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Sleep as a thermobiological state transition

El sueño como transición de estado termobiológico

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Abstract

Sleep has long been conceptualized as the interplay between circadian timing and homeostatic pressure, reflecting a fundamental biological need essential for survival, neural restoration, and functional integrity. Nevertheless, emerging evidence challenges this binary framework and instead positions thermoregulation as a central organizing principle of sleep biology. This review reframes sleep as a thermobiological phase transition, in which precisely orchestrated shifts in brain and body temperature are not passive byproducts but primary drivers that initiate, structure, and govern sleep. Across species, entry into non-rapid eye movement sleep is accompanied by an active decline in core and cortical temperature, mediated by preoptic hypothalamic circuits that integrate peripheral thermal inputs with central sleep-promoting networks. Behavioral strategies, including peripheral warming and microclimate optimization, further facilitate these transitions, underscoring the organism's active role in fulfilling its biological need for sleep. At the molecular level, temperature-dependent programs link sleep-associated cooling to synaptic maintenance, circadian gene expression, and neuroprotection. Rapid eye movement sleep, in contrast, is constrained by thermal permissiveness and reflects optimized energy allocation under favorable conditions. Disruption of sleep–thermoregulatory integration has direct functional consequences and is increasingly recognized as a contributor to disability, particularly in neurological disorders such as synucleinopathies, where impaired temperature control coexists with sleep fragmentation and early disease markers. This bidirectional disruption amplifies cognitive, motor, and autonomic dysfunction, reducing quality of life and functional independence. By integrating physiological, circuit-level, and clinical perspectives, this framework redefines sleep as a dynamic thermoregulatory process embedded within a broader adaptive system. Recognizing temperature as a core determinant of sleep not only advances mechanistic understanding but also identifies modifiable pathways to mitigate disability and improve patient outcomes.

Keywords: *Sleep, Thermoregulation, NREM sleep, REM sleep, Preoptic hypothalamus, Disability*

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Introduction

Sleep and thermoregulation have traditionally been studied as separate physiological systems: the former regulated by circadian and homeostatic processes, and the latter by mechanisms that maintain internal temperature set-points[(1)]. Over the past decade, however, converging animal and human evidence has reframed this view: temperature regulation and sleep are dynamically coupled through overlapping hypothalamic circuits, peripheral afferents, and molecular programs, with demonstrable effects on sleep initiation, architecture, and continuity[(2, 3)]. This synthesis challenges the canonical "two-process model" of sleep and positions thermoregulation as a fundamental third axis[(4)], with direct diagnostic and therapeutic implications for neurology and sleep medicine (**Table 1**).

In endothermic vertebrates, particularly mammals and birds, transitions from wakefulness to non-rapid eye movement (NREM) sleep coincide with steep declines in core and cortical temperature, driven not only by circadian phase but also by the sleep state itself [(5, 6)]. However, this pattern should not be generalized to all species. Across the phylogenetic scale, sleep-like states range from simple behavioral quiescence, reduced responsiveness, and circadian rest–activity rhythms in ectotherms to the organized NREM–REM architecture typical of mammals and birds[(7-9)]. In ectothermic species, including amphibians and many reptiles, body

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INVESTIGACIÓN en DISCAPACIDAD
Vol. 12, 2026 pp e3-e19

Framework	Canonical two-process model	Thermoregulatory state-transition model
Core drivers of sleep	Circadian rhythms (Process C) and sleep homeostasis (Process S) regulate timing and depth of sleep (4)	Sleep emerges as a thermoregulatory adaptation, with state transitions orchestrated by peripheral and central thermal signals (5, 6)
NREM physiology	Sleep onset coincides with a circadian-driven decline in temperature. Cooling is secondary to central sleep processes.	Cortical and core temperature decline (~0.2 °C) is actively driven by NREM sleep, independent of circadian timing or locomotion, indicating causality (5, 6).
REM physiology	REM is a stage of heightened brain activity, modulated mainly by circadian and homeostatic factors.	REM is thermally constrained—maximal at thermoneutrality, suppressed when thermal permissiveness is lost (16, 17).
Behavioural strategies	Nest building, curling posture, and use of blankets are interpreted as ancillary or comfort behaviours.	Conserved thermoregulatory behaviours directly facilitate sleep initiation by shaping peripheral microclimates; passive warming reduces sleep latency by more than 35% (13, 15).
Neurocircuitry	The preoptic hypothalamus regulates sleep and thermoregulation in parallel, with partially overlapping networks.	Preoptic neurons integrate both processes: NOS1+ glutamatergic and galaninergic neurons co-induce hypothermia and NREM sleep; their ablation fragments sleep and produces hyperthermia (12, 67).
Molecular mediators	Sleep–wake cycles influence gene expression primarily through circadian and synaptic activity.	NREM-linked cooling induces CIRBP and RBM3, which regulate circadian clocks, synaptic resilience, and neuroprotection in Alzheimer's and prion disease (6, 23).
Energetic role	Energy conservation is modest, accounting for ~5–15% of daily expenditure (83).	Sleep is a thermodynamically optimized state enabling neuroplasticity, immune recalibration, and molecular repair, with amplified energetic benefits (~30–35%).
Clinical implications	Sleep disorders are often framed in terms of circadian or homeostatic dysregulation.	Insomnia, REM sleep behaviour disorder, and Parkinsonian thermoregulatory failure reflect disrupted thermal–sleep integration. Emerging therapies include peripheral warming, BAT activation, and targeted preoptic neuromodulation (29).
Conceptual focus	Sleep is a neurophysiological phenomenon with temperature changes as secondary correlates.	Sleep is a thermoregulatory state transition, during which consciousness is suspended to maintain the brain within optimal thermal gradients for cognition and repair.

Table 1. Reconceptualizing sleep: from the two-process model to a thermoregulatory state-transition model.

temperature depends strongly on environmental conditions and behavioral thermoregulation rather than on internally generated heat production[8, 10]. In mice, nitric-oxide-synthase (NOS1)–expressing neurons in the median and medial preoptic (MnPO/MPO) areas co-induce hypothermia and NREM sleep, while galaninergic neurons in the lateral preoptic (LPO) area link sleep homeostasis to temperature reduction[11, 12]. These findings reveal a shared control hub where thermal and sleep signals converge.

Peripheral thermal strategies further illustrate this coupling. Human randomized controlled studies show that modest passive warming—such as bathing or extremity warming 1–2 h before bedtime—shortens sleep latency, increases efficiency, and enhances early-night slow-wave sleep[13, 14]. A recent meta-analysis confirmed that as little as 10 minutes of warm bathing (40–42.5 °C) reduces sleep latency by approximately 36%[13]. Mechanistically, these interventions accelerate distal vasodilation, steepen the distal–proximal skin temperature gradient, and facilitate core heat loss, thereby promoting sleep onset[15]. Such low-cost interventions are particularly relevant in older adults, patients with insomnia, and

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those with autonomic comorbidities.

Rapid eye movement (REM) sleep presents distinct thermoregulatory constraints. Heat-defence mechanisms are attenuated during REM, making it more vulnerable to ambient conditions. REM sleep is maximal near thermoneutrality, and melanin-concentrating hormone (MCH) neurons modulate its expression in response to thermal permissiveness[16, 17]. This "thermal gating" of REM has clinical salience: in neurodegenerative conditions such as Parkinson's disease, impaired thermoregulation often co-occurs with REM sleep behaviour disorder (RBD), highlighting opportunities for environment- and circuit-targeted interventions[18, 19].

At the molecular level, brain cooling during NREM sleep induces expression of cold-inducible proteins such as CIRBP and RBM3, which regulate circadian transcriptional programs and exert neuroprotective effects[6, 20-22]. Recent work shows that RBM3 upregulation protects synapses in models of Alzheimer's disease and prion pathology, while antisense approaches are being explored for translational applications[23]. Emerging evidence also implicates CIRBP in hypothalamic neurons under metabolic stress, linking sleep cooling to cellular resilience[24]. These findings suggest that the energetic savings of sleep (≈5–15% of daily expenditure) underestimate its thermodynamic and proteostatic roles[25].

Clinically, the thermoregulatory–sleep interface is most evident in synucleinopathies [26]. Isolated RBD conveys an approximately 70% conversion risk to Parkinson's disease or related disorders within 10–12 years[27, 28]. Patients with Parkinson's disease often exhibit nocturnal core-temperature abnormalities, altered sweat responses, and heat/cold intolerance that degrade sleep quality[29]. Integrating temperature profiling (e.g., distal–proximal gradient, sweat testing) into sleep assessment may improve early risk stratification and open the door to individualized, temperature-aware therapy.

Taken together, recent findings argue for a paradigm shift: sleep should be conceptualized as a thermobiological state transition, regulated by peripheral microclimates, preoptic network motifs, and temperature-sensitive gene programs. For clinicians, this perspective highlights thermal manipulation as an underused, safe, and accessible intervention for sleep disorders; for neuroscientists, it calls for models that integrate circadian, homeostatic, and thermoregulatory control into a unified triad. This review challenges the prevailing paradigm by proposing that sleep is fundamentally a thermobiological state transition, in which precisely orchestrated changes in brain and body temperature are not epiphenomena but the primary forces that initiate, structure, and sustain sleep itself.

Thermoregulation across the sleep–wake cycle: Integrating circadian and sleep-dependent mechanisms

The interplay of circadian timing and sleep-dependent processes orchestrates thermoregulation (**Table 2**). Even under conditions of controlled activity, such as bed-rest protocols, humans maintain a robust 24-h core body temperature rhythm with an amplitude of approximately 0.8–1.0 °C, oscillating around a mean internal temperature close to 37 °C[2]. This circadian pattern is characterized by a progressive decline in core temperature beginning 1–2 h before habitual sleep onset and reaching a nadir during the night, typically in the latter part of the sleep episode or close to the early morning hours [30]. Notably, the steepest temperature decline coincides with the highest probability of non-rapid eye movement (NREM) sleep onset, underscoring the synchrony between thermoregulatory and sleep-promoting processes[15]. In parallel, state-dependent brain temperature changes occur across sleep–wake transitions: in mice, each transition from wakefulness to NREM sleep decreases cortical temperature by approximately 0.2 °C, whereas REM sleep is associated with a smaller increase of approximately 0.1–0.2 °C, remaining below waking levels[3].

Experimental protocols that dissociate circadian timing from the sleep–wake cycle demonstrate that

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INVESTIGACIÓN en DISCAPACIDAD
Vol. 12, 2026 pp e3-e19

Key finding	Commentary/critique
↓ NREM sleep reduces core and cortical temperature	Robust across species and independent of circadian phase → but causality unresolved: does cooling drive NREM, or follow it? (5, 6)
Thermoregulation is suspended during REM	REM maximized at thermoneutrality → but mechanism of thermal gating unclear (MCH neurons vs vascular redistribution) (16, 17).
Nesting and curling precede sleep	Conserved strategies across mammals and birds → adaptive ambiguity: energy conservation vs active facilitation of sleep onset (44).
Peripheral warming promotes NREM	Strong human data (↓ sleep latency >35%) → but inter-individual variability is high, and afferent pathways in humans are poorly mapped (13, 15).
MnPO/MPO neurons co-regulate temperature and sleep	NOS1+ and galaninergic neurons integrate cooling and NREM induction → but heterogeneity of preoptic populations complicates functional dissection (12, 67).
Brain cooling upregulates CIRBP and RBM3	Provides molecular link to sleep depth and neuroprotection → but evidence remains largely rodent-based, with limited human validation (6, 23).
BAT thermogenesis modulates sleep	BAT activation enhances NREM; β3-agonists are effective experimentally → but adult human relevance remains debated (58).
Parkinson's disease: ↓ REM + impaired thermoregulation	Clinically compelling overlap of REM and autonomic dysfunction → but mechanistic links (MCH, preoptic circuits) speculative (29).

Table 2. Thermoregulation–sleep interactions and critical appraisal.

the sleep state exerts an independent and dominant influence on thermal control. Across circadian phases, NREM sleep reliably lowers core body temperature, indicating that sleep transitions themselves are thermoregulatory events[6]. This principle also applies to animal models: in mice, cortical and core temperatures decline in parallel with increased sleep propensity, a pattern that is uncoupled from locomotor activity[5, 11]. Detailed recordings show that each transition from wake to NREM sleep decreases cortical temperature by ~0.2 ° C, with rapid rebound upon arousal. By contrast, REM sleep produces only modest increases (~0.1–0.2 °C), never reaching the thermal levels of wakefulness[6, 17].

Melatonin secretion further links circadian and thermal regulation. In humans, melatonin release precedes sleep onset, paralleling the fall in core temperature and subjective sleepiness[31]. However, interspecies differences highlight that melatonin is not universally essential for sleep–temperature coupling. CBA mice exhibit peak melatonin late in the dark phase—coinciding with the waning of activity—whereas most laboratory strains lack endogenous melatonin synthesis[32]. In rats, exogenous melatonin induces hypothermia during the light phase but not during the dark phase, indicating a complex, phase-dependent modulation of thermoregulation and sleep[33, 34].

Together, these insights challenge traditional models that privilege circadian rhythms or activity alone as the primary regulators of body temperature during sleep. Instead, they highlight the immediate role of sleep state transitions in shaping thermoregulatory dynamics. Clinically, this reframing has implications for disorders characterized by impaired sleep–temperature integration, such as insomnia, circadian rhythm sleep–wake disorders, and neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease[35]. Recognizing sleep as a thermoregulatory state transition may open avenues for targeted interventions—ranging from peripheral warming strategies to melatonin-based chronotherapy—designed to restore synchrony between thermal physiology and sleep architecture.

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Life-course and sex-specific modulation of sleep thermoregulation

Sleep-related thermoregulation varies across the lifespan. In early life, especially in neonates, heat exchange is faster and less stable than in adults because of a high surface area-to-volume ratio, limited insulation, reduced muscle mass, and reliance on non-shivering thermogenesis. Unlike adults, neonates may maintain or even enhance homeothermic responses during active sleep compared with quiet sleep, and cool environments can increase active sleep at the expense of quiet sleep, indicating that the sleep–temperature relationship is strongly shaped by developmental maturation of autonomic and metabolic thermoeffectors[36].

In reproductive-age women, sleep-related thermoregulation is modulated by ovarian hormones. Core body temperature is typically 0.3–0.7 °C higher in the post-ovulatory luteal phase than in the follicular phase, largely in parallel with progesterone, and these cyclic changes may influence nocturnal temperature, circadian amplitude, sleep quality, and autonomic regulation[37, 38]. Pregnancy represents an additional thermoregulatory challenge because maternal heat balance must support both maternal and fetal physiology; although sleep-specific evidence remains limited, heat exposure during pregnancy can disrupt maternal thermoregulation and has been associated with adverse pregnancy outcomes, suggesting increased vulnerability to heat-related sleep disruption under climate warming[39].

Menopause introduces a distinct thermoregulatory phenotype. Declining estradiol levels and altered hypothalamic signalling, including hyperactivity of kisspeptin–neurokinin B–dynorphin pathways, are implicated in vasomotor symptoms such as hot flashes and night sweats, which involve cutaneous vasodilation, sweating, abrupt heat-loss responses, and sleep disruption[40]. More broadly, sex- and age-related differences in thermal perception, sweating, cutaneous vasodilation, body composition, and heat tolerance may shape vulnerability to sleep disturbance, particularly in older adults. These differences are clinically relevant because ageing, menopause, autonomic dysfunction, and neurodegenerative disease frequently converge in the same populations, including those at risk for synucleinopathies[41].

Nesting and sleep posture: thermoregulatory strategies for energy conservation during sleep

Sleep-preparatory behaviours such as nest building in rodents exemplify evolutionarily conserved strategies that optimize thermal efficiency and energy balance. These behaviours are not incidental but appear to be actively regulated within sleep–wake circuitry. In mice, nest construction is initiated before sleep onset and has been linked to inhibition of ventral tegmental dopaminergic neurons, highlighting a neuronal mechanism that integrates motivation, thermoregulation, and sleep drive[42].

Nests provide a local thermal microenvironment approximating thermoneutral conditions, thereby reducing the energetic burden of maintaining core body temperature during rest. Rodents consistently select warmer, insulated sites near thermoneutrality, where they spend most of their rest phase[43]. Nevertheless, nest utility is context-dependent: when ambient temperatures exceed the thermoneutral zone, nest construction declines and nest quality deteriorates—behavioural adaptations that minimize the risk of overheating[44].

The metabolic stakes of these strategies are particularly evident in small mammals. Mice housed at 10 °C expend more than three times the energy of those at thermoneutrality, compensating for this through hyperphagia. Provision of nesting material mitigates this burden, reducing food intake and improving survival, particularly in offspring[45]. Recent work confirms that even subtle thermal enrichment—via nesting material, shelters, or bedding—enhances welfare, growth, and immune function, supporting the translational relevance of housing conditions for experimental reproducibility [46].

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Investigación en Discapacidad
Vol. 12, 2026 pp e3-e19

Comparable energy-saving strategies are observed across species. Migratory birds such as the garden warbler tuck their heads into their plumage during rest, trading increased predation risk for reduced thermal loss[47]. In mammals, curling postures reduce the exposed surface area and facilitate heat retention [48]. In humans, analogous behaviours—including fetal postures or blanket use—serve comparable thermodynamic purposes, underscoring the universality of pre-sleep thermal optimization[49, 50].

Taken together, these findings suggest that nesting and sleep posture are not merely adaptive reflexes but reflect conserved, neurally orchestrated mechanisms that couple thermoregulation with sleep initiation and maintenance. Recognizing sleep as a behavioural and physiological state optimized for thermodynamic efficiency reframes how sleep should be conceptualized in both experimental and clinical contexts. For translational neuroscience, this perspective emphasizes the importance of controlling thermal microenvironments in animal research. It offers low-cost, non-pharmacological opportunities to improve sleep quality in humans, including in populations vulnerable to thermal dysregulation such as infants, older adults, and patients with neurodegenerative disease.

Preparing for sleep: microclimates, peripheral warming, and the thermoregulatory basis of NREM sleep

Beyond energy conservation, thermoregulatory behaviours such as curling into a ball, wearing nightclothes, or seeking shelter under blankets play a fundamental role in sleep initiation and maintenance. This principle is exemplified by the "warm bath effect," in which passive body warming prior to bedtime reliably facilitates sleep onset and continuity. Controlled studies have shown that taking warm baths or showers 1 to 2 hours before bedtime reduces sleep latency, prolongs early sleep episodes, and increases NREM intensity, as measured by electroencephalography [51]. Similarly, targeted warming of distal extremities, including the hands and feet, promotes the transition to NREM sleep, consistent with the thermoregulatory shift required for state transition [51].

A meta-analysis of 13 clinical trials confirmed the robustness of this effect: as little as 10 minutes of water-based warming reduced sleep onset latency by approximately 36%[13]. Mechanistically, these improvements are mediated by peripheral vasodilation, which facilitates heat transfer from the core to the periphery, leading to a modest decline in core temperature—a thermodynamic change that favours sleep initiation[15].

Such behaviours reflect the active creation of local skin microclimates that optimize thermal balance. In humans, the distal-to-proximal skin temperature gradient serves as a reliable physiological marker of sleep propensity: as sleep approaches, distal regions, such as the hands and feet, warm relative to proximal regions, such as the torso, facilitating peripheral heat loss and promoting the decline in core body temperature[52]. The magnitude of these peripheral changes is physiologically meaningful. While core body temperature is maintained near 37 °C, distal skin temperature is more labile and varies with ambient conditions and vasomotor tone. For example, at an ambient temperature of approximately 23 °C, the hands and feet may be 7–8 °C cooler than the core, whereas at 35 °C they may be only 3–4 °C cooler, reflecting increased distal vasodilation and enhanced heat dissipation. Around sleep onset, rapid distal warming can also occur; under constant-routine conditions, finger temperature has been reported to increase by approximately 1–3 °C, with rates approaching 0.8 °C/min[53, 54]. In everyday sleeping conditions, the use of nightwear and duvets generates a skin microclimate of approximately 33–35 °C, about 2–3 °C warmer than during wakefulness, while core body temperature falls by about 1 °C, creating a net pre-sleep gradient change of up to 4 °C[55]. These values illustrate why relatively small absolute changes in peripheral temperature can strongly influence heat loss, sleep propensity, and the transition into NREM sleep.

This thermoregulatory mechanism is conserved across species. In rodents, increasing ambient

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temperature toward thermoneutrality enhances NREM sleep, whereas excessive warming induces heat stress and sleep disruption[5]. Ablation of skin thermosensitive afferents using capsaicin abolishes warmth-induced increases in NREM, implicating peripheral rather than central pathways in the somnogenic effect[56]. Although direct hypothalamic warming can trigger NREM sleep, modest ambient warming does not significantly raise brain temperature, underscoring the primacy of peripheral inputs[57].

Brown adipose tissue (BAT) thermogenesis provides further evidence of peripheral contribution. In rodents, uncoupling protein 1 (UCP-1)–mediated BAT activity warms skin microenvironments and supports sleep initiation. UCP-1 knockout mice fail to show normal NREM enhancement in response to immune challenges such as TNF-α or IL-1β, whereas pharmacological activation of BAT with β3-adrenergic agonists increases NREM sleep[58]. In humans, BAT remains detectable in adulthood, and recent studies suggest that non-shivering thermogenesis contributes more substantially to thermal balance than previously recognized[25]. In neonates, where BAT is abundant, thermogenesis plays an especially critical role in sleep physiology due to the high surface area-to-volume ratio and limited muscle mass.

An intriguing yet underexplored line of evidence concerns the relationship between stress and thermoregulation. Acute stressors in rodents—including social defeat and restraint—paradoxically promote NREM sleep while activating BAT thermogenesis, suggesting that stress-induced peripheral warming may contribute to sleep induction[59].

Together, these findings call for a broader conceptual framework that situates NREM sleep as a thermobiological state, actively shaped by peripheral thermal inputs, microclimate regulation, and BAT function. For clinicians, this perspective supports the use of simple, low-cost interventions—such as peripheral warming, bedding optimization, or targeted BAT activation—to enhance sleep quality. For neuroscientists, it highlights the need to integrate peripheral thermosensory pathways into models of sleep regulation, with implications for disorders ranging from insomnia to neurodegeneration.

Geographic and climatic modulation of sleep-related thermoregulation

Geographic and climatic context can substantially shape the thermoregulatory demands of sleep. In cold and subpolar climates, the main challenge is preventing excessive heat loss during prolonged nocturnal immobility. Bedding, clothing, posture, and indoor heating help preserve a warm skin microclimate and reduce the energetic cost of maintaining core temperature. Although adequate bedding may preserve sleep architecture, cold exposure can still modify autonomic cardiovascular responses, indicating persistent thermal strain[60, 61].

In temperate climates, the sleep environment may more readily support distal vasodilation, peripheral heat loss, and the pre-sleep decline in core body temperature. However, this depends on the local sleep microclimate, including indoor temperature, humidity, air movement, bedding insulation, clothing, and housing quality, rather than geographic temperature alone[60, 62].

In hot climates, especially hot–humid regions or areas with persistently elevated nighttime temperatures, insufficient nocturnal heat dissipation becomes the main challenge. Heat exposure can blunt the normal fall in core body temperature, increase wakefulness, and reduce slow-wave and REM sleep. Recent climate-health studies further show that warmer nights are associated with shorter sleep duration and poorer sleep continuity, particularly among socioeconomically disadvantaged groups, individuals with chronic disease, and populations with limited access to cooling technologies[39, 62-64].

Behavioral and technological adaptations—including bedding selection, ventilation, fans, cooling materials, housing design, and air conditioning—can partly compensate for these geographic differences. However, unequal access to these resources may turn

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Investigación en Discapacidad
Vol. 12, 2026 pp e3-e19

climate-related sleep disruption into a socioeconomic disparity. This issue is increasingly relevant under climate change, as extreme heat and warmer nights may amplify inequalities in sleep health[39, 63, 64].

Neurocircuitry linking thermoregulation and sleep: shared pathways and functional overlap

The integration of thermal cues into sleep-regulating networks is increasingly recognized as a central mechanism of sleep biology (**Figure 1**). Sensory neurons in the skin detect changes in environmental temperature via transient receptor potential (TRP) channels, particularly TRPM2, which are activated by warming stimuli[65]. These signals ascend via the lateral parabrachial nucleus to the preoptic hypothalamus, where the median preoptic (MnPO) and medial preoptic (MPO) areas serve as major integrative hubs[66]. Within these nuclei, glutamatergic neurons engage downstream thermoregulatory centres—including the dorsomedial hypothalamus and rostral raphe pallidus—initiating effector responses such as vasodilation, sweating, panting, and suppression of brown adipose tissue thermogenesis.

Subpopulations of hypothalamic neurons expressing brain-derived neurotrophic factor (BDNF), pituitary adenylate cyclase-activating polypeptide (PACAP), and TRPM2 respond to external warming. Optogenetic or chemogenetic activation of these cells elicits hypothermia, but these effects are often reported at supraphysiological temperatures (>38 ° C), conditions that do not naturally promote sleep in rodents[67]. Consequently, the physiological role of these neurons in sleep initiation under thermoneutral

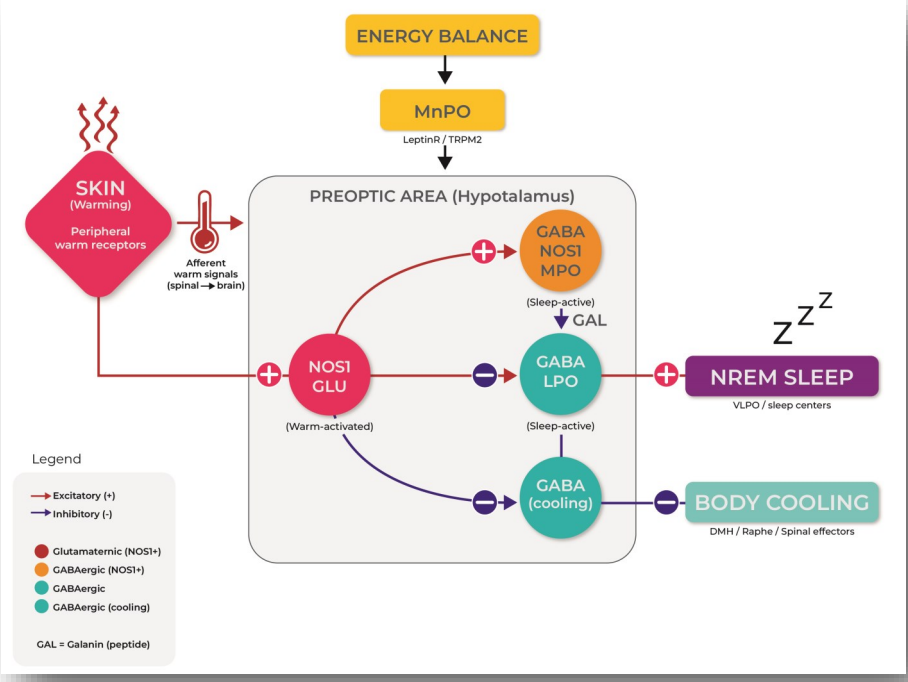


Figure 1. Thermosensory integration in the preoptic hypothalamus couples peripheral warming to sleep induction and thermoregulatory output. Peripheral skin warming is detected by cutaneous thermoreceptors and conveyed via spinal afferents to the preoptic area (POA) of the hypothalamus. Within the POA, warm-sensitive NOS1-expressing glutamatergic neurons (NOS1$^+$/Glu) act as an integrative node that links thermal inputs to sleep- and temperature-regulating circuits. Activation of NOS1$^+$/Glu neurons excites NOS1$^+$ GABAergic neurons in the median preoptic nucleus (MnPO/MPO), which are sleep-active and promote non–rapid eye movement (NREM) sleep. In parallel, these neurons engage GABAergic populations in the lateral preoptic area (LPO), reinforcing inhibition of arousal-promoting systems within the ventrolateral preoptic (VLPO) network; galanin (GAL) signalling contributes to this inhibitory tone. Concurrently, NOS1$^+$/Glu neurons suppress GABAergic pathways associated with thermogenesis and cooling control, thereby facilitating heat dissipation through descending projections to the dorsomedial hypothalamus (DMH), raphe nuclei and spinal effectors. Energy balance signals, including leptin receptor (LeptinR) and TRPM2-mediated pathways in the MnPO, modulate this circuit. Together, these interactions define a coordinated mechanism by which peripheral warming promotes sleep onset while reducing core body temperature. Red arrows indicate excitatory connections; blue arrows indicate inhibitory connections.

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conditions remains unresolved.

Recent advances clarify how thermoregulatory inputs directly interface with sleep-regulatory circuits. Exposure to thermoneutral ambient temperatures activates nitric oxide synthase 1 (NOS1)–positive glutamatergic neurons in the MnPO and MPO, which simultaneously drive hypothermia and non-rapid eye movement (NREM) sleep[5, 11]. Whereas projections to classic thermoregulatory centres mediate hypothermia, sleep induction involves local GABAergic neurons within the MPO, some of which also express NOS1. Experimental activation of these GABAergic neurons enhances NREM sleep with minimal effect on body temperature, demonstrating that sleep induction can be dissociated from hypothermic responses[68].

The MnPO exerts both excitatory and inhibitory control over the lateral preoptic (LPO) area, a region long recognized as a key sleep-promoting area. Galanin- and GABA-expressing neurons in the LPO induce consolidated NREM sleep when activated optogenetically or chemogenetically, typically accompanied by a fall in core temperature[12]. Lesion studies reinforce their role: ablation of LPO galanin neurons results in fragmented sleep, impaired recovery after sleep deprivation, and chronic hyperthermia despite preserved circadian rhythmicity[68].

Molecular profiling has revealed marked hetero geneity within preoptic galaninergic neurons. While most are GABAergic, subsets co-release glutamate or monoamines, suggesting a combinatorial coding of thermoregulatory and sleep functions[69]. This heterogeneity may explain paradoxical findings, such as increased total sleep but disrupted architecture following galanin-neuron ablation, which likely reflects compensatory activity in parallel sleep-promoting networks.

Taken together, these findings delineate an integrated system in which thermal signals from the skin are relayed to hypothalamic circuits that regulate both sleep and body temperature. The convergence of thermoregulatory and sleep-promoting neurons within the preoptic hypothalamus provides a mechanistic basis for the facilitation of NREM sleep by warmth. Clinically, this framework emphasizes the importance of peripheral thermal cues in influencing sleep onset and continuity, underscoring the role of dynamic thermal feedback loops in regulating circadian and homeostatic drives. Recognizing sleep as a thermobiological process reframes its regulation and opens new avenues for temperature-targeted therapies in insomnia, circadian rhythm disorders, and neurodegeneration.

Thermal regulation and REM sleep: implications for physiology and neurodegenerative disease

REM sleep presents distinctive thermoregulatory challenges that set it apart from both wakefulness and NREM sleep (**Table 3**). In rodents, thermoregulatory responses are effectively suspended during REM, leaving the animal more vulnerable to fluctuations in ambient temperature[70]. Whereas NREM sleep is associated with a progressive decline in core and cortical temperatures, REM induces a rise in brain temperature, attributed to preferential vertebral rather than carotid blood flow—a phenomenon described in foundational physiology studies and subsequently confirmed in high-resolution animal models[71].

These REM-associated thermoregulatory features should be interpreted within a broader evolutionary context. Well-defined NREM and REM sleep states are most clearly established in mammals and birds, whereas REM-like states described in reptiles, fish, cephalopods, and other taxa remain heterogeneous and should be interpreted cautiously because their homology with mammalian REM sleep is still debated[8, 9]. Comparative evidence suggests that REM sleep is closely linked to endothermy, autonomic instability, muscle atonia, and state-dependent changes in brain temperature. However, REM expression varies markedly across phylogeny: monotremes show unusually high REM-like activity, birds show comparatively short REM episodes, and cetaceans appear to lack conventional REM sleep despite large brain size and

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Investigación en Discapacidad
Vol. 12, 2026 pp e3-e19

Domain	Key insights	Translational/clinical opportunities	Outstanding questions
NREM cooling	Core/cortical temperature drops actively shape NREM onset and depth (5, 6)	Non-invasive peripheral warming or cooling devices to enhance sleep initiation and depth.	Can brain cooling biomarkers (e.g., CIRBP, RBM3) be leveraged as objective sleep quality indicators in humans?
REM thermal constraints	REM sleep is suppressed outside thermoneutrality; MCH neurons mediate thermal gating (16, 17)	Ambient temperature optimization in sleep labs and clinical trials; targeted MCH-based therapeutics.	How do REM thermal limits contribute to vulnerability in neurodegeneration (e.g., Parkinson's, RBD)?
Behavioural strategies	Nesting, curling, blankets, and extremity warming conserved across species (13, 44).	Behavioural prescriptions (warm baths, bedding optimization) as low -cost interventions for insomnia.	What neural circuits link behavioural thermoregulation to central sleep induction?
Neurocircuitry integra-tion	Preoptic NOS1+ and galaninergic neurons co-regulate temperature and NREM sleep (12, 67).	Potential for neuromodulation or pharmacological targeting of preoptic pathways.	Can cell-type–specific interventions separate thermoregulation from sleep control for therapeutic use?
Molecular mediators	Cold-shock proteins (CIRBP, RBM3) are upregulated during NREM cooling and are linked to neuroprotection (6, 23).	Use of mild hypothermia or cooling mimetics in neurodegenerative disorders.	Are CIRBP/RBM3 reliable biomarkers for human sleep-dependent brain resilience?
BAT thermogenesis	BAT activation promotes NREM; β3-adrenergic agonists are effective in rodents (58).	Pharmacological BAT activation to improve sleep in patients with impaired thermoregulation.	What is the role of BAT in adult human sleep regulation and neurodegeneration?
Clinical neurology	Parkinson's disease patients show impaired thermoregulation and altered REM/NREM dynamics (29).	Temperature-based sleep therapies (warming, BAT modulation) for Parkinson's, RBD, and insomnia.	How do disrupted thermal–sleep circuits accelerate neurodegenerative disease progression?

Table 3. Translational and clinical implications of thermoregulation–sleep interactions.

complex behavior[9, 10]. These observations support the possibility that REM sleep contributes to the regulation of brain temperature and metabolic state during sleep, while also emphasizing that its function and thermoregulatory expression are species-dependent.

In humans, thermoregulatory responses are attenuated but not completely abolished during REM. For example, sweating and vasodilation can occur but are consistently blunted relative to other vigilance states [72]. These attenuated mechanisms suggest that REM operates within a narrow thermal window. Indeed, rodent studies show that REM sleep expression is maximal at thermoneutrality: the proportion of REM sleep doubles as ambient temperature increases from 22 °C to 29 °C, but declines sharply at 36 °C, consistent with thermodynamic gating of REM [73].

At the circuit level, melanin-concentrating hormone (MCH) neurons in the hypothalamus appear central to this thermal gating. MCH receptor 1 knockout mice exhibit a lack of the typical thermoneutral preference for REM sleep, whereas optogenetic inhibition of MCH neurons abolishes REM sleep at thermoneutrality[17]. Conversely, stimulation of these neurons enhances REM expression in a temperature-dependent manner[17]. These findings support an "energy allocation" model, in which REM is preferentially expressed during periods of thermal efficiency, potentially optimizing metabolic resources under favorable ambient conditions.

The clinical relevance of this REM-thermoregulatory interface is particularly salient in Parkinson's disease and related synucleinopathies[26]. REM sleep behavior disorder (RBD)—a parasomnia defined by

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loss of REM atonia—is among the strongest prodromal markers of Parkinson's disease and dementia with Lewy bodies[74], with up to 75% of individuals with RBD converting within 10–12 years [27, 28, 75]. Importantly, patients with Parkinson's disease frequently demonstrate impaired thermoregulation[74, 75], including reduced nocturnal core body temperatures and abnormal sweat responses, which correlate with RBD severity[29]. Recent work further suggests that autonomic dysfunction and altered preoptic–MCH circuitry may mediate this dual vulnerability[76].

Mechanistically, this association may reflect the convergence of partially overlapping brainstem, autonomic, hypothalamic, and circadian systems. Brainstem circuits generate REM atonia, autonomic pathways regulate sweating, vasomotor tone, and cardiovascular stability, and hypothalamic–circadian networks shape nocturnal core body temperature rhythms. Thus, RBD may represent not only motor disinhibition during REM sleep, but also co-disruption of thermoregulatory and autonomic circuits that normally help maintain REM within a narrow thermal range.

Clinical studies support this interpretation. In Parkinson's disease, nocturnal core body temperature profiles show reduced mesor and reduced nocturnal amplitude, and this reduced amplitude correlates with RBD symptom severity, lower REM sleep percentage, and longer sleep onset latency[18]. Reduced nocturnal core body temperature amplitude has also been reported in idiopathic RBD, Parkinson's disease with RBD, and dementia with Lewy bodies, but not in Parkinson's disease without RBD, suggesting a closer relationship with RBD-associated circuitry than with Parkinson's disease per se[19]. Consistently, galvanic skin responses are reduced in Parkinson's disease with RBD compared with controls and Parkinson's disease without RBD, supporting prominent sudomotor involvement in this phenotype[77]. Together, these findings suggest that impaired REM atonia, flattened nocturnal temperature rhythms, and autonomic dysfunction may be linked clinical expressions of synuclein-related involvement of REM-generating, circadian, thermoregulatory, and peripheral autonomic pathways. In this framework, REM sleep contributes to thermal control as a thermally permissive state: when neurodegeneration narrows this permissive window, REM becomes fragmented, heat dissipation becomes less efficient, and sleep becomes less restorative, providing a plausible link between RBD, nocturnal thermoregulatory dysregulation, sleep fragmentation, and downstream disability in synucleinopathies.

Brain cooling and the function of sleep: metabolic regulation, gene expression, and beyond

One of the enduring puzzles in sleep science is why reductions in core and cortical temperature consistently accompany NREM sleep, and why this cooling contrasts so markedly with the thermodynamic profile of REM sleep. At the systemic level, NREM-associated cooling has traditionally been interpreted as an energy-conserving mechanism. Yet, direct metabolic savings from a typical eight-hour sleep period account for only 5–15% of daily energy expenditure [78]. More recent hypotheses propose that sleep facilitates the redistribution of metabolic and cellular resources in ways incompatible with wakefulness, yielding a net energetic benefit of up to 30–35%[79]. For instance, sleep preferentially enhances immune and glymphatic functions, enabling greater efficiency in cellular housekeeping and immunological processing[80, 81].

Beyond whole-body metabolism, brain cooling during NREM sleep exerts direct molecular effects. Cold-inducible genes—including CIRBP (cold-inducible RNA-binding protein) and RBM3 (RNA-binding motif protein 3)—are upregulated at the reduced brain temperatures characteristic of NREM sleep[6]. These proteins modulate the expression of circadian clock genes and appear integral to the molecular architecture of sleep regulation. Experimental sleep deprivation suppresses CIRBP expression, suggesting that temperature-driven transcriptional programs may serve as physiological markers of sleep duration and quality. Mice lacking CIRBP display impaired REM

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Investigación en Discapacidad
Vol. 12, 2026 pp e3-e19

sleep, further supporting a role in state-specific neuronal maintenance[6].

RBM3 expression has been linked to synaptic resilience and neuroprotection in experimental models of prion disease and Alzheimer's pathology, particularly in the hippocampus [23]. This suggests that NREM-associated cooling contributes to long-term synaptic preservation and memory consolidation through these cold-shock proteins. Under baseline conditions, cortical temperature changes across individual sleep–wake transitions are modest but reproducible: wake-to-NREM transitions decrease cortical temperature by approximately 0.2 ◦ C, whereas REM sleep produces smaller increases of approximately 0.1–0.2 °C, remaining below waking levels[3]. These routine ultradian fluctuations are distinct from the larger cooling observed during intensified recovery sleep after prolonged wakefulness, where cortical temperature reductions may exceed 2 °C within 1 hour[82].
Neurocircuitry studies further connect thermoregulation and homeostatic sleep drive. Galaninergic neurons of the lateral preoptic (LPO) area have been shown to coordinate both hypothermia and recovery sleep after deprivation, suggesting a mechanistic convergence between temperature regulation and sleep homeostasis[12].

Still, temperature-dependent gene expression provides only a partial account of sleep's complexity. Evidence from Djungarian hamsters shows that recovery sleep following torpor differs in EEG architecture from that following sleep deprivation, indicating that superficially similar states engage distinct physiological mechanisms[83]. Moreover, existing models—whether focused on energy conservation or cellular housekeeping—do not fully explain sleep's most defining feature: the reversible suspension of consciousness. Any comprehensive theory must therefore integrate how altered consciousness, thermoregulation, and molecular maintenance are intertwined.

Taken together, these findings support a reframing of sleep as a thermobiological state that unites systemic energy redistribution, temperature-sensitive molecular signalling, synaptic protection, and altered consciousness. Clinically, this integrated perspective has important implications: patients with neurodegenerative disorders often display combined disturbances in sleep–wake regulation and thermoregulatory capacity, raising the possibility that targeted thermal or molecular interventions could mitigate both sleep fragmentation and disease progression.

Sleep, thermoregulation and disability: restoring thermal physiology to improve quality of life

Sleep-related disorders are a major determinant of disability across neurological and systemic disorders, yet their contribution to functional decline is often underestimated. New evidence reframes this relationship: impaired sleep is not merely a symptom but a mechanistic amplifier of disability, and thermoregulatory dysfunction sits at the centre of this interaction. The integration of sleep and temperature control is essential for maintaining physiological resilience, and its disruption contributes to fatigue, cognitive impairment, autonomic instability, and reduced independence in daily life[3, 84].

Thermoregulation provides a critical bridge between sleep quality and functional capacity. Under physiological conditions, the transition to NREM sleep is accompanied by coordinated peripheral vasodilation and a decline in core body temperature, facilitating restorative sleep architecture[85, 86]. When this process is impaired—as observed in ageing, neurodegenerative disease, and chronic illness—sleep becomes fragmented and inefficient. Patients frequently report nocturnal awakenings, non-restorative sleep, and daytime somnolence, all of which directly impair motor performance, cognition, and emotional regulation[87]. In disorders such as Parkinson's disease, where autonomic dysfunction is prominent, altered sweating, impaired vasomotor responses, and abnormal nocturnal temperature rhythms exacerbate both sleep disruption and disability[29, 88].

From a functional perspective, thermoregulatory failure contributes to a cycle of vulnerability. Poor

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sleep reduces the capacity to regulate body temperature during the following day, while impaired thermoregulation further degrades subsequent sleep. This bidirectional loop amplifies disability by increasing fall risk, slowing reaction times, worsening executive dysfunction, and reducing tolerance to environmental stressors such as heat or cold[89, 90]. In older adults, even subtle impairments in nocturnal heat dissipation are associated with decreased sleep efficiency and increased frailty, highlighting the clinical relevance of thermal physiology in maintaining independence [86].

Importantly, thermoregulation represents a modifiable pathway with direct translational potential. Interventions that enhance peripheral heat dissipation—such as passive body warming before sleep, optimization of bedding microclimates, or targeted warming of distal extremities—can restore the physiological gradient required for sleep initiation[13, 15]. These strategies are low-cost, scalable, and particularly valuable in populations with limited access to pharmacological treatments or high sensitivity to sedative side effects[85]. In patients with neurological disease, combining thermal interventions with behavioural and rehabilitative strategies may improve both nocturnal recovery and daytime function.

In practical terms, a temperature-aware approach to disability reduction in Parkinson's disease, RBD, and related synucleinopathies could include complementary clinical actions. Nocturnal temperature patterns, distal–proximal skin temperature gradients, sweating abnormalities, orthostatic symptoms, nocturia, and sleep fragmentation may be documented as part of the non-motor assessment, given their association with RBD-related synucleinopathy, reduced nocturnal core body temperature amplitude, and autonomic dysfunction[18, 19, 77]. The sleep environment can also be individualized by adjusting bedroom temperature, bedding, nightwear, ventilation, and access to cooling or warming devices to facilitate peripheral heat dissipation without inducing cold stress[60, 61]. In parallel, circadian reinforcement strategies—regular sleep–wake timing, morning light exposure, daytime activity, and appropriately timed melatonin when clinically indicated—may help stabilize sleep, temperature, and autonomic rhythms in Parkinson's disease[91]. Patients with RBD should also receive targeted safety measures and sleep-specialist evaluation for pharmacological and non-pharmacological treatment[92]. Finally, autonomic dysfunction should be actively screened and managed, because impaired sweating, orthostatic hypotension, nocturnal blood pressure dysregulation, and urinary symptoms can worsen sleep quality, falls, fatigue, and daytime function. These actions do not replace disease-specific treatment, but provide modifiable targets through which thermoregulatory stabilization may improve sleep quality, nocturnal safety, and functional independence.

Beyond behavioural approaches, emerging insights into brown adipose tissue activation, peripheral thermosensory pathways, and hypothalamic circuitry suggest future avenues for precision therapies[93, 94]. Targeting these systems could enable individualized modulation of sleep–temperature coupling, particularly in patients with autonomic dysfunction or neurodegenerative disease. Integrating thermal profiling into clinical assessment—through measures such as distal–proximal temperature gradients or nocturnal temperature variability—may further refine risk stratification and guide intervention[85].

Reconceptualizing sleep as a thermobiological process shifts the clinical focus from symptomatic management to mechanistic restoration. In this framework, improving thermoregulation is not an adjunct but a central strategy to reduce disability. By restoring the physiological conditions that enable efficient sleep, it becomes possible to enhance cognitive performance, motor function, and overall quality of life. This perspective is particularly relevant for ageing populations and patients with chronic neurological disorders, in whom small improvements in sleep can translate into meaningful gains in autonomy and well-being.

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Investigación en Discapacidad
Vol. 12, 2026 pp e3-e19

Discussion

Sleep research has long been grounded in the canonical "two-process model," in which circadian and homeostatic drives are considered the primary forces shaping sleep timing and depth [4]. This framework has been invaluable, but is now insufficient. New evidence from neurophysiology, behaviour, and molecular biology compels a disruptive reframing: sleep is not merely influenced by thermoregulation—it is itself a thermoregulatory adaptation[53].

The evidence is clear. First, the onset and consolidation of NREM sleep depend on a rapid decline in cortical and core body temperature, a process actively driven by the sleep state itself rather than simply reflecting circadian drift[5, 6]. Brain temperature falls by ~0.2 °C during NREM, rebounds upon waking, and oscillates predictably with sleep–wake transitions—placing thermal gradients at the centre of sleep dynamics. By contrast, REM sleep is tightly constrained by ambient conditions and is suspended when thermal permissiveness is lost[16, 17].

Second, thermoregulatory behaviours—such as nest building in rodents, curling postures in mammals, or peripheral warming rituals in humans—are conserved strategies that directly facilitate sleep onset. Passive warming through baths, showers, or extremity heating reduces sleep latency by more than one-third, an effect abolished when thermosensitive afferents are disabled[13, 15]. Such evidence challenges the assumption that sleep is purely centrally generated, instead positioning peripheral microclimates as gatekeepers of state transition.

Third, neurocircuitry studies reveal that preoptic neurons not only coexist with thermoregulation but also integrate it with sleep. Glutamatergic/NOS1^{+} neurons in the median and medial preoptic areas co-induce hypothermia and NREM sleep in response to thermoneutral cues[67]. Galaninergic neurons in the lateral preoptic area promote both sustained sleep and core temperature reduction, whereas their loss fragments sleep and induces chronic hyperthermia, despite intact circadian rhythms[12]. These findings underscore that sleep and thermoregulation are not parallel processes but inseparable outputs of a unified hypothalamic architecture.

Fourth, NREM-linked cooling induces transcriptional programs central to neuronal resilience. Cold-inducible proteins, such as CIRBP and RBM3, regulate circadian clocks, enhance synaptic stability, and confer neuroprotection in models of Alzheimer's and prion diseases[6, 23]. This evidence reframes the energy role of sleep: not a modest 5–15% saving in caloric expenditure[83], but a thermodynamically optimized phase for neuroplasticity, immune recalibration, and molecular repair.

Together, these insights overturn the traditional assumption that temperature changes are secondary by-products of sleep. Instead, sleep itself emerges as a thermoregulatory state-transition process, orchestrated to exploit thermal gradients for adaptive ends. Circadian and homeostatic processes remain vital, but they are insufficient without incorporating thermal dynamics into a triadic model of sleep regulation[2].

This perspective has profound clinical implications. Disorders such as insomnia, REM sleep behaviour disorder, and thermoregulatory failure in Parkinson's disease may arise from disrupted integration of thermal and sleep circuits[29, 95-97]. Interventions that target peripheral warming, brown adipose tissue activation, or hypothalamic thermo-sleep circuits could inaugurate a new generation of temperature-based sleep therapies. Beyond clinical neurology, this reframing challenges us to reconsider consciousness itself as a thermobiological phenomenon: sleep as the price we pay not simply for wakefulness, but for keeping the brain within the narrow thermal range where cognition and repair can coexist.

Conclusion

This work supports a fundamental shift in how sleep is conceptualized. Rather than a passive outcome of circadian and homeostatic processes, sleep emerges as a thermobiological state transition in which

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coordinated changes in brain and body temperature actively drive its initiation, structure, and function. Evidence across behavioural, circuit-level, and molecular domains converges to show that thermoregulation is not ancillary but central to sleep biology, linking peripheral microclimates, hypothalamic integration, and temperature-sensitive gene programs to neuronal maintenance and system-level efficiency. This framework not only challenges established models but also opens a translational pathway: targeting thermal dynamics—through behavioural, environmental, or neurobiological interventions—may offer accessible and mechanistically grounded strategies to improve sleep and modify disease trajectories. Ultimately, integrating thermoregulation into sleep science reframes sleep as an adaptive process that preserves brain function within optimal thermal limits, with implications that extend from basic neuroscience to clinical medicine.

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INVESTIGACIÓN en DISCAPACIDAD
Vol. 12, 2026 pp e3-e19

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