



Review

Thalamic Stroke: An Opportunity to Study the Brain Mechanisms of Sleep–Wake and Cognition

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Abstract: The thalamus, and its projections to the cerebral cortex, are crucial for regulating sleep rhythms, such as sleep spindles, and for maintaining arousal and sleep homeostasis. Moreover, they play a significant role in memory, executive functioning, and attention. Altered thalamocortical circuitry caused by vascular lesions affects sleep–wake architecture and may contribute to cognitive deficits observed in thalamic stroke patients. This review summarizes the biology of the thalamus and current knowledge regarding the impact of thalamic circuitry on sleep regulation and cognition, drawing from clinical and pre-clinical studies. Furthermore, deep brain stimulation and transcranial magnetic stimulation are discussed as possible therapeutic approaches targeting thalamic circuits. Understanding the role of the thalamus in sleep and cognition opens new avenues for developing novel therapeutic strategies to improve sleep and cognitive functions in affected individuals.

Keywords: thalamus; cognitive functioning; sleep; memory; sleep spindles; slow waves; attention; arousal; stroke; thalamic stroke



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1. Introduction

Cognition refers to the ability of the brain to perceive, identify, memorize, and remember complex stimuli as a fundamental aspect of brain function. Conversely, cognitive dysfunction is an umbrella term covering deficiencies in any cognitive domain (e.g., memory), usually defined as a decline in neuropsychological performance [1].

Cognitive functioning is linked to demographic, developmental, genetic, cardiovascular, and metabolic profiles, with cognitive dysfunction being most common in neurological and psychiatric illnesses including brain injury, progressive neurological diseases, and depression [2,3]. Cognitive dysfunction also manifests in diagnostically healthy individuals, for example after sleep deprivation [4].

Sleep is another factor that is related to cognition and cognitive dysfunction: sufficient sleep is necessary for normal cognitive performance, whereas sleep–wake disorders (SWD) are associated with cognitive dysfunction [4]. While the specific functions of sleep are still a matter of ongoing research, they may include memory consolidation, brain clearance, anabolism, and plasticity [5,6]. Indeed, clinical studies have demonstrated the negative impact of SWD (i.e., insomnia, sleep-disordered breathing (SDB), daytime dysfunction, rapid eye movement (REM), sleep behavior disorder) and alterations in sleep duration on cognitive abilities [7–9].

Several brain circuits have been identified as being particularly significant for sleep–wake and cognition. They include the reticular activating system (arousal, attention, sleep–wake transitions, and circadian rhythms [10]), the cortical–hippocampal–cortical circuit (sleep-dependent memory consolidation [11,12]), the basal forebrain circuit (REM sleep, cortical activation, attention [13–15]), and the prefrontal–amygdala circuit (sleep-related emotional reactivity, attention [16–18]).

Emerging research provides compelling evidence for the crucial role of sleep in plasticity and memory consolidation [19–24]. Through a dynamic interaction between hippocampal (HC) and neocortical networks, new memories, acquired during wakefulness, transform into stable long-term representations during sleep. During NREM sleep, information flows via complex loops characterized by the co-occurrence of slow waves (transient oscillatory events between 1 and 4 Hz), spindles (oscillations between 10 and 16 Hz), and hippocampal ripples. This process optimizes plasticity [25] and leads to long-term synaptic modifications, often in a region-specific manner. Slow waves and spindles are known to be generated and modulated by thalamocortical loops, which rely on a delicate balance of excitation and inhibition in thalamic and cortical circuits. Furthermore, the coupling of hippocampal and neocortical networks requires interregional cross-frequency coordination, incorporating sleep oscillations such as slow waves and spindles in thalamocortical circuits, along with hippocampal ripples driven by hippocampal–entorhinal cortex synaptic activity [26,27]. Despite accumulating evidence, gaps still exist in our understanding of the mechanisms supporting memory consolidation. These mechanisms might include the propagation of slow oscillations propagating from the anterior to the posterior cortex and the consistent occurrence of spindles in centroparietal regions.

In summary, sleep, as an essential physiological process, has a paramount impact on brain functioning. Impaired sleep may lead to cognitive dysfunction and impede restorative processes, potentially contributing to chronic conditions. Recognizing the importance of sleep and addressing SWD is crucial for sustaining optimal cognitive function and overall well-being.

This review focuses on the thalamus and its associated neuronal circuits, with the aim of providing a current synopsis of their role in sleep and cognition. Studying thalamic lesions enables researchers to follow an experiment of nature that offers a unique view for investigating sleep and cognition. Therefore, case–control studies involving patients with isolated thalamic stroke were analyzed to determine the impact of thalamic vascular lesions on sleep and cognition in humans. Additionally, the article explores the function of thalamic circuits based on experimental studies. Finally, prospective therapeutic approaches targeting the thalamus are discussed.

2. Thalamus and Anatomical Vascular Territories

The thalamus of mammals encompasses several groups of nuclei with predominant specialized roles, including the anterior nuclei (cognition, sleep), medial nuclei (cognition, sleep), ventral and lateral nuclei (motor and sensory processing), geniculate nuclei (vision and hearing), pulvinar (attention and visuo-spatial orientation), and intralaminar nuclei (pain and spatial orientation) [28–31]. The evolutionary development of the forebrain, including the thalamus, occurred independently in various groups of vertebrates [32]. Nonetheless, mammals share a considerable proportion of structures (Figure 1A). The thalamus is densely interconnected with the cerebral cortex in primates, forming reciprocal relationships critical for consciousness, perception, and cognition [33].

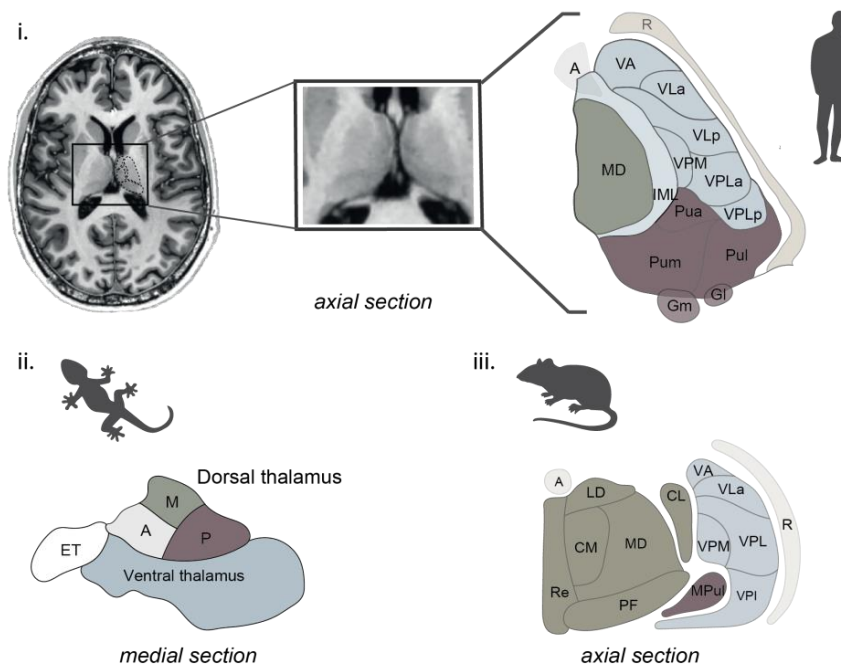
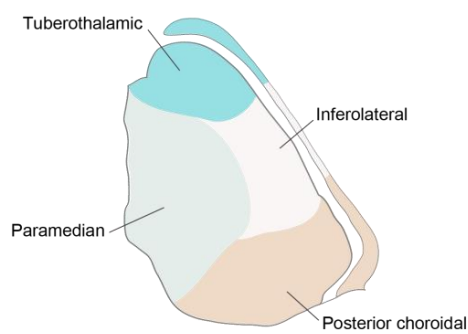
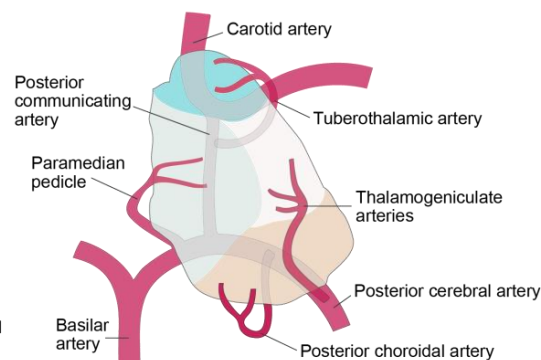
A. Anatomical parcellations across species**B. Thalamic vascular territories****C. Vascular supply of the thalamus**

Figure 1. The thalamus in humans. (A) A 7T T1-weighted MRI of the human thalamus and main thalamic nuclei. Main thalamic nuclei across species: (i) anatomical parcellation from the human thalamus (adapted from [31]). (ii) Salamander (adapted from Wicht, 1988 [34]), and (iii) mouse (adapted from Jankowski, 2013 [35]) and human (adapted from Mai & Majtanik, 2017 [36]). (B) Vascular supply of the thalamus. (C) Thalamic vascular territories. Abbreviations: A—anterior, CL—centrolateral, CM—centromedial, ET—eminencia thalami, Gl—lateral geniculate, Gm—medial geniculate, IL—intralaminar, LD—laterodorsal, M—medial, MD—mediodorsal, PF—parafascicular, Pua—pulvinar anterior, Pul—pulvinar lateral, Pum—pulvinar medial, R—reticularis, VA—ventral anterior, VLa—ventrolateral anterior, VLp—ventrolateral posterior, VPLa—ventroposterolateral anterior, VPLp—ventroposterolateral posterior, VPM—ventroposteromedial.

Although specificities in connectivity or activity exist between species, these differences in complexity are thought to fulfill needs in the physiological regulation of each species. The pulvinar, for example, is the largest thalamic nucleus in primates, and it has evolved to be particularly large and complex in humans compared to other mammals [28]. The causes for this development are most likely related to the primates' unique behavioral and cognitive abilities (e.g., visual information processing, coordination of responses to visual stimuli, and integration of visual data with other sensory modalities [37,38]). However, the precise roles of the pulvinar are still being researched. Similarly, the human prefrontal cortex is markedly larger than that of other primates and rodents and may be shaped by

human-specific executive functions, emotions, and social interactions [39]. Additionally, neuronal firing patterns may vary between rodents and humans, reflecting subtle differences in sleep–wake cycles. For example, the quicker sleep–wake cycle in rodents might correspond to faster shifts in neuronal activity in the hypothalamus [40–42] in response to metabolic need, which differs between species.

In terms of vasculature, the thalamus is predominantly supplied by small vessels originating from the posterior communicating artery and the P1 and P2 segments of the posterior cerebral artery [43] (Figure 1C). Despite the wide variation, thalamic vascular supply is categorized into anterior, paramedian, inferolateral, and posterior territories [44]. The vascular supply of the thalamus in rodents follows similar principles. In mice, for example, the thalamus is mostly supplied by the branches of the posterior cerebral artery; however, the exact distributions of small branches may vary [44]. Furthermore, it should be noted that the anterior choroidal artery is responsible for supplying the dorsal part of the thalamus in mice, whereas this vascular supply is not observed in humans [44].

Despite the challenges arising from the lack of standardized nomenclature, particularly with respect to the lateral nuclei, discrepancies in anatomical variation, the impact of age-related microstructural degradation [36], and interspecies variations, investigations involving human and animal subjects provide valuable insights into understanding the role of the thalamus in sleep and cognition. Table 1 summarizes case–control studies in thalamic stroke patients, whereas Box 1 and Figure 2 illustrate the principles applied to the models of thalamic stroke in rodents.

Box 1. Stroke animal models.

The validation of animal models used to study brain disorders relies on (1) the ability of those models to re-capitulate human disorders and physiological response to treatments; (2) the level of similarity between their symptomatology and that found in humans; and (3) the analogy between the etiology of the disorder in mice and in humans. During the history of stroke research, several models of this pathology have been developed, all presenting advantages and disadvantages. Stroke animal models offer the opportunity for invasive measurements and interventions that are not feasible in human studies. Techniques such as electrophysiology, optogenetics, pharmacological manipulations, and recently stroke lesions in the thalamus (Figure 2) can provide detailed in-sights into thalamic activity and its impact on sleep and cognition. Lastly, animal models facilitate longitudinal and developmental studies, enabling the investigation of dynamic changes in thalamic structure and function over time from the onset of the stroke. Moreover, animal models permit the study of the thalamic vasculature, providing insights into the relationship between thalamic blood flow, neuronal activity, circuit plasticity, and cognitive processes. By leveraging these advantages, animal models play a crucial role in advancing our understanding of the thalamus and its contributions to sleep, cognition, and vascular dynamics.

Table 1. The overview of case–control studies in thalamic stroke (TS) patients compared to the control group investigating sleep and cognitive functioning.

Reference	TS		Control		Time Post-Stroke	Sleep Symptoms	Sleep Assessment	Sleep Alterations	Cognitive Assessment	Cognitive Domains Affected
Santamaria et al., 2000 [45]	Unilateral TS	N = 13	Age- and sex-matched volunteers	N = 18	7–21 dps	Hypersomnolence, daytime sleepiness, altered level of consciousness	PSG	↓ TST, ↓ NREM2, ↓ SS density	-	-
Hermann et al., 2008 [46]	Paramedian TS	N = 31	Age-matched patients with PNS	N = 12	5–30 dps	Hypersomnolence, psychomotor slowing	PSG	↑ NREM1, ↓ NREM2, ↓ SS density, ↓ SS power	Attention, executive functioning, verbal memory, visual memory, object naming	Attention, executive functioning, verbal and visual memory
Danet et al., 2015 [47]	Unilateral left TS	N = 12	Age- and education-matched volunteers	N = 25	<90 dps	-	-	-	Executive functioning, verbal memory, visual memory, object naming	Verbal memory, executive functioning, object naming
Kraft et al., 2015 [48]	Isolated unilateral TS	N = 16	Age- and sex-matched volunteers	N = 52	1–132 mps	-	-	-	Computer-based attention tests	Spatial bias, processing speed
Wu et al., 2016 [49]	Minor TS	N = 27	Age and sex-matched volunteers, ↑RDI in TS	N = 12	14 and 90 dps	Hypersomnolence, daytime sleepiness	PSG	↑ SL, ↓ SE, ↑ NREM1, ↓ NREM2, ↓ NREM3	Global cognitive functioning, verbal memory	Global cognitive functioning, verbal memory
Mensen et al., 2018 [50]	Uni- and bilateral TS	N = 9	Young healthy adults	N = 9	5–8 dps	-	hd -EEG	↓ SS power	-	-
Jaramillo et al., 2021 [51]	Unilateral TS	N = 12	Age-, sex- and AHI-matched extrathalamic stroke patients	N = 11	3 dps	Daytime sleepiness	hd -EEG	↓ SWA	Visual memory, visuospatial functioning	No significant differences
Temel et al., 2021 [52]	Thalamic hemorrhage	N = 28	Age-, sex- and AHI-matched volunteers	N = 28	3–6 mps	-	-	-	Global cognitive functioning, verbal memory, executive functioning, verbal fluency	Global cognitive functioning, verbal memory, executive functioning, verbal fluency
Scharf et al., 2022 [53]	Unilateral TS	N = 37	Age- and sex-matched volunteers	N = 37	1, 6, 12, 24 mps	Hypersomnolence, reduced vigilance	-	-	Attention, executive functioning, verbal memory, visual memory, verbal fluency	Verbal memory, executive functioning, verbal fluency

AHI—apnea-hypopnea index, dps—days post-stroke, ESS—Epworth Sleepiness Scale, hd-EEG—high-density EEG, mps—months post-stroke, PSG—polysomnography, SE – sleep efficiency, SL—sleep latency, SS—sleep spindle, SWA—slow wave activity, TS—thalamic stroke, TST—total sleep time.

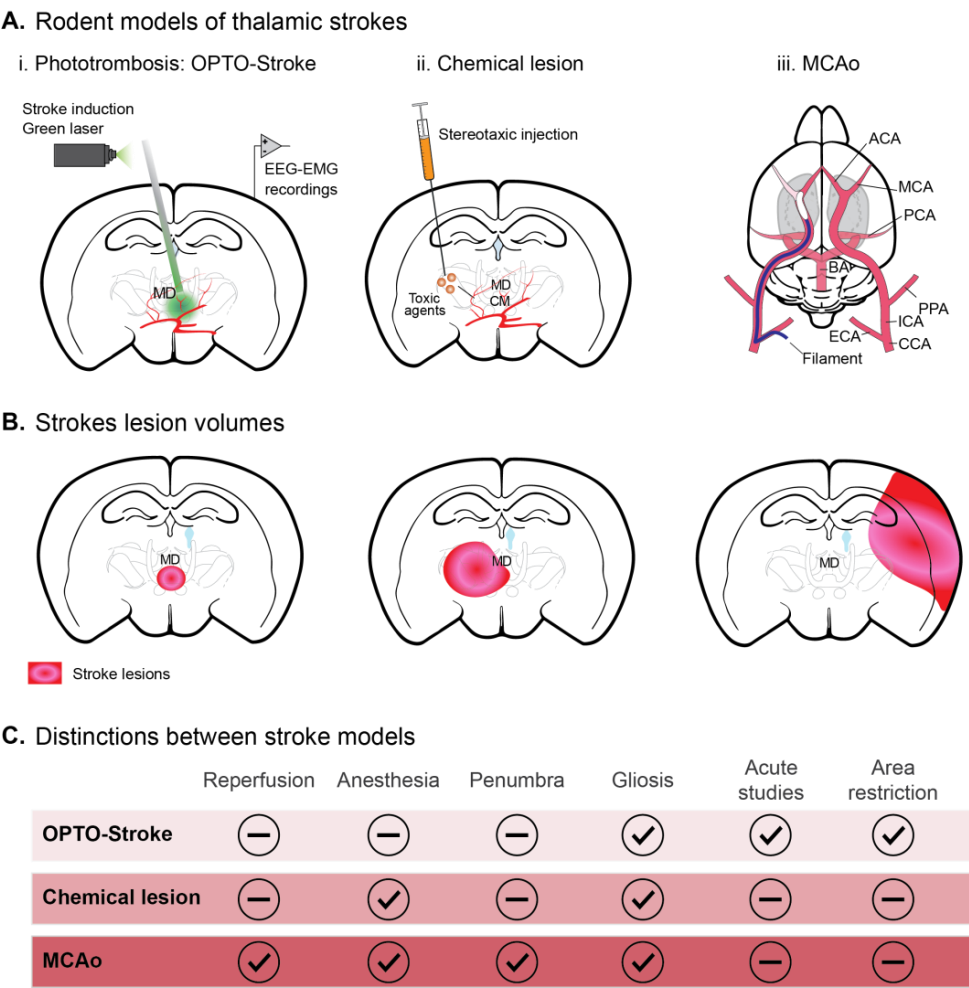


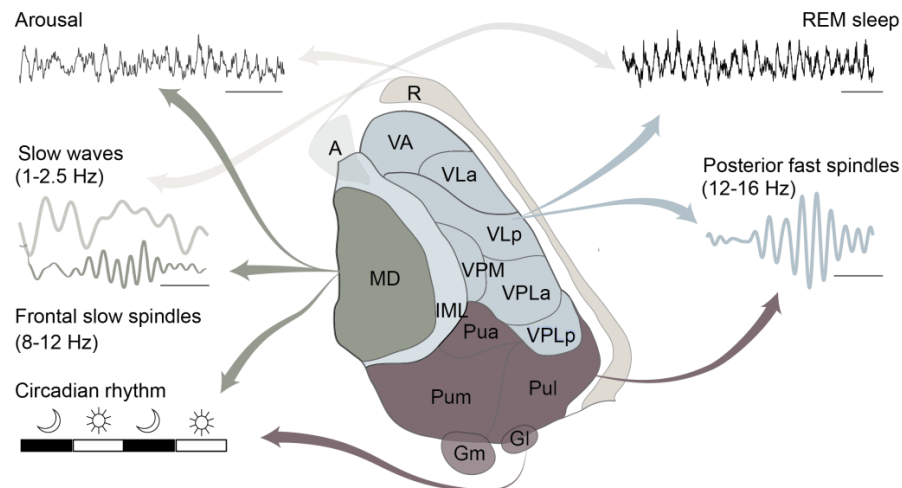
Figure 2. Models of thalamic stroke in rodents. **(A)** Experimental manipulations. **(i)** Phototrombosis. Opto-STROKE: This method involves injecting a photosensitive dye into the bloodstream and then activating it with focused light to induce clot formation in a specific thalamic vessel. The new approach to light-induced stroke allowing increased spatial resolution is opto-STROKE [54]. **(ii)** Chemical lesion: Direct stereotactic injection. Agents like excitotoxins (e.g., NMDA or quinolinic acid) or thrombotic agents (e.g., endothelin) can be injected directly into the thalamus to create localized lesions that mimic the effects of a stroke [55,56]. **(iii)** MCAo model: Middle Cerebral Artery (MCA) Occlusion (MCAo) via a filament inserted through the external carotid artery to MCA origin. Although the MCA primarily supplies the cerebral cortex, this method can affect deeper structures like the thalamus, depending on the extent and duration of the occlusion [57]. **(B)** Schematic representation of the stroke lesion across animal models shown in **(A)**. **(C)** Key distinctions per stroke model. Abbreviations: ACA—anterior cerebral artery, BA—basilar artery, CCA—common carotid artery, ECA—external carotid artery, EEG—electroencephalography, EEG—electromyography, ICA—internal carotid artery, MCA—middle cerebral artery, MCAo—middle cerebral artery occlusion, MD—mediodorsal thalamus, PCA—posterior cerebral artery, PPA—pterygopalatine artery.

3. The Thalamus and Sleep

The thalamus plays a multifaceted role in sleep regulation and involves several complex aspects (Figure 3A). Firstly, the thalamocortical circuitry is of paramount importance for the generation and coordination of electroencephalographic (EEG) rhythms during sleep. Sleep spindles, which are the cortical manifestations of thalamic neuronal oscillations, are affected in patients with thalamic stroke [58]. Section 5 provides details about the effect of thalamic lesions on sleep spindles. According to studies conducted on humans, the anterior, mediodorsal, and posterior thalamic nuclei are involved in spindle gener-

ation [47–50]. However, little is known about the thalamic contribution to functionally distinct sleep spindle subtypes, predominantly frontal slow (8–12 Hz) and predominantly parietal fast (12–16 Hz) spindles [59,60]. Fast spindles have been linked to sleep-dependent memory consolidation [60], whereas knowledge about slow spindles' function is sparse. The neuroimaging study by Schabus et al., which showed that thalamic peak voxels for slow spindles were compatible with the mediodorsal nucleus, while peak voxels for fast spindles were compatible with the ventral posterior lateral and pulvinar nuclei, lends support to the heterogeneity in thalamic sleep spindle regulation [61].

A. The role of the thalamus in sleep



B. The role of the thalamus in cognition

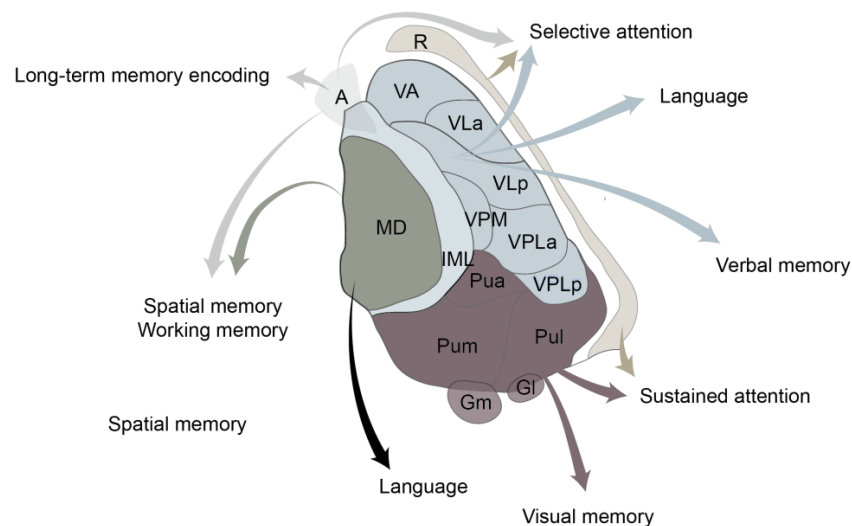


Figure 3. The functions of the thalamus. **(A)** The role of the thalamus in sleep. **(B)** The role of the thalamus in cognition. Abbreviations: A—anterior, CL—centrolateral, CM—centromedial, ET—eminientia thalami, GI—lateral geniculate, Gm—medial geniculate, IL—intralaminar, LD—laterodorsal, M—medial, MD—mediodorsal, PF—parafascicular, Pua—pulvinar anterior, Pul—pulvinar lateral, Pum—pulvinar medial, R—reticularis, VA—ventral anterior, VLa—ventrolateral anterior, VLp—ventrolateral posterior, VPLa—ventroposterolateral anterior, VPLa—ventroposterolateral posterior, VPM—ventroposteromedial. Parcellation adapted from Carrera [31].

Spindles originate mainly in the thalamus during sleep, and are modulated through corticothalamic and intrathalamic mechanisms [62–70], while thalamic slow waves, large-scale neuronal activity, are principally driven by global cortical activity [71]. Throughout

the slow oscillations, neocortical and thalamic neurons fluctuate between periods of intense synaptic activity (up states) and almost complete silence (down states) [72]. An experimental study in naturally sleeping–waking rats showed that blocking thalamic output to the neocortex markedly (up to 50%) reduced the frequency of slow waves; however, the selective stimulation of thalamocortical neurons enhanced slow waves in a low delta frequency band (0.75–1.5 Hz) [73]. Clinical studies in thalamic stroke lesions have further contributed to the evidence for the role of the thalamus in sleep, which is emphasized in Section 5 of this review. Moreover, the evidence from intracranial recordings from human epilepsy patients demonstrated that slow oscillations in the anterior thalamus precede neocortical slow oscillations, whereas concurrently recorded slow oscillations in the mediodorsal thalamus are led by neocortical slow oscillations [74].

Thalamocortical networks, which include the reticular nucleus and the neocortex, have been shown to enhance cortical slow oscillations and decrease arousal [75]. Alternative evidence suggests that the thalamus plays a regulatory role in the states of wakefulness and alertness, operating within the context of the ascending reticular arousal system, which serves as the primary network responsible for arousal in the brain [76]. During wakefulness, this system originates in the brainstem and activates the thalamus and the cortex via a well-defined ‘bottom-up’ pathway [76]. Local interactions may also be considered, in which thalamic-layer-specific inputs into the cortex may reflect arousal degrees [77,78]. Recent studies suggest the existence of a less investigated ‘top-down’ pathway that also contributes to arousal maintenance. This ‘top-down’ pathway includes the projections from the neocortex (salience network), amygdala (to the medial geniculate nucleus), or hypothalamus to the thalamus [76,78–83]. The mediodorsal thalamus, which is part of the paramedian vascular territory, projects to the prefrontal cortex and has been identified as a key effector in the arousal circuitry [84]. Additionally, glutamatergic neurons of the paraventricular thalamus (PVT), a component of the mediodorsal thalamus, are highly active during wakefulness [81]. PVT suppression reduces wakefulness, while PVT activation induces a transition from sleep to wakefulness [81]. The projections from the nucleus accumbens and from hypocretin neurons in the lateral hypothalamus to PVT glutamatergic neurons act as effector pathways for wakefulness [81]. It has been demonstrated that stimulating the ventromedial thalamus causes awakening from NREM sleep and cortical activation [85]. Furthermore, it has been demonstrated that a brainstem-to-mediadorsal thalamic glutamatergic pathway mediates sound-induced arousal from slow-wave sleep, enabling the transition to wakefulness [86]. Overall, the mediodorsal thalamus constitutes a key diencephalic node that controls forebrain arousal.

Lastly, the thalamus might regulate circadian rhythms. Experimental studies have shown that PVT is interconnected with the master circadian pacemaker, the hypothalamic suprachiasmatic nucleus, and is densely innervated by orexinergic neurons, which play a key role in arousal and state transitions [87]. Furthermore, PVT [87] and intergeniculate and ventrolateral geniculate nuclei [88] all receive direct and indirect photic input that might contribute to the transition to vigilance in response to light. Similar results were acquired by Chrobok et al., who identified the lateral geniculate nucleus as a light-entrainable oscillator, whose phase may be advanced by retinal input at the beginning of the projected night [89]. Finally, in mice, the centromedial thalamus was found to modulate transitions between sleep stages, transitions between sleep and wake, and brain-wide cortical activity during sleep [90].

Albeit less investigated, the recent evidence points to the involvement of the thalamus in the regulation of REM sleep, as it receives cholinergic activation from the brainstem during this sleep stage [91]. In mice, the optogenetic activation of neurons in the anterior dorsal thalamus increased the sleep spindle rate and the likelihood of transition to REM sleep [92]. Moreover, imaging studies of sleep have shown high activity in the thalamus during REM sleep [93–95], especially during phasic REM sleep [95,96]. Notably, projections from the central medial thalamus to the prefrontal cortex have been found to modulate parvalbumin cells in cortical layers 2/3, which are necessary for the consolidation of emo-

tional memories during REM-sleep [97]. Although experimental findings suggest that the thalamus is involved in the regulation of REM sleep, no significant differences in REM sleep quantity have been observed in thalamic stroke patients [45,46,50,51]. The microarchitecture of REM sleep (e.g., saw-tooth waves) in thalamic stroke patients is still not well characterized, and this topic may open new avenues for future research.

4. The Thalamus and Cognition

Clinical studies have greatly advanced our understanding of the role of the thalamus in cognition and consciousness [42,57,60,65,93]. Section 5 provides insights into the impact of thalamic vascular lesions on sleep and cognition.

Based on corroborating works in the clinical literature, experimental studies conducted on rodents have demonstrated that lesions in the anterior thalamic nucleus result in substantial deficits in reference, spatial, and working memory. Supporting the clinical literature, experimental studies in rodents have demonstrated that the lesions of the anterior thalamic nucleus led to substantial deficits in reference, spatial, and working memory [98,99]. Consequently, the lesions of the anterior thalamic nucleus disrupted the processing of environmental cues and the monitoring of the position of the animal within the environment [100]. These spatial impairments align with the electrophysiological properties of the anterior thalamic nucleus, which contains cells encoding information about spatial location [101–103]. A study in mice has confirmed that the anteroventral subdivision of the anterior thalamic nucleus is required during the maintenance phase of a spatial working memory task. This function engages the anteroventral–parasubiculum–entorhinal cortex circuit [101–103]. Moreover, the lesions of the anterior thalamic nucleus impair performance when animals are expected to combine item memory with additional features, like temporal order and location [104,105]. The anteromedial thalamus preferentially encodes salient memories and gradually increases correlations with the cortex to facilitate the tuning and synchronization of cortical ensembles, as well as the gating of long-term memory consolidation in the cortex [106].

Similarly, lesions of the mediodorsal thalamic nucleus in rodents cause impairments in spatial and temporal discrimination [107], but temporal order memory impairments following the lesions of the anterior thalamic nucleus emerge only in the presence of multiple items [108,109]. While the lesions of the mediodorsal thalamic nucleus disrupt performance in spatial and working memory tasks, this is due to strategic components of the task rather than deficiencies in spatial memory [110]. Remarkably, memory deficits were correlated with spindle and slow wave decline following opto-stroke [54]. This supports the prevailing assumption that the mediodorsal thalamus plays a crucial role in working memory due to its projections to the prefrontal cortex [111,112].

The thalamus regulates attentional selection, and all major components appear to be involved. A functional magnetic resonance imaging study in healthy volunteers showed the role of the ventrolateral and, notably, anterior thalamus in biasing attention [113]. Responses in the ventrolateral and anterior thalamic nuclei tracked the learning of the predictiveness of abstract associations and their application in directing attention [113]. Moreover, a study in epileptic patients demonstrated that the high frequency electric stimulation of the anterior thalamus improved attentional capture by emotional stimuli [114]. According to an experimental study in ferrets, theta oscillations in the posterior thalamus play a central role in orchestrating thalamic signaling during sustained attention [114]. Using multi-electrode recordings in mice, Chen et al. demonstrated that the neurons of the thalamic reticular nucleus, which are associated with sleep spindles, were also linked to alpha oscillations during attention [115].

Figure 3 provides a simplified summary of the role of the thalamus in cognition based on reports in human and animal models.

5. Thalamic Stroke: A Model for Sleep-Dependent Plasticity and Cognition

Table 1 outlines how thalamic stroke can cause a wide range of SWD and cognitive deficits. Given the profound impact that sleep and cognitive functioning have on the recovery process and overall quality of life after stroke, medical practitioners could derive significant advantages from understanding these symptoms.

Hypersomnolence is a distinguishing feature of sleep symptoms associated with thalamic stroke. This phenomenon, which has been well-documented in multiple case-control studies and case reports, is particularly prevalent in patients with anterior (80%) and paramedian (50%) thalamic stroke [53]. In some cases, hypersomnolence may manifest as up to 20 h of daily sleep behavior [116]. Moreover, patients with thalamic stroke may exhibit the symptoms of excessive daytime sleepiness [117]. Specifically, an Epworth Sleepiness Scale score in thalamic stroke patients was reported as a mean of 8–9 points, compared to 5–6 in the control group (extrathalamic and no-stroke) [49,51]. The stroke restricted to paramedian thalamus was described as being associated with severe arousal disturbances. In the case of a patient with bilateral thalamic stroke, the arousal index, both in NREM and REM sleep, was lower in acute stroke compared to 6 weeks post-stroke [118].

These sleep alterations were mostly linked with the features of non-rapid eye movement (NREM) sleep in thalamic stroke patients. Individuals with paramedian thalamic stroke and severe hypersomnia, for example, experienced a reduced quantity of slow-wave NREM3 sleep [116]. The reduction in NREM2 and NREM3 in thalamic stroke patients was also described in comparison to an age- and sex-matched no-stroke control group [45,49]. Overall, vigilance disturbances are more common in patients with bilateral paramedian compared to unilateral paramedian thalamic stroke (92% versus 21%) [119].

There is consistent evidence that thalamic stroke alters NREM-sleep microarchitecture. Several studies reported the decrease in slow spindle density and power in thalamic stroke patients [45,46,50]. Sleep spindles were the most affected in frontal and central regions [46]. Mensen et al. showed that left-sided and bilateral lesions of the paramedian thalamus affect sleep spindles to the larger extent compared to right-sided lesions using high-density electroencephalography (hd-EEG) [50]. However, since the study is small (N = 9) and the authors do not report the lesion volume, the effect of the lesion volume rather than its laterality on sleep spindles cannot be ruled out. An additional hd-EEG study showed the reduced overnight slow wave (SW) slope changes in thalamic versus extrathalamic stroke [51]. Interestingly, the subjective sleepiness in these patients tended to be high in patients with a pronounced reduction in overnight slope changes [51].

Considering the well-known role of sleep spindles and slow waves in neuroplasticity [60,120], changes in NREM-sleep microarchitecture following thalamic stroke might underlie the cognitive deficits described in these patients. However, the primary impact of the thalamic lesion on these cognitive deficits remains unclear.

Among the most noteworthy cognitive manifestations in thalamic stroke are thalamic amnesia and thalamic dementia. Thalamic amnesia, a memory impairment unique to thalamic stroke, often results in deficits in verbal and working memory, but not in visual memory [46,47,49,53]. Danet et al. showed that lesions of the mammillothalamic tract and of the mediodorsal thalamic nucleus cause memory impairment, more severely in the case of the mammillothalamic tract and less so in the case of the mediodorsal thalamic nucleus, thus highlighting the role played by these two structures in memory circuits [47]. In addition, verbal memory deficits have been attributed to lesions in anterior and inferolateral vascular territories, whereas visual memory impairments have been reported in lesions affecting posterior territory [43,46,48,53].

In contrast, thalamic dementia—typically caused by anterior or paramedian thalamic stroke [46,53,121,122]—is characterized by temporal and spatial disorientation, behavioral changes (e.g., agitation or apathy), the impairment of executive functions (e.g., abstract thinking, working memory, cognitive flexibility), attentional deficits, and the relative preservation of motor or sensory functions [46,121–125]. Such complex impairments accentuate the role of the thalamus in diverse cognitive functions.

Moreover, other deficits of high brain functions have been described in thalamic stroke and have been attributed to specific lesion topography. Cohort studies have reported instances of mood lability, including depression and anxiety in thalamic stroke patients [46,121–125]. However, the evidence concerning the association of mood disturbances with thalamic stroke topography is limited. Liebermann et al. showed that patients with lesions of the posterior thalamus had significantly more emotional disturbances and elevated anxiety levels (Hospital Anxiety and Depression Scale, Anxiety Score) than patients with anterior lesions [126], whereas the recent study by Scharf et al. showed the association of depression and anxiety (Hospital Anxiety and Depression Scale, Anxiety and Depression Score) with anterior but not paramedian or inferolateral thalamic stroke [127]. These affective disturbances, while multifactorial, emphasize the role of the thalamus in emotional regulation.

Lastly, disinhibition syndromes, including delirium or inappropriate behaviors, have been reported in thalamic stroke, specifically paramedian stroke [31,128,129]. These data indicated that the involvement of the dorsomedian nucleus, intralaminar nuclei, and medial part of the ventral lateral nucleus in the modulation of social behaviors and impulse regulation.

Mounting evidence points to the role of REM sleep in cognition and emotional regulation. Although cognitive disturbances in thalamic stroke have been linked to the changes in NREM-sleep, emotional disturbance might indicate the involvement of REM sleep. While the studies in thalamic stroke patients did not demonstrate statistically significant differences in the quantity of REM sleep, knowledge of the microarchitecture of REM sleep in thalamic stroke patients is limited (as shown in Table 1). Future studies should focus on the inclusion of REM sleep as a possible contributor to cognitive and emotional disorders, especially in patients with medial and anterior thalamic stroke.

Despite the consistent evidence of the influence of the thalamic lesion per se on sleep and cognition, recent advances in stroke animal models (see Box 1 and Figure 2) allow precise experimental control and enable researchers to observe the effects of the manipulation of specific thalamic circuits on sleep and cognition [54,92,130–132].

Lenzi et al. adopted the following approach, using an “opto-Stroke” model (shown in Figure 2) to selectively induce a lesion in the medial thalamus [54]. Their study in mice effectively replicated the reduction in NREM sleep and increased sleep instability, common in patients with medial thalamic stroke [54]. Furthermore, a lesion in the medial thalamus reduced alpha EEG power during transitions from wakefulness to NREM sleep as well as a significant reduction in frontal sleep spindle power, which was positively correlated with deficiencies in working memory [54]. Interestingly, there was no alteration in motor performance and anxiety, highlighting the specificity of the effects related to medial thalamic lesions [54].

These investigations underline the value of animal models in understanding the role of the thalamus in sleep and cognition and offer the opportunity for invasive measurements and interventions that are not feasible in human studies.

6. The Thalamus and the Interaction between Sleep and Cognition

The thalamus might modulate the association between healthy sleep and cognition.

Firstly, as previously mentioned, the thalamus participates in the regulation of local sleep oscillations during NREM sleep, such as sleep spindles and slow waves. These local sleep oscillations are associated with memory consolidation during sleep [133,134], learning [135–137], and executive functions [138,139], possibly providing the environment for neuroplasticity and cellular homeostasis [70,140]. In a general sample of stroke patients, Siccoli et al. described a correlation between the amount of slow-wave sleep and REM sleep with attention at acute stroke and with verbal and visual memory at subacute stroke [141]. Despite not achieving statistical significance, a study in patients with isolated thalamic stroke found deficits in the short-term visual memory of patients with diminished nighttime slope changes, suggesting a central role of the thalamus in synaptic renormalization [51].

Overall, thalamic stroke patients often exhibit incomplete neurological and functional recovery [46,53]. Based on the findings from Jaramillo et al. [51], this could be pathophysiologically attributed to the reduced neuroplasticity related to changes in sleep. Hermann et al. showed that patients with incomplete recovery from chronic stroke had a high need for sleep both immediately after their stroke and after one year, even though there was no association between stroke outcome and the severity of neurological symptoms, sleep efficiency, and sleep architecture [46]. Anterior and paramedian thalamic stroke is associated with the most significant changes in sleep (see above). However, Scharf et al. reported a satisfactory cognitive recovery in patients with anterior and paramedian thalamic stroke, whereas the recovery in patients with inferolateral thalamic stroke was incomplete [53]. This discrepancy could be attributed to different compensatory mechanisms (e.g., multiple centers in the brain with homologous functions), or recovery potentials (e.g., good synaptic plasticity due to the vascular collaterals). Moreover, the inferolateral region has been implicated in the control of fast sleep spindle activity [61]. In turn, fast sleep spindle activity has been shown to be essential for sleep-dependent neuroplasticity [142] compared to slow spindle activity emerging from the mediodorsal thalamic nucleus [61].

Secondly, while REM microarchitecture was not reported in thalamic stroke patients, evidence from translational studies points to the involvement of the thalamus in the regulation of REM sleep [93,94]. REM sleep, in turn, provides an environment for the synaptic remodeling essential to cognitive functioning by activating salient features such as ponto-geniculo-occipital waves, theta synchrony, and the increased transcription of plasticity-related genes [143].

Certain chronic sleep–wake disorders, such as insomnia [144], sleep-disordered breathing [145], and narcolepsy [146], have been associated with long-term changes in the thalamocortical circuitry that might lead to cognitive dysfunction, with sleep patterns and cognitive changes resembling those seen in thalamic stroke patients. Excessive daytime sleepiness, for example, is a common symptom of sleep–wake disorders. It is often accompanied by attention deficits [147] and may foreshadow cognitive decline [148]. Plante et al. described the association between excessive daytime sleepiness and the reduced resting-state connectivity between the bilateral thalamus and left rostral striatum (caudate/putamen) [149]. Moreover, excessive daytime sleepiness was shown to be related to the disrupted dopaminergic and serotonergic modulation of the thalamus [146,150].

Overall, this evidence emphasizes the crucial role of the thalamus in the modulation of the association between healthy sleep and cognition through the regulation of local sleep oscillations and through the contribution to synaptic remodeling and neuroplasticity. Furthermore, the evidence from patients suffering from thalamic stroke and other sleep–wake disorders further suggests that disruptions in thalamocortical circuitry may result in cognitive dysfunction.

7. Thalamic Dynamics as the Window of Opportunity

Understanding the complex relationship between the thalamus, sleep, and cognition provides us with valuable insights into potential therapeutic interventions for cognitive impairment linked to sleep. Consequently, targeting the thalamus appears to be a promising approach to enhance both sleep and cognition in neurological and psychiatric disorders.

Although existing drugs that influence major neurotransmitter systems in the thalamus, such as GABA or glutamate, play vital roles in regulating cognition, sleep, and wakefulness [151], there is still room to explore alternative clinical approaches that may offer new options. Some examples are provided below.

Neuromodulation by Deep Brain Stimulation (DBS) involves the surgical implantation of an electrode to transmit electrical impulses to specific parts of the brain. DBS has been utilized to treat various neurological conditions (e.g., Parkinson's disease and epilepsy) [152]. It may help to restore normal thalamocortical activity if applied to the thalamus, potentially improving sleep and cognition. Buenzli et al. showed that DBS applied to the anterior nucleus of the thalamus increased slow wave activity in NREM sleep [153].

The experimental study in mice showed a proof-of-principle restoration of electrophysiologic and behavioral measures of consciousness with a stimulation of intralaminar thalamic nuclei after seizures [154]. Moreover, the stimulation of the auditory thalamus could generate auditory percepts [155,156], and this finding is being investigated for potential treatments for conditions such as tinnitus [157].

Transcranial Magnetic Stimulation (TMS) uses magnetic fields to stimulate nerve cells in the brain [158] and can be applied to target the thalamus. However, applying TMS to deeper structures like the thalamus remains challenging, and hence continued research is needed to develop effective protocols. A recent trial demonstrated an analgesic effect of TMS for 10 consecutive days in patients with thalamic pain [159]. Moreover, potential alternative targeting areas for TMS have surfaced. Targeting the cerebellum, which projects to the thalamus, for example, showed promising results in the treatment of various neurological and neuropsychiatric conditions, including ataxia, essential tremor, dystonia, depression, schizophrenia, and autism spectrum disorders [160]. However, further research is needed to uncover the therapeutic potential of TMS, including the optimal stimulation protocols and long-term consequences.

Neurofeedback is a type of biofeedback that uses real-time displays of brain activity—most commonly, EEG—to teach the self-regulation of brain function [161]. Individuals who learn to consciously control their thalamocortical activity may potentially improve sleep and cognition. Bearden et al. reported that biofeedback training improved EEG characteristics in a patient with thalamic and cortical stroke [154,162]. The trial of the real-time functional MRI neurofeedback showed an increase in the activity of mediodorsal thalamic nuclei and posterior alpha EEG power [163].

8. Concluding Remarks

In conclusion, the thalamus is a true powerhouse for the regulation of sleep and cognition, with involvements spanning across multiple aspects.

Clinical and experimental models have supported the role of the thalamus in the regulation of sleep and wakefulness. Mounting evidence indicates its involvement in the generation and synchronization of sleep rhythms, with the anterior and medial parts recently being highlighted. Key studies have addressed the complex task of the circuit dissection in order to distinguish the contribution of different thalamic nuclei to specific cognitive domains, including sleep-dependent memory consolidation and emotional regulation. Concurrently, functional imaging and clinical studies have further supported the topographic role of different thalamic nuclei to these important physiological processes.

It is essential to recognize the large impact of thalamic dynamics on the regulation of NREM sleep and sleep-dependent physiological processes. Nevertheless, recent research has revealed a gap in our understanding of the involvement of the thalamus in regulating REM sleep and REM-dependent cognitive functions, such as emotional regulation. This knowledge gap presents an excellent opportunity for further exploration and investigation.

Furthermore, the thalamus participates in arousal regulation through the ascending reticular arousal system. The thalamus also influences circadian rhythms and facilitates transitions between different sleep stages. It remains unclear whether sleep–wake alterations in thalamic stroke are caused by a homeostatic sleep drive, sleep fragmentation, or imbalances in neurotransmitter systems, like serotonin and GABA, that have a strong impact on state transition. The field of stroke research, both clinically and experimentally, offers a promising pathway for addressing these numerous unanswered inquiries.

The thalamus is essential for cognitive function. The anterior and mediodorsal thalamic nuclei are vital for memory and executive functioning, whereas other thalamic areas are crucial for attention. Given the overlap in the functions of different thalamic regions, further investigation into the specific involvement of thalamic nuclei in cognition is required, especially with the rodent models allowing specific nuclei targeting.

The interaction between sleep and cognition is complex, and disruptions in thalamo-cortical circuitry associated with chronic sleep–wake disorders can contribute to cognitive impairments and impede recovery from thalamic stroke. Since therapeutic approaches targeting the thalamus hold promise in improving sleep and cognition in individuals with neurological and psychiatric disorders, the detailed shifts in EEG dynamics following thalamic stroke and their cascading effects on sleep and cognitive functions warrant further exploration.

We are currently on the cusp of technological advancements that, when combined with novel improvements in computational modeling, will enable us to predict recovery based on EEG patterns and implement non-invasive therapeutic approaches. Sleep provides an opportunity to improve plasticity and to restore proper brain dynamics observed in neurological disorders.

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