Control of sleep in mammals

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MERCK
Be well

The onset of mammalian sleep is associated with an increase in the activity of sleep-active neurons and a decrease in the activity of wake-active neurons. In most mammals, including humans, sleep consists of rapid eye movement (REM) and non-REM (NREM) phases. Studies, most of which have been conducted in rodents or cats, show that neurons that are active during NREM sleep are scattered in groups between the basal forebrain and the medulla. By contrast, the pons, a major site of REM-active neurons, is sufficient for the generation of REM sleep. The suprachiasmatic nucleus (SCN) regulates sleep tendency over the 24-hour period. Here, we provide an overview of the current understanding of sleep generation, pathology and function.

Sleep basics

Sleep comprises two distinct states: REM sleep and NREM sleep. When going to sleep, individuals usually enter the NREM state, which is characterized by high-voltage cortical slow waves (as observed on EEGs), slow but regular respiration rate and heart rate, and a reduction in muscle tone (as observed on EMGs) compared with waking levels. The REM sleep state usually follows NREM sleep and is characterized by low-voltage cortical waves that resemble those observed in the awake state in humans, cats and dogs. In rodents, prominent cortical theta waves (4–8 Hz) occur during REM sleep. REM sleep is also characterized by irregular respiration and heart rate, penile erections and clitoral engorgement, rapid eye movements and, paradoxically, minimal muscle tone. The NREM and REM states alternate throughout sleep, and individuals can experience awakenings from either state. Direct transitions from waking to REM sleep are generally seen only in pathological conditions such as narcolepsy. The displayed traces come from mice.

The amount of time spent awake versus asleep is under circadian regulation (see below) and homeostatic regulation. The neural mechanisms of homeostatic control remain unclear, although adenosine has been implicated in the control of NREM sleep[1–3], accounting for the activating effects of the adenosine receptor antagonist caffeine. The interaction between the circadian and homeostatic mechanisms has been modelled by Borbely[4]. Deprivation of sleep or REM sleep results in a 'rebound' of the deprived states after the period of deprivation. The amount of lost sleep is not usually recovered, but the recovery sleep can be considered to be more 'intense', with higher-voltage slow waves during NREM sleep and more rapid eye movements and twitching during REM sleep.
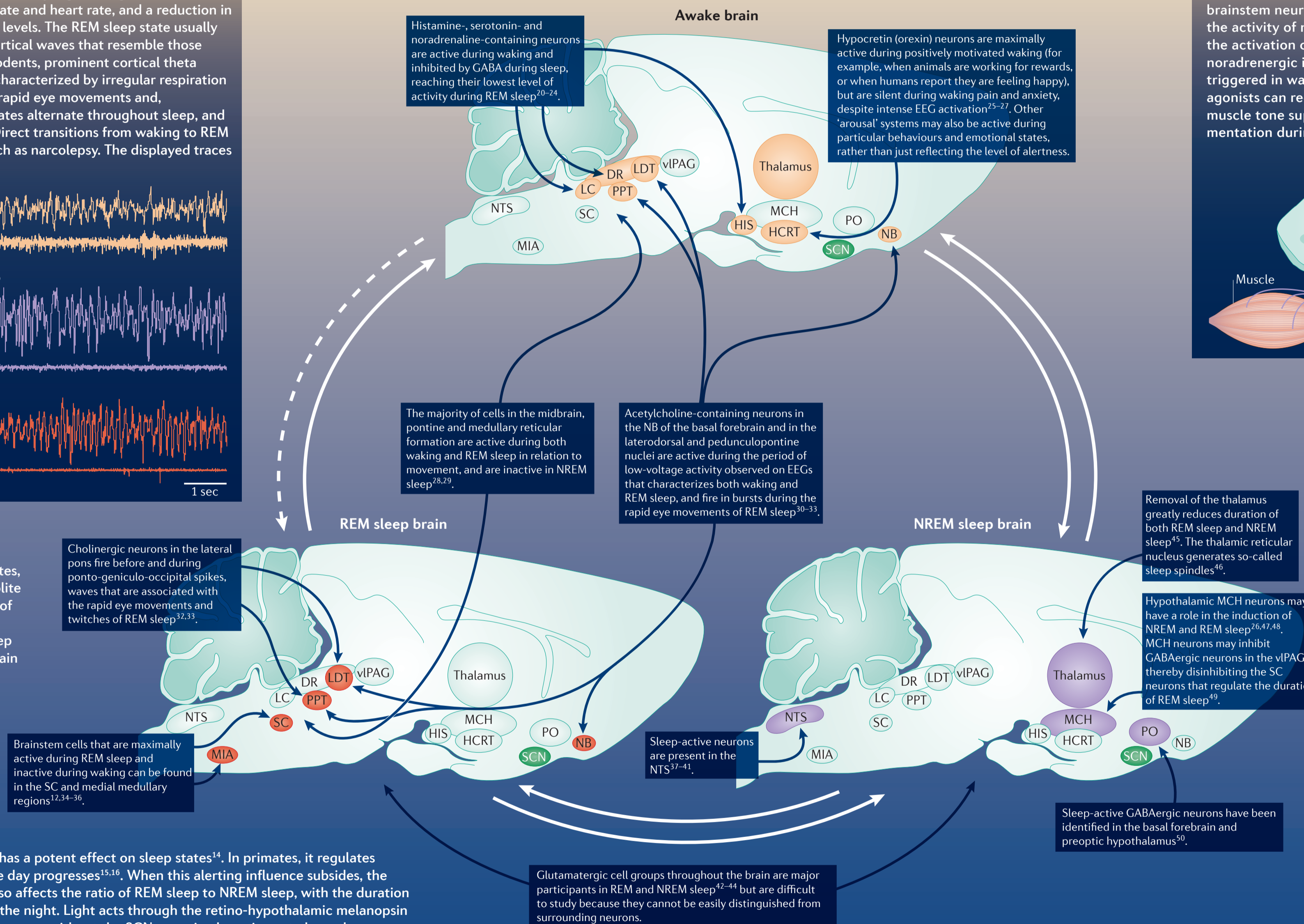
Awake
EEG
EMG

NREM sleep
EEG
EMG

REM sleep
EEG
EMG

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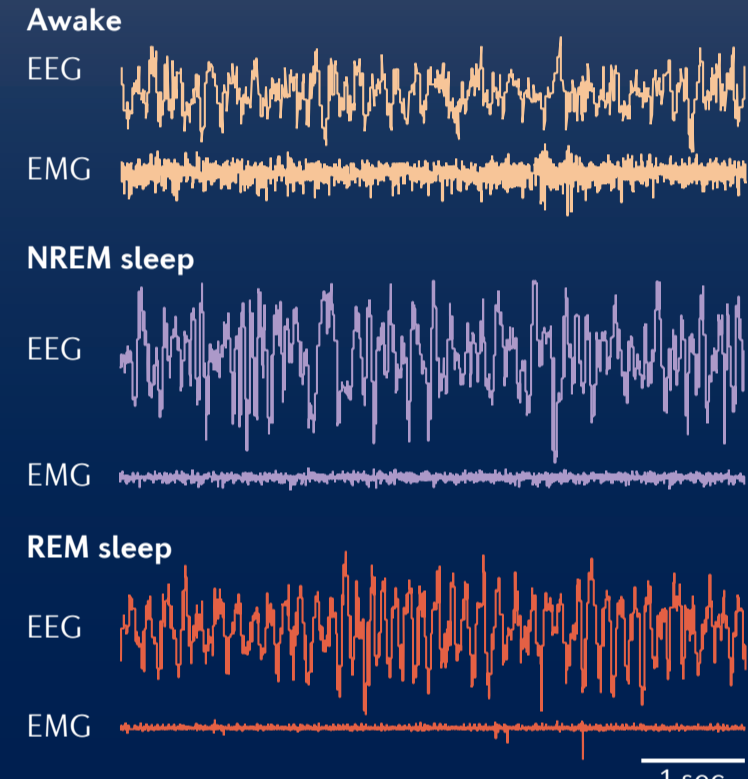
Why we sleep

There is little agreement on the functional role of sleep states, with synaptic sculpturing and homeostasis[5,6], brain metabolite clearance[7] and immune function[8] being recent hypotheses of sleep function. Daily sleep duration varies tremendously across mammalian species, ranging from 2 to 20 hours. Sleep duration is not strongly correlated with brain size or the brain weight–body weight ratio across species, but is associated with species-specific diet: herbivores sleep the least, omnivores sleep more and carnivores sleep the most[9]. This pattern is consistent with sleep having an adaptive role in acquiring food and conserving energy. Sleep parameters in humans are not correlated with learning ability[10,11] or intelligence quotient[12,13].
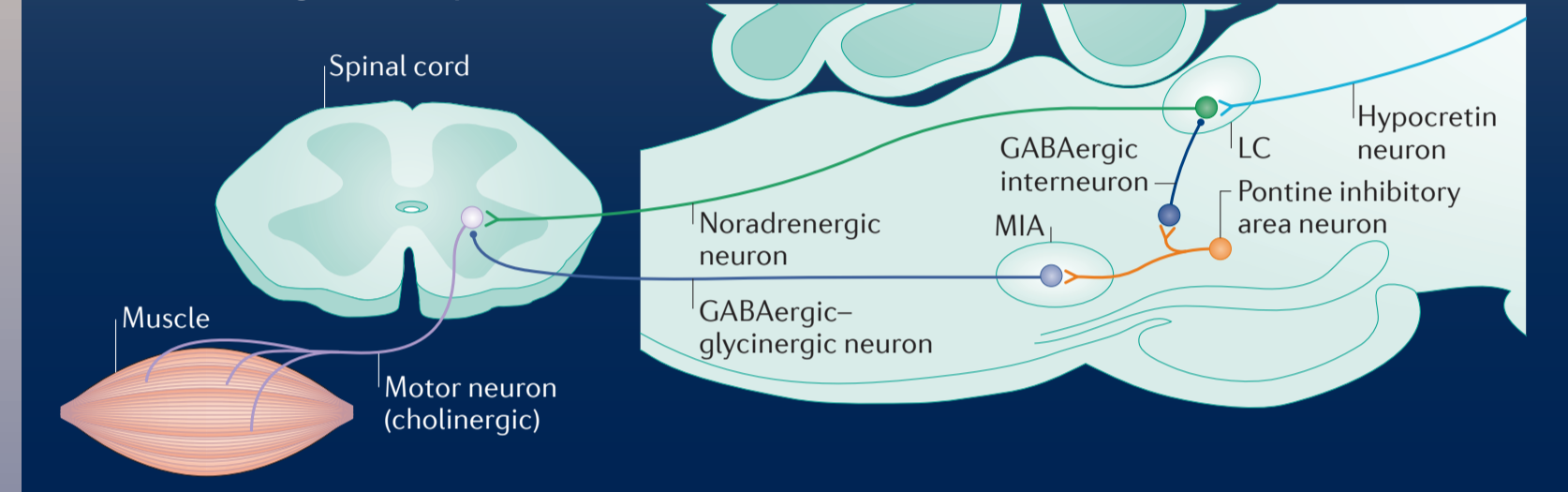
Circadian control of sleep

The SCN is the major synchronizer of 24-hour rhythms and has a potent effect on sleep states[14]. In primates, it regulates a circadian alerting signal that counteracts sleepiness as the day progresses[15,16]. When this alerting influence subsides, the NREM–REM sleep cycle is initiated. The circadian rhythm also affects the ratio of REM sleep to NREM sleep, with the duration and intensity of REM sleep periods increasing at the end of the night. Light acts through the retino-hypothalamic melanopsin system to entrain the circadian rhythm to the solar day[17]. However, without the SCN, an animal continues to have the expected amount of NREM sleep and REM sleep, indicating that the SCN is not essential for the production of these states[18,19].

The sleep cycle and neural correlates of sleep and awake states

Awake brain

Histamine-, serotonin- and noradrenaline-containing neurons are active during waking and inhibited by GABA during sleep, reaching their lowest level of activity during REM sleep[20–24].

Hypocretin (orexin) neurons are maximally active during positively motivated waking (for example, when animals are working for rewards, or when humans report they are feeling happy), but are silent during waking pain and anxiety, despite intense EEG activation[25–27]. Other 'arousal' systems may also be active during particular behaviours and emotional states, rather than just reflecting the level of alertness.

The majority of cells in the midbrain, pontine and medullary reticular formation are active during both waking and REM sleep in relation to movement, and are inactive in NREM sleep[28,29].

Acetylcholine-containing neurons in the NB of the basal forebrain and in the laterodorsal and pedunculopontine nuclei are active during the period of low-voltage activity observed on EEGs that characterizes both waking and REM sleep, and fire in bursts during the rapid eye movements of REM sleep[30–33].

REM sleep brain

Cholinergic neurons in the lateral pons fire before and during ponto-geniculo-occipital spikes, waves that are associated with the rapid eye movements and twitches of REM sleep[32,33].

Brainstem cells that are maximally active during REM sleep and inactive during waking can be found in the SC and medial medullary regions[12,34–36].

NREM sleep brain

Removal of the thalamus greatly reduces duration of both REM sleep and NREM sleep[45]. The thalamic reticular nucleus generates so-called sleep spindles[46].

Hypothalamic MCH neurons may have a role in the induction of NREM and REM sleep[26,47,48]. MCH neurons may inhibit GABAergic neurons in the vlPAG, thereby disinhibiting the SC neurons that regulate the duration of REM sleep[49].

Sleep-active neurons are present in the NTS[37–41].

Sleep-active GABAergic neurons have been identified in the basal forebrain and preoptic hypothalamus[50].

Glutamatergic cell groups throughout the brain are major participants in REM and NREM sleep[42–44] but are difficult to study because they cannot be easily distinguished from surrounding neurons.

Loss of muscle tone during REM sleep

Motor neurons receive projections from a GABA–glycine motor-inhibitory system in the medial medulla[51] and facilitation from the noradrenergic neurons in the LC and from other noradrenergic brainstem neurons[52,53]. During waking, a caudal projection from hypocretin cells to the LC maintains the activity of noradrenergic cells[12,54–57]. During REM sleep, muscle tone is reduced or eliminated by the activation of the GABA–glycine input on to motor neurons and simultaneous inactivation of the noradrenergic input, under the control of the pons[58]. This same pattern can be pathologically triggered in waking in individuals with narcolepsy, resulting in cataplexy[51–53]. Noradrenergic agonists can reduce cataplexy in individuals with narcolepsy. In REM sleep behaviour disorder, this muscle tone suppression system does not get fully activated, resulting in an 'acting out' of dream mentation during REM sleep[59].

Spinal cord
Hypocretin neuron
GABAergic interneuron
LC
Noradrenergic neuron
Pontine inhibitory area neuron
MIA
GABAergic–glycinergic neuron
Muscle
Motor neuron (cholinergic)

Sleep pathologies

Disorder	Clinical features	Underlying deficit	First-line treatment
Insomnia[60]	Inability to fall asleep or maintain sleep; feelings of inadequate sleep (even after non-shortened sleep)	Unknown in most cases; rarely, brain lesions; can occur with hyperarousal, depression or PTSD	Cognitive behavioural therapy
Sleep apnea[61]	Interrupted, obstructed breathing, causing hypoxia	Small-diameter airway and reduced tone in airway muscles, leading to airway collapse during sleep	Continuous positive airway pressure, delivered through a mask
REM sleep behaviour disorder[59]	Acting out dreams; injury during sleep	Damage to motor suppression regions in brainstem	Clonazepam
Periodic leg movement disorder; often seen in combination with 'restless legs' syndrome[62]	Regular twitches, usually of the legs	Unknown; potentially a brainstem abnormality	Dopamine agonists
Narcolepsy[63]	Sleepiness; cataplexy; hallucinations at sleep onset and offset; sleep paralysis	Loss of hypocretin neurons[55,56]; a greatly increased number of histaminergic neurons[64,65]	Stimulants to counteract sleepiness; antidepressants or noradrenergic agonists to prevent cataplexy; sodium oxybate for both symptoms

Abbreviations
DR, dorsal raphe
EEG, electroencephalogram
EMG, electromyograph
HCRT, hypocretin
HIS, histamine
LC, locus coeruleus
LDT, laterodorsal tegmental nucleus
MCH, melanin-concentrating hormone
MIA, medullary inhibitory area
NB, nucleus basalis
NREM, non-rapid eye movement
NTS, nucleus of the solitary tract
PO, preoptic hypothalamus
PPT, pedunculopontine tegmental nucleus
PTSD, post-traumatic stress disorder
REM, rapid eye movement
SC, subcoeruleus
SCN, suprachiasmatic nucleus
vlPAG, ventrolateral periaqueductal grey

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Competing interests statement
The authors declare no competing interests.

Reference list for the poster | **Control of sleep in mammals**
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1. Bjorness, T. E. & Greene, R. W. Adenosine and sleep. *Curr. Neuropharmacol.* **7**, 238–245 (2009).
2. Porkka-Heiskanen, T. Sleep regulatory factors. *Arch. Ital. Biol.* **152**, 57–65 (2014).
3. Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E. & McCarley, R. W. Control of sleep and wakefulness. *Physiol. Rev.* **92**, 1087–1187 (2012).
4. Borbely, A. A. & Achermann, P. in *Principles and Practice of Sleep Medicine* (eds Kryger, M. H., Roth, T. & Dement, W. C.) 405–417 (Elsevier Saunders, 2005).
5. Krueger, J. M., Obal, F. J. & Fang, J. Why we sleep: a theoretical view of sleep function. *Sleep Med. Rev.* **3**, 119–129 (1999).
6. Tononi, G. & Cirelli, C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* **81**, 12–34 (2014).
7. Xie, L. *et al*. Sleep drives metabolite clearance from the adult brain. *Science* **342**, 373–377 (2013).
8. Opp, M. R. Sleeping to fuel the immune system: mammalian sleep and resistance to parasites. *BMC Evol. Biol.* **9**, 8 (2009).
9. Siegel, J. M. Clues to the functions of mammalian sleep. *Nature* **437**, 1264–1271 (2005).
10. Ackermann, S., Hartmann, F., Papassotiropoulos, A., de Quervain, D. J. & Rasch, B. No associations between interindividual differences in sleep parameters and episodic memory consolidation. *Sleep* **38**, 951–959 (2014).
11. Rasch, B., Pommer, J., Diekelmann, S. & Born, J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nat. Neurosci.* **12**, 396–397 (2009).
12. Siegel, J. M. in *Principles and Practice of Sleep Medicine* (eds Kryger, M. H., Roth, T. & Dement, W. C.) 92–111 (Elsevier, 2011).
13. Siegel, J. M. The REM sleep-memory consolidation hypothesis. *Science* **294**, 1058–1063 (2001).
14. Partch, C. L., Green, C. B. & Takahashi, J. S. Molecular architecture of the mammalian circadian clock. *Trends Cell Biol.* **24**, 90–99 (2014).
15. Edgar, D. M., Dement, W. C. & Fuller, C. A. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep–wake regulation. *J. Neurosci.* **13**, 1065–1079 (1993).
16. Lee, M. L., Swanson, B. E. & de la Iglesia, H. O. Circadian timing of REM sleep is coupled to an oscillator within the dorsomedial suprachiasmatic nucleus. *Curr. Biol.* **19**, 848–852 (2009).
17. Santhi, N. *et al*. The spectral composition of evening light and individual differences in the suppression of melatonin and delay of sleep in humans. *J. Pineal Res.* **53**, 47–59 (2012).
18. Coindet, J., Chouvet, G. & Mouret, J. Effects of lesions of the suprachiasmatic nuclei on paradoxical sleep and slow wave sleep circadian rhythms in the rat. *Neurosci. Lett.* **1**, 243–247 (1975).
19. Shiromani, P. J. et al. Sleep rhythmicity and homeostasis in mice with targeted disruption of mPeriod genes. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **287**, R47–R57 (2004).
20. Aston-Jones, G. & Bloom, F. E. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep–waking cycle. *J. Neurosci.* **1**, 876–886 (1981).
21. McGinty, D. J. & Harper, R. M. Dorsal raphe neurons: depression of firing during sleep in cats. *Brain Res.* **101**, 569–575 (1976).
22. Nitz, D. & Siegel, J. M. GABA release in the posterior hypothalamus of the cat as a function of sleep/wake state. *Amer. J. Physiol.* **40**, R1707–R1712 (1996).
23. Nitz, D. & Siegel, J. M. GABA release in the dorsal raphe nucleus: role in the control of REM sleep. *Amer. J. Physiol.* **273**, R451–R455 (1997).
24. Nitz, D. & Siegel, J. M. GABA release in the cat locus coeruleus as a function of the sleep/wake state. *Neuroscience* **78**, 795–801 (1997).
25. McGregor, R., Wu, M.-F., Barber, G., Ramanathan, L. & Siegel, J. M. Highly specific role of hypocretin (orexin) neurons: differential activation as a function of diurnal phase, operant reinforcement vs. operant avoidance and light level. *J. Neurosci.* **31**, 15455–15467 (2011).
26. Blouin, A. M. *et al*. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. *Nat. Commun.* **4**, 1547 (2013).
27. Baimel, C. et al. Orexin/hypocretin role in reward: implications for opioid and other addictions. *Br. J. Pharmacol.* **172**, 334–348 (2015).
28. Siegel, J. M. & Tomaszewski, K. S. Behavioral organization of reticular formation: studies in the unrestrained cat. I. Cells related to axial, limb, eye, and other movements. *J. Neurophysiol.* **50**, 696–716 (1983).
29. Siegel, J. M., Tomaszewski, K. S. & Wheeler, R. L. Behavioral organization of reticular formation: studies in the unrestrained cat: II. Cells related to facial movements. *J. Neurophysiol.* **50**, 717–723 (1983).
30. Jones, B. E. Modulation of cortical activation and behavioral arousal by cholinergic and orexinergic systems. *Ann. N. Y. Acad Sci.* **1129**, 26–34 (2008).
31. Lapierre, J. L. *et al*. Cortical acetylcholine release is lateralized during asymmetrical slow-wave sleep in northern fur seals. *J. Neurosci.* **27**, 11999–12006 (2007).
32. Steriade, M., Pare, D., Datta, S., Oakson, G. & Curro, D. Different cellular types in mesopontine cholinergic nuclei related to ponto-geniculo-occipital waves. *J. Neurosci.* **10**, 2560–2579 (1990).
33. Steriade, M., Datta, S., Pare, D., Oakson, G. & Curro, D. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J. Neurosci.* **10**, 2541–2559 (1990).
34. Siegel, J. M. Behavioral relations of medullary reticular formation cells. *Exp. Neurol.* **65**, 691–698 (1979).
35. Siegel, J. M. *et al*. Activity of medial mesopontine units during cataplexy and sleep-waking states in the narcoleptic dog. *J. Neurosci.* **12**, 1640–1646 (1992).
36. Luppi, P. H. *et al*. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Med. Rev.* **15**, 153–163 (2011).
37. Eguchi, K. & Satoh, T. Characterization of the neurons in the region of solitary tract nucleus during sleep. *Physiol. Behav.* **24**, 99–102 (1980).
38. Euchi, K. & Satoh, T. Convergence of sleep-wakefulness subsystems onto single neurons in the region of cat's solitary tract nucleus. *Arch. Ital. Biol.* **118**, 331–345 (1980).
39. Golanov, E. V. & Reis, D. J. Neurons of nucleus of the solitary tract synchronize the EEG and elevate cerebral blood flow via a novel medullary area. *Brain Res.* **892**, 1–12 (2001).
40. Key, B. & Mehta, V. Changes in electrocortical activity induced by the perfusion of 5 hydroxtryptamine into the nucleus of the solitary tract. *Neuropharmacology* **16**, 99–106 (1977).
41. Magnes, J., Moruzzi, G. & Pompeiano, O. Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract. *Arch. Ital. Biol.* **99**, 33–67 (1961).
42. Lai, Y. Y. & Siegel, J. M. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. *J. Neurosci.* **11**, 2931–2937 (1991).
43. Lai, Y. Y., Clements, J. & Siegel, J. Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry. *J. Comp. Neurol.* **336**, 321–330 (1993).
44. Lai, Y. Y. *et al*. Brainstem projections to the ventromedial medulla in cat: retrograde transport horseradish peroxidase and immunohistochemical studies. *J. Comp. Neurol.* **408**, 419–436 (1999).
45. Villablanca, J. & Salinas-Zeballos, M. E. Sleep–wakefulness, EEG and behavioral studies of chronic cats without the thalamus: The 'athalamic' cat. *Arch. Ital. Biol.* **110**, 383–411 (1972).
46. Steriade, M. Sleep, epilepsy and thalamic reticular inhibitory neurons. *Trends Neurosci.* **28**, 317–324 (2005).
47. Jego, S. *et al*. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. *Nat. Neurosci.* **16**, 1637–1643 (2013).
48. Konadhode, R. R. et al. Optogenetic stimulation of MCH neurons increases sleep. *J. Neurosci.* **33**, 10257–10263 (2013).
49. Luppi, P. H., Clement, O. & Fort, P. Paradoxical (REM) sleep genesis by the brainstem is under hypothalamic control. *Curr. Opin. Neurobiol.* **23**, 786–792 (2013).
50. Szymusiak, R., Gvilia, I. & McGinty, D. Hypothalamic control of sleep. *Sleep Med.* **8**, 291–301 (2007).
51. Siegel, J. M. *et al*. Neuronal activity in narcolepsy: identification of cataplexy-related cells in the medial medulla. *Science* **252**, 1315–1318 (1991).
52. John, J., Wu, M.-F., Boehmer, L. N. & Siegel, J. M. Cataplexy-active neurons in the posterior hypothalamus: implications for the role of histamine in sleep and waking behavior. *Neuron* **42**, 619–634 (2004).
53. Wu, M. F. *et al*. Locus coeruleus neurons: cessation of activity during cataplexy. *Neuroscience* **91**, 1389–1399 (1999).
54. Peyron, C. *et al*. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J. Neurosci.* **18**, 9996–10015 (1998).
55. Peyron, C. *et al*. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat. Med.* **6**, 991–997 (2000).
56. Thannickal, T. C. *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* **27**, 469–474 (2000).
57. Schwarz, P. B., Mir, S. & Peever, J. H. Noradrenergic modulation of masseter muscle activity during natural rapid eye movement sleep requires glutamatergic signalling at the trigeminal motor nucleus. *J. Physiol.* **592**, 3597–3609 (2014).
58. Mileykovskiy, B. Y., Kiyashchenko, L. I., Kodama, T., Lai, Y. Y. & Siegel, J. M. Activation of pontine and medullary motor inhibitory regions reduces discharge in neurons located in the locus coeruleus and the anatomical equivalent of the midbrain locomotor region. *J. Neurosci.* **20**, 8551–8558 (2000).
59. Schenck, C. H. Rapid eye movement sleep behavior disorder: current knowledge and future directions. *Sleep Med.* **14**, 699–702 (2013).
60. Buysse, D. J. Insomnia. *JAMA* **309**, 706–716 (2013).
61. Donovan, L. M., Boeder, S., Malhotra, A. & Patel, S. R. New developments in the use of positive airway pressure for obstructive sleep apnea. *J. Thorac. Dis.* **7**, 1323–1342 (2015).
62. Hogl, B. & Comella, C. Therapeutic advances in restless legs syndrome (RLS). *Mov. Disord.* **30**, 1574–1579 (2015).
63. Thorpy, M. Update on therapy for narcolepsy. *Curr. Treat. Options Neurol.* **17**, 1–12 (2015).
64. John, J. *et al*. Greatly increased numbers of histamine cells in human narcolepsy with cataplexy. *Ann. Neurol.* **74**, 786–793 (2013).
65. Valko, P. O. *et al*. Increase of histaminergic tuberomammillary neurons in narcolepsy. *Ann. Neurol.* **74**, 794–804 (2013).