is correlated with overnight improvement in speed and accuracy of the task, highlighting putative cerebellar involvement. Interestingly, re-exposure to the actual task in the awake state may not even be required for enhancing consolidation. Neural representations of experiences can also become reactivated during sleep itself, stabilizing associated memories in long-term memory (Figure 3C). van Dongen and colleagues [100] initiated this reactivation process for specific memories on object–sound–location associations during SWS and showed that post-sleep memory accuracy was positively correlated with sound-related fMRI signals during sleep in the thalamus, medial temporal lobe, and cerebellum. Sleep may not only

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(upper left), subjects synchronized the timing of their button press with the auditory cues and kept pressing even after the cues disappeared [84]. The results (right) showed that the relative variation in the temporal difference between button presses and learned rhythm significantly decreased after sleep. fMRI analysis (lower left) revealed that learning-related cerebellar activation during motor timing was modulated by sleep. (C) Multisensory learning. In an object-location task (spatial memory and discrimination), participants learned the location of object pictures displayed on the grid pattern background, while sounds were presented simultaneously (left) [100]. Subsequent to the learning session, participants were asked to place the object images on the memorized locations. The cerebellar activity during the task-related sound presentation (middle image) during slow-wave sleep was positively correlated with the performance level of the post-sleep task (right). Images were adapted with permission from [84,87,100,156]. fMRI, functional magnetic resonance imaging; REM, rapid eye movement.

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promote consolidation of procedural memories formed during the day, but it might also have an impact on the first acquisition of very new memories. Indeed, Fifer and colleagues [101] showed that new associative reflexes like conditioned eyeblink responses can be readily acquired in infants while sleeping. It remains to be elucidated to what extent the putative down-states of cerebellar neurons at the various sleeping stages directly affect acquisition and consolidation of procedural memories [40]. The positive correlations provided earlier highlight the probability that sleep has an advantageous impact on both motor and cognitive forms of implicit learning, several of which may be mediated by the cerebellum.

Concluding Remarks and Future Perspectives
Many studies indicate that the cerebellum shows activity patterns characteristic of sleep and vice versa that this activity may affect sleep architecture. In general, cerebellar activity is increased during REM sleep compared with NREM sleep. All afferents, including not only the climbing fiber and mossy fiber pathways, but also the classical level setting systems, may exert regulatory effects on sleep state-dependent cerebellar activity. The output neurons of the cerebellum show clock gene expressions and are well connected with the wake–sleep network. Malfunctions of the cerebellum lead to changes in sleep, but not to abolishment of sleep. Further investigations involving multiple single-unit recordings of both cerebellar and extracerebellar neurons during various sleep stages are necessary to evaluate cerebellar physiology and its dynamic interactions with other cortical and subcortical structures (see Outstanding Questions). The cerebellum plays an important role in memory formation of motor and possibly also cognitive skills as well as the consolidation thereof. The functional role of individual sleep stages in cerebellar processing may change during memory formation and consolidation, and shift from upstream cerebellar cortical activity to downstream structures. All these aspects should be further investigated from a theoretical perspective (Box 3), integrating existing knowledge of physiological data, cerebellum-dependent learning models, and models of memory consolidation during sleep.

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