THE COGNITIVE NEUROSCIENCE OF SLEEP: NEURONAL SYSTEMS, CONSCIOUSNESS AND LEARNING

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Sleep can be addressed across the entire hierarchy of biological organization. We discuss neuronal-network and regional forebrain activity during sleep, and its consequences for consciousness and cognition. Complex interactions in thalamocortical circuits maintain the electroencephalographic oscillations of non-rapid eye movement (NREM) sleep. Functional neuroimaging affords views of the human brain in both NREM and REM sleep, and has informed new concepts of the neural basis of dreaming during REM sleep — a state that is characterized by illogic, hallucinosis and emotionality compared with waking. Replay of waking neuronal activity during sleep in the rodent hippocampus and in functional images of human brains indicates possible roles for sleep in neuroplasticity. Different forms and stages of learning and memory might benefit from different stages of sleep and be subserved by different forebrain regions.

CIRCADIAN RHYTHMS
Biological rhythms of physiology and behaviour that have a 24-h periodicity, which have evolved in response to the 24-h astronomical cycle to which all organisms are exposed.

ULTRADIAN RHYTHMS
Biological rhythms that have a periodicity of less than 24 h, such as the approximately 90-min REM–NREM cycle of the adult human.

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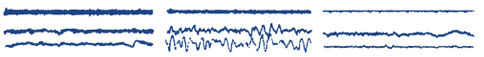
Can the neurobiology of sleep help us to understand the neural basis of conscious experience? Does sleep have consequences for cognitive functions such as learning and memory? We have recently reviewed the genetic, cellular and subcortical mechanisms that control the CIRCADIAN RHYTHMS of sleeping and waking, as well as the ULTRADIAN regularity of alternating rapid eye movement (REM) and non-REM (NREM) stages of sleep[1]. Here, we extend this examination of sleep upwards in the hierarchy of biological organization. We first consider regional changes in neuronal activity during sleep, and relate them to the accompanying alterations in conscious experience. Then we examine the functional significance of the neurobiological changes associated with sleep, with respect to their impact on the efficiency of waking cognition.

Traditionally, changes in the functions of neuronal systems have been measured at the level of organismal physiology by electrophysiological techniques, including electroencephalography (EEG), ELECTRO-OCULOGRAPHY (EOG) and electromyography (EMG), which are collectively termed polysomnography (PSG) and used to characterize sleep. Historically, there has also been a keen interest in the electrophysiology and functional significance of the brain-activated REM sleep state, given that it supports the greatest frequency and intensity of dreaming, and its EEG bears a marked similarity to that of waking[2,3]. In recent years, NREM sleep has been increasingly investigated in terms of its underlying electrophysiology[4,5], its accompanying subjective experiences[6], and its role in information transfer and organization in support of waking performance, exemplified by learning and memory[7–10]. FIGURE 1a shows how observations at the level of cerebral electrophysiology in sleep lead to the consideration of conscious experience and cognitive performance.

Technological innovations that have changed our picture of the brain basis of experience in waking and sleep include advances in quantitative electrophysiology, the advent of functional neuroimaging, and the ability to record the waking and sleep of subjects outside the sleep laboratory. Here, we show how it is now possible to map upwards from the level of neuromodulatory systems to the functional geography of the human brain and, finally, to cognition[3,8,11]. FIGURE 1b shows key brain regions involved in the control of

a

Behavioural state		Wake	NREM	REM
Cognitive consequences		Acquisition of information	Iteration of informatiion	Integration of information
Conscious experience	Sensation and perception	Vivid, externally generated	Dull or absent	Vivid, internally generated
	Thought	Logical progressive	Logical perseverative	Illogical bizarre
	Movement	Continuous voluntary	Episodic involuntary	Commanded but inhibited
Surface recordings	EMG			
	EEG			
	EOG			
Single-cell depth recordings (cat)	PGO waves in lateral geniculate nucleus			
	Aminergic systems (5-HT and NA)	 REM off		
	Cholinergic systems	 REM on		

b

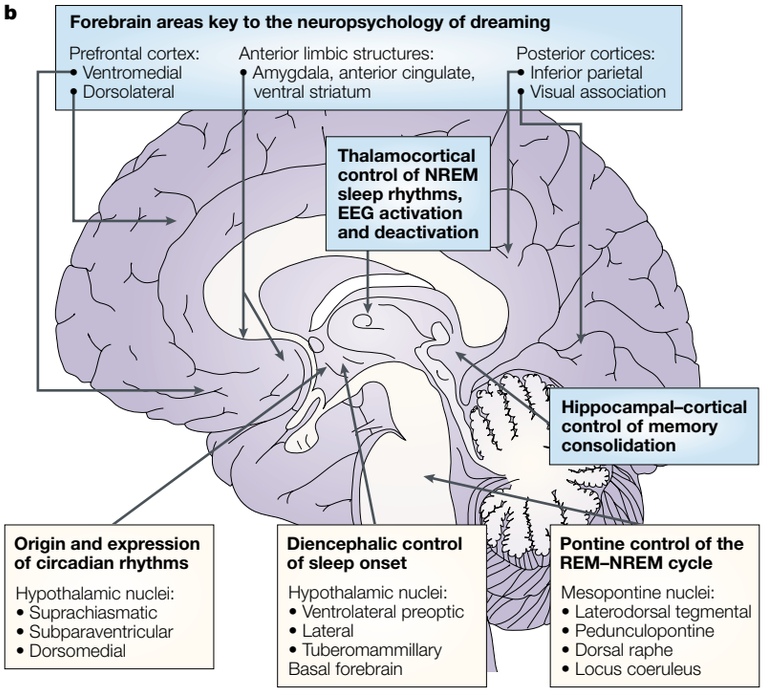


Figure 1 | **Levels of organization of sleep. a** | Manifestation of the three cardinal states of consciousness at levels of neural organization from the cellular generators of the non-rapid eye movement (NREM)–REM cycle in the pontine brainstem to the state-dependent processing of cognitive information in the forebrain. At the bottom level, depth recordings from single neurons in the pontine brainstem of the cat show the reciprocal waning of firing in REM-off aminergic cells and waxing of firing in cholinergic REM-on cells[1,3]. Also depicted are the ponto-geniculo-occipital (PGO) waves that are proposed to convey pseudosensory information from the REM-activated subcortex to the neocortex during dreaming[2]. The second level (surface recordings) illustrates the characteristic physiological signs of each state in human polysomnographic (PSG) recordings that consist of electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) output[1,94]. The third level lists variations in conscious experience during waking, NREM and REM sleep dreaming. The top level shows a proposed role for each state in the processing of information related to learning and memory. 5-HT, 5-hydroxytryptamine (serotonin); NA, noradrenaline. **b** | Brain regions of interest in the neurobiology of sleep. The blue boxes represent areas that are key to the generation of the EEG rhythms of sleep, the subjective experience of sleep mentation or dreaming, and sleep's effects on cognition, which are considered in this review. The subcortical regions (cream-coloured boxes) constitute the loci of control for the regulation of sleep–wake transitions and the control of REM–NREM alternation, which are considered in REF. 1. Anatomical image adapted, with permission, from REF. 129 © 1996 Appleton & Lange.

sleep–wake and REM–NREM cycles, along with the associated cognitive phenomena and functions. The upper tier of structures is considered in this review; the lower tier is described in REF. 1.

Electrophysiology of the sleeping brain

Quantitative electrophysiology in animals and increasingly sophisticated processing of human scalp EEG signals have gradually revealed how widespread cortical and subcortical systems generate the characteristic electrical rhythms of the different stages of sleep. Meanwhile, neuroimaging has allowed researchers to infer state-dependent increases and decreases in the net activity of neuronal populations in specific subcortical and cortical regions. Investigators who use these techniques are focusing attention increasingly on the role of sleep in neuroplasticity, learning and memory[8,11–15]. In this section, we attempt to integrate the findings from these diverse sources and to present a unified picture.

Thalamocortical generation of NREM oscillations

At all levels of the neuraxis (including ascending activating systems of the brainstem and diencephalon, thalamic relay nuclei and the neocortex), most neurons show decreased firing during the transition from waking to NREM sleep[4]. These changes probably result from the classical disfacilitation of rostral areas by diminished excitation from neural systems that ascend from the brainstem[4], and they validate Moruzzi and Magoun's original concept[16] of a reticular activating system. FIGURE 2 illustrates the anatomical structures and key cell types that are involved in the production and control of thalamocortically generated sleep rhythms.

For THALAMOCORTICAL OSCILLATIONS to begin, several neuromodulatory influences on thalamocortical networks must attenuate. These activating inputs include noradrenergic neurons from the LOCUS COERULEUS, serotonergic (5-hydroxytryptamine (5-HT)-synthesizing) projections from the DORSAL RAPHE NUCLEUS, histaminergic neurons from the tuberomammillary nucleus, orexinergic neurons from the lateral hypothalamus, and cholinergic neurons from the mesopontine tegmentum and basal forebrain[1]. Such inputs diminish under the influence of circadian and homeostatic signals from the hypothalamus that are thought to be linked to sleep–wake switching mechanisms[17]. Just as diminution of ascending activation allows thalamocortical oscillatory rhythms to emerge, such oscillations are abolished by the renewal of ascending cholinergic activation in REM sleep, and of cholinergic, aminergic and, possibly, histaminergic and orexinergic activation in waking[4].

Drawing on two decades of work in animal models, Steriade's group has begun to advance mechanistic models and functional hypotheses for the thalamocortical oscillations that appear as waveforms of characteristic morphology and frequency in the human scalp EEG in NREM sleep[4,14,15]. During NREM, thalamocortical neurons are globally inhibited by sustained GABA (γ-aminobutyric acid) input from the thalamic reticular nucleus, resulting in firing rates that are far below those of waking[4]. Such inhibition attenuates and gates the

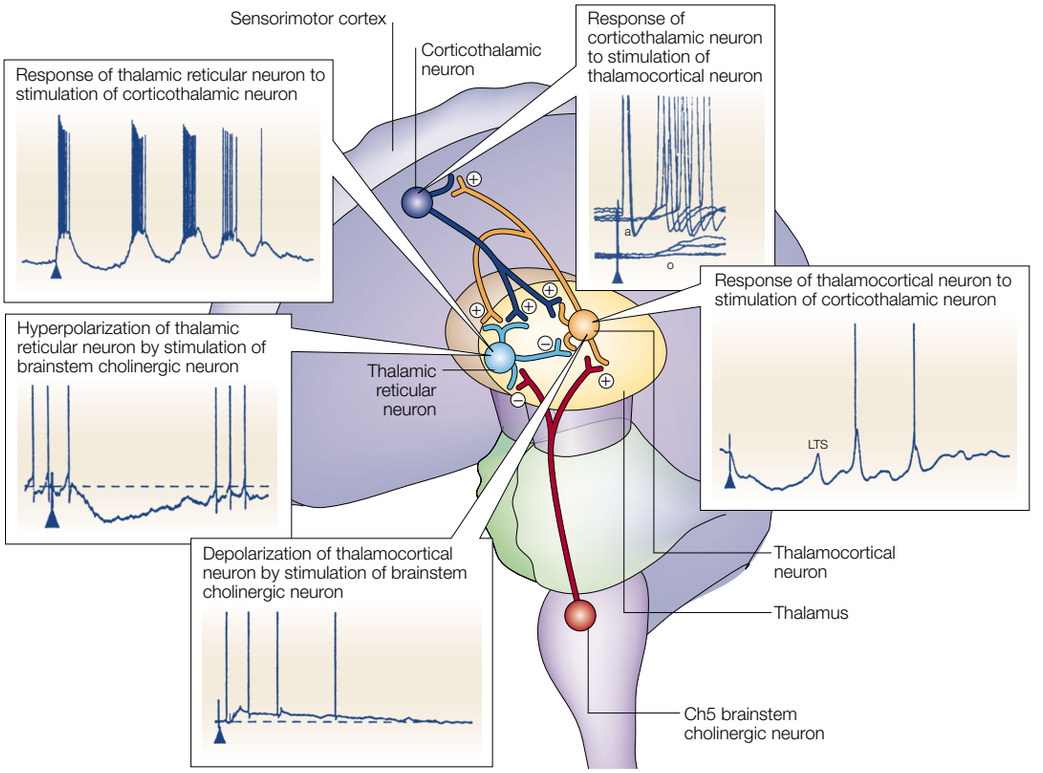


Figure 2 | **The thalamocortical machinery for the generation of oscillatory rhythms of NREM sleep and associated plasticity processes.** Structures involved in the production of thalamocortically generated non-rapid eye movement (NREM) sleep rhythms. Anatomical structures with representative, schematically depicted neurons include the cholinergic pedunculopontine tegmental nucleus of the mesopontine brainstem (Ch5), the reticular nucleus of the thalamus (which envelops the other thalamic nuclei), the combined specific (thalamocortical relay) and nonspecific (diffusely projecting) thalamic nuclei (mostly glutamatergic and excitatory), and the cortex (specific sensory regions of which are the targets of specific thalamic relay nuclei, whereas specific cortical motor regions project to different thalamic relay nuclei). Reticular thalamic neurons send inhibitory GABA (γ-aminobutyric acid)-releasing projections to other thalamic neurons, whereas most thalamocortical and corticothalamic neurons send excitatory glutamatergic projections. Local thalamic and cortical inhibitory interneurons are not shown. Intracellular recordings depicted include: depolarizing (excitatory) effects of ascending cholinergic stimulation on excitatory thalamocortical neurons, in contrast to the inhibitory effect of such stimulation on inhibitory reticular thalamic neurons; excitatory effects resulting from stimulation of thalamocortical and corticothalamic neurons on each other (a, antidromic action potential; LTS, low-threshold spike; o, orthodromic action potential in response to the same stimulus as a); and the characteristic spindle-frequency response of thalamic reticular neurons to excitatory corticothalamic stimulation. Modified, with permission, from REF. 15 © 2000 Elsevier Science.

ELECTRO-OCULOGRAPHY
The polysomnographic measurement of eye movement by electrodes mounted adjacent to each eye, which detect movements of the electrical dipole produced by the retina.

THALAMOCORTICAL OSCILLATIONS
Characteristic rhythmic variations in brain electrical potential that are thought to reflect summated interactions between excitatory and inhibitory neurons of the cortex and thalamus; they emerge when sensory input and ascending arousal from the brainstem reticular activating system to thalamic relay cells diminish during NREM sleep.

LOCUS COERULEUS
A nucleus of the brainstem that is the main supplier of noradrenaline to the brain.

DORSAL RAPHE NUCLEUS
A nucleus of the brainstem that comprises a large cluster of serotonin-containing neurons. An important supplier of serotonin to the forebrain and to other brainstem nuclei.

corticopetal transmission of information from thalamic sensory-relay areas that occurs during waking[15]. By contrast, most cortico-cortical neurons fire at nearly waking levels during NREM, and some even increase their mean firing rates[4,15]. This shift in balance between exteroceptive input through the thalamus in waking to off-line intrinsic excitation of the cortex in NREM is a hallmark of sleep that helps us to understand the abrupt and distinctive changes in consciousness that occur at sleep onset[18] and in NREM sleep[6].

The characteristic oscillatory waveforms of NREM sleep in the cat are shown in FIG. 3a. They include sleep spindles (sigma frequency, 12–15 Hz), delta waves (1–4 Hz), the K-complex waveform, and slow oscillations (0–1 Hz)[4,15]. Spindles, K-complexes and delta waves are all characteristic features of the human NREM sleep EEG (FIG. 3b). The slow oscillation has also been described in the human EEG[19] and using the magnetoencephalogram (MEG)[20].

The slow oscillation of NREM sleep originates in the cortex[4,15]. It results from a prolonged hyperpolarization of cortical neurons, seen in the surface EEG as a high-amplitude negative field potential. This is followed by a depolarized phase during which cortical cells fire vigorously and spontaneously, temporarily boosting mean rates of neocortical neuronal firing during NREM to levels up to and above those of waking. The intense burst firing might be important in plasticity processes, including neocortical consolidation of learning and memory[4,15].

Steriade has used ablation and simultaneous intracellular recordings in the cat to establish the following rules about the generation of NREM sleep rhythms. The depolarization phase of the cortical neuronal ensemble's slow oscillation constitutes the synchronizing pulse for thalamic spindle generation. This cortical depolarization followed by its triggered spindle constitutes the K-complex. Delta waves have a dual origin: they can be generated within the thalamus alone, through an

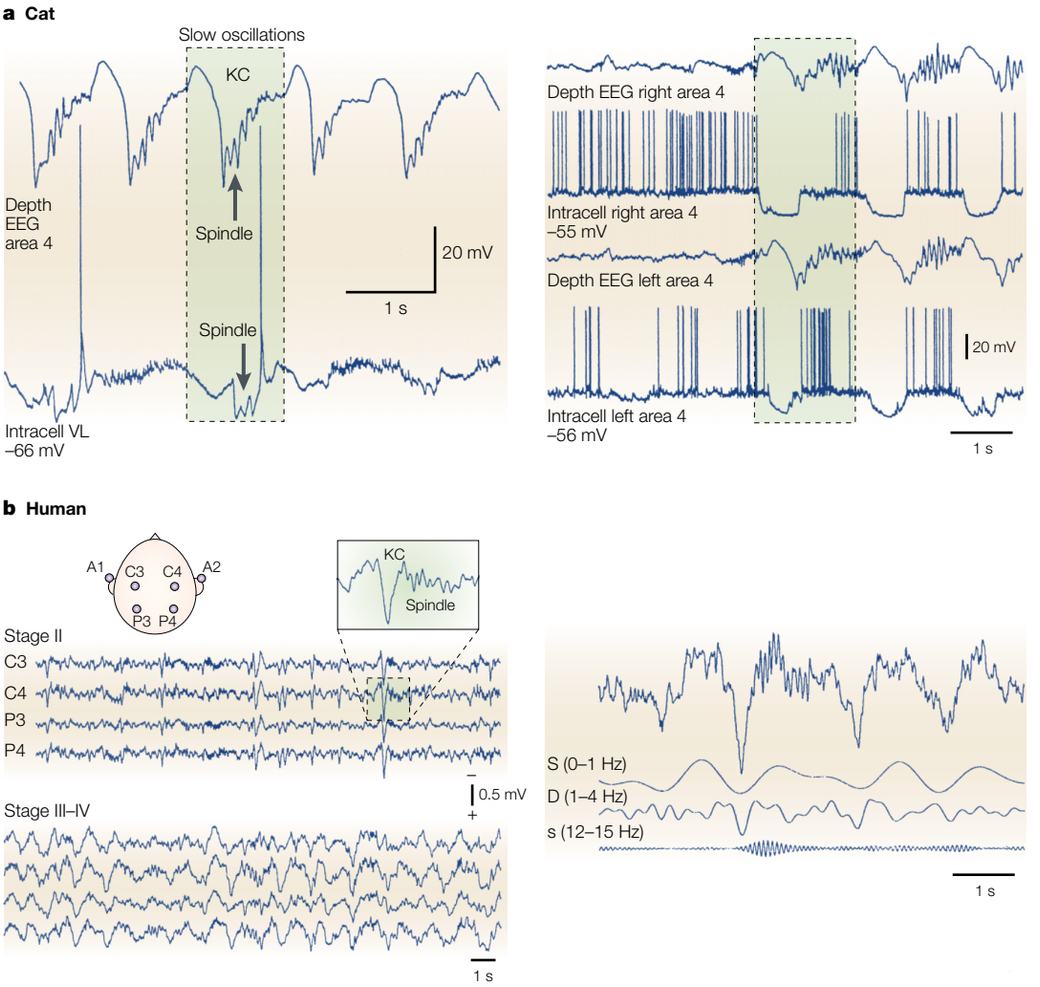


Figure 3 | **Relationships between the NREM oscillatory waveforms proposed by Steriade**[15]. **a** | Combined intracellular (intracell) and depth recordings during non-rapid eye movement (NREM) sleep in the cat (VL, ventral lateral thalamocortical neuron). **b** | Scalp electroencephalography (EEG) in human stage II and delta (stage III and IV) NREM sleep (A, reference electrode placed over mastoid process or auricle of ear; C, central scalp electrode; P, parietal scalp electrode). In the cat, the depolarized (excitatory) phase of the cortically generated slow oscillation (green box in right panel of **a**) is believed to trigger and synchronize the characteristic NREM thalamic combined spindle/K-complex (KC) waveform (green box in left panel of **a**). In the human, a similar KC (left panel of **b**), as well as a similar temporal relationship between slow (S), delta (D) and spindle (s) oscillations (right panel of **b**), is seen during stage II NREM.

interaction between intrinsic thalamic cell-membrane currents[21], and they can also be generated entirely within the cortex, surviving thalamectomy[21]. Cortically generated delta waves might result from cortical excitation of inhibitory thalamic interneurons. These interneurons hyperpolarize the thalamocortical cells, which then feed a synchronizing pulse back to the cortex[4].

Steriade[4,14,15] suggests that a re-entrant cortico-thalamo-cortical loop is responsible for the EEG of NREM sleep, and that the cortical slow oscillation provides the envelope in which the characteristic waveforms (spindles, K-complexes and delta waves) are nested. In humans, as in the cat, the slow oscillations of NREM sleep are thought to influence spindle and delta-wave generation[19,22].

The intense discharge of neocortical neurons during the depolarization phase of the slow oscillation might provide signals that are used in synaptic reorganization, plasticity and the consolidation of information acquired in waking[4,14,15]. To test the hypothesis that learning and memory can result from the phasic depolarization of cortical neurons at the end of each slow oscillation, Steriade's group used intracellular recording techniques to study the augmentation that results from driving cortical neurons experimentally with electrical pulses that have the same frequency as spindles[4,14,15]. Spindles might have a role in neuronal plasticity by inducing LONG-TERM POTENTIATION (LTP), which is presumed to underlie the plastic changes that are associated with learning and memory[23]. LTP can be induced experimentally in specific hippocampal circuits, and also occurs in neocortical circuits[24,25]. Although sleep spindles have not yet been linked specifically to LTP, natural spindles, as well as spindle frequencies produced in an experimental model, have been shown to produce long-lasting changes in neuronal responsiveness[26].

LONG-TERM POTENTIATION (LTP). An enduring increase in postsynaptic responsiveness as a result of high-frequency (tetanic) stimulation of presynaptic neurons. It is measured both as the amplitude of excitatory postsynaptic potentials and as the magnitude of postsynaptic-cell population spike. LTP is most often studied in the hippocampus and is often considered to be the cellular basis of learning and memory.

TWO-PROCESS MODEL
An influential theory of sleep–wake regulation proposed by Alexander Borbély, which states that sleep–wake propensity results from the combined influence of an intrinsic circadian pacemaker and a homeostatic process that depends on the duration of previous waking.

SOMNOGEN
An agent that promotes sleep. Endogenous somnogens accumulate during prolonged waking, tending to favour sleep regardless of the phase of the circadian cycle. Putative somnogens include adenosine, cytokines, hormones, melatonin, oleomide and prostaglandins.

SLOW-WAVE ACTIVITY
A spectral analytic measure of total power in slow-oscillation and delta frequencies of the electroencephalogram (0.5–4.5 Hz) in NREM sleep, which is thought to be sensitive to the degree of pre-sleep homeostatic sleep pressure.

EXECUTIVE FUNCTION
A cluster of high-order capacities, which include selective attention, behavioural planning and response inhibition, and the manipulation of information in problem-solving tasks.

WORKING MEMORY
The representation of items held in consciousness during experiences or after the retrieval of memories. This form of memory is short-lasting and associated with the active rehearsal or manipulation of information.

SLEEP INERTIA
The persistence of subjective sleepiness and cognitive slowing after awakening from sleep, especially SWS.

PREFRONTAL CORTEX
The non-motor sectors of the frontal lobe that receive input from the dorsomedial thalamic nucleus and subserve working memory, complex attentional processes and executive functions such as planning, behavioural inhibition, logical reasoning, action monitoring and social cognition.

Human electrophysiology. At the level of the output of neuronal assemblies in humans, quantitative EEG techniques continue to illuminate the structure of sleep and its control mechanisms. A basic principle of sleep-cycle control in humans is articulated in Borbély's TWO-PROCESS MODEL, in which sleep–wake state transitions result from the combined effects of circadian factors (process C) and homeostatic factors (process S)[5,22,27]. During sleep, a third regulator, the ultradian REM–NREM oscillator, comes into play[1]. Circadian input causes a greater or lesser tendency for sleep at specific times of the day[28], whereas homeostatic sleep drive increases with increasing time spent awake[22]. The cellular and molecular basis of sleep homeostasis is being investigated through the search for endogenous SOMNOGENS, such as adenosine[29].

A reliable electrophysiological correlate of sleep drive that is mediated by time spent awake has been identified in the form of SLOW-WAVE ACTIVITY (SWA) — an EEG spectral analytic index of the predominance of slow oscillations and delta waves (0.5–4.5 Hz)[22]. SWA is analogous to, but more accurate than, the percentage of time scored as slow-wave sleep (SWS; stages III and IV NREM), which is the traditional PSG measure of SWS[5,22]. (See REF. 22 for the extensive evidence that SWA indexes human homeostatic sleep pressure.)

Human SWA is closely related to the hyperpolarization of thalamocortical neurons during NREM in the cat, and both are likely to be enhanced by increased homeostatic sleep pressure. A waking EEG index that is considered to be a marker of increasing homeostatic sleep pressure is theta/low-frequency alpha (5.25–9 Hz) activity, which increases during extended wakefulness[30]. This index has been used to show that people at the 'short sleeper' end of the normal continuum of human sleep need are more resistant to homeostatic sleep pressure[30]. In contrast to SWA, spindle-frequency activity, another spectral analytic measure of NREM, has no relationship to sleep homeostasis[22]. This defining rhythm of lighter, stage II NREM might reflect brain activity that is related to sleep-mediated functions other than purely homeostatic, restorative ones. Plasticity-related activity as a candidate function for spindle-wave generation is indicated by the experimental spindle augmentation studies described above[4].

The identification of SWA as a marker of homeostatic sleep pressure has allowed the Borbély group to link the temporal progression of sleep pressure to its regional distribution in the surface EEG. One of their most notable findings has been that there is greater SWA in frontal than in parietal and occipital regions during the first NREM episode of the night[31,32]. Increases in SWA that are induced by sleep deprivation are especially prominent in frontal areas[32]; therefore, SWA might indicate an especially high need for recovery sleep in the region of the brain that is the seat of EXECUTIVE FUNCTION and WORKING MEMORY[32].

Finelli *et al.*[32] reported that frontal deficits on neuropsychological tasks emerge after sleep deprivation[33]. This might reflect higher dependence of the frontal cortex on sleep relative to more posterior regions[32,33]. Frontal deficits are especially characteristic of sleep disruption that results from experimental deprivation or from disorders such as obstructive sleep apnoea[33,34]. A positron emission tomography (PET) study has shown that frontal areas lag behind more posterior ones in reactivation after awakening[35]. These data indicate that frontal areas might be the first part of the cortex to fall asleep, the part that is most dependent on sleep homeostatic processes, and the last part to wake up — in other words, the part of the brain that is most affected by SLEEP INERTIA[36,37].

Many other neuronal-systems-level findings on sleep have been provided by quantitative electrophysiology, including MEG[20,38] and the computational localization of EEG signal generators[39,40]. Important findings that are beyond the scope of this review include descriptions, during REM, of cognition-associated gamma-frequency (30–80 Hz) oscillations[38,41], and the loss of their synchrony between frontal and posterior cortices during REM[42]. These observations begin to explain why we can become conscious during REM sleep, even though we are cut off from externally generated perceptions. In dreams, we experience fully formed imagery, but process it in unique, distinctive ways, while believing ourselves to be awake.

Brain imaging in humans. PET studies of NREM sleep reveal a decrease in global cerebral energy metabolism and blood flow compared with both waking and REM[3,11,43]. Moreover, energy metabolism decreases progressively with greater depth of NREM sleep[44]. By contrast, global cerebral energy metabolism during REM sleep is equal to or greater than that which occurs during waking[11,44].

During NREM sleep, significant regional declines in glucose or oxygen use relative to waking occur in the pons, thalamus, hypothalamus and caudate nucleus, as well as in lateral and medial regions of the PREFRONTAL CORTEX[45–47] (FIG. 4b). The finding that blood flow in the thalamus decreases with increased delta EEG activity is relevant to our discussion of oscillatory thalamocortical sleep rhythms[48]. Decreased blood flow in the thalamus and in the prefrontal and multimodal parietal association cortices accompanies the onset and deepening of NREM sleep[11,49–51].

During REM sleep (FIG. 4b), blood flow increases in the pons, midbrain and thalamus[46,52], amygdala[52], hypothalamus and BASAL GANGLIA[46]. Medial limbic-related cortices such as the anterior cingulate are also activated[46,52], but dorsolateral prefrontal areas remain less active than in waking[46,47,52] (FIG. 4a). This pattern is in keeping with older views of NREM and REM as deactivated and activated sleep phases, respectively, but these studies highlight important differences between brain regions that help us to understand the distinction between our conscious experiences of these states.

In REM sleep, there is relative deactivation of the dorsolateral prefrontal cortex compared with the globally activated state of waking[46,52]. By contrast, activation of LIMBIC AND PARALIMBIC REGIONS of the forebrain is increased[46,52,53] (FIG. 4a). Nofzinger *et al.*[54] have termed the activated area the 'anterior paralimbic REM activation

area', and describe it as a "bilateral confluent paramedian zone which extends from the septal area into ventral striatum, infralimbic, prelimbic, orbitofrontal and anterior cingulate cortex"[53]. Frontal deactivation has also been described in the first functional magnetic resonance imaging (fMRI) study of REM sleep[55], and portions of the ventromedial, limbic-related prefrontal cortices, and closely associated medial subcortex and cortex, have been shown to reactivate in REM following their deactivation, relative to waking, in NREM[54,56,57]. The restoration of a normal REM sleep increase in glucose metabolism relative to waking in portions of the anterior paralimbic REM activation area is a sensitive indicator of recovery from depression[54,57].

The selective activation of these areas is significant to our theory of the synthesis of instinctual drives and emotional feelings, together with associative cognition, in dreaming[3]. PET researchers have interpreted their findings in such terms, including the selective processing, in REM, of emotionally influenced memories[52,58], or the integration, in REM, of neocortical function with basal forebrain and hypothalamic motivational and reward mechanisms[53]. FIGURE 4a illustrates brain areas that are activated or deactivated in REM versus waking; FIG. 4b shows PET images of differences in regional brain activity between the cardinal behavioural states. These findings distinguish REM sleep brain activation from that of waking.

Recent studies have also revealed a possible human equivalent of the phasic activation signals seen in feline REM sleep (ponto-geniculo-occipital or PGO WAVES). Quantitative EEG techniques in humans have shown PGO-wave-like activity involving the pons, midbrain, thalamus, hippocampus and visual cortex[40]. Similarly, a recent $H_2{}^{15}O$ PET study in humans has shown that REM eye-movement density correlates with activation in the lateral geniculate nucleus and primary occipital cortex[59].

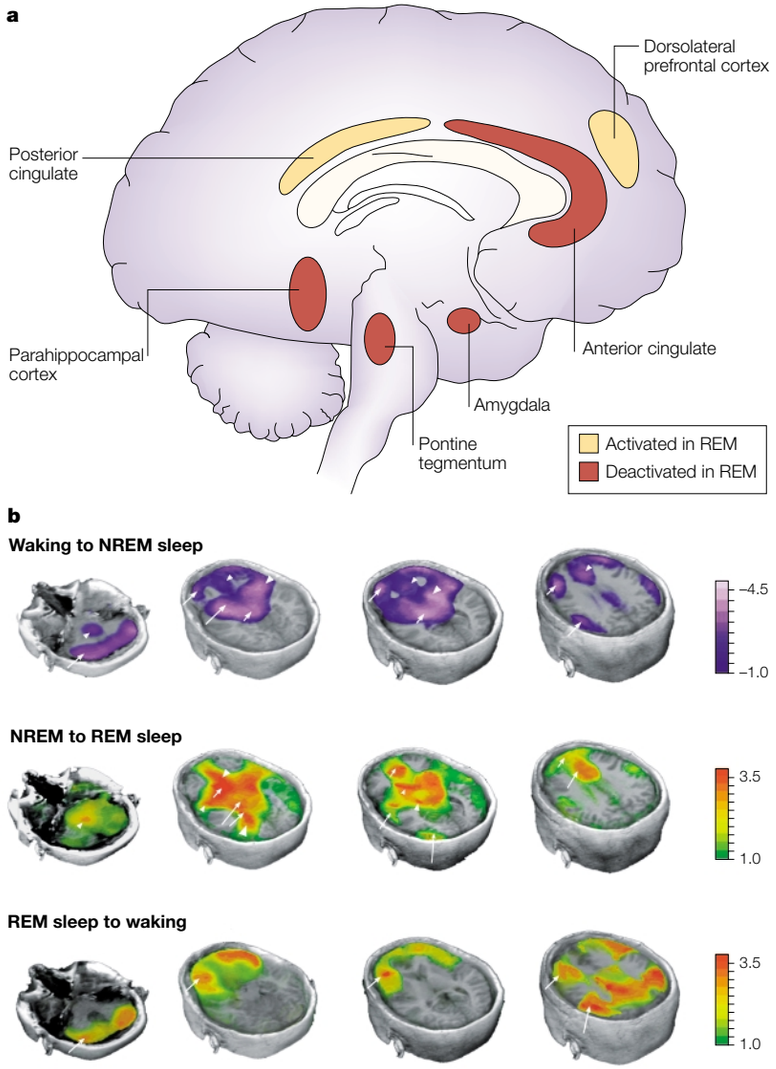


Figure 4 | **Brain activation during sleep and waking. a** | Sagittal view of the human brain showing areas that were activated or deactivated in rapid eye movement (REM) sleep compared with waking and/or non-REM (NREM) sleep in two or more of three positron emission tomography (PET) studies[46,52,53]. A schematic (rather than a morphologically realistic) view is shown of only the areas that could be easily matched between two or more studies. Considerably more extensive areas of activation and deactivation are reported in individual studies. The depicted areas are, therefore, representative portions of larger areas that subserve similar functions (such as limbic-related cortex, ascending activation pathways and multimodal association cortex[130]). **b** | Successive coronal sections of the brain showing changes in relative activity between waking and NREM, NREM and REM, as well as REM and waking, using $H_2{}^{15}O$ PET. *z*-score contrasts between the respective pairs of behavioural states are indicated. Values are *z*-scores that represent the significance level of changes in regional cerebral blood flow at each voxel. Reproduced, with permission, from REF. 46 © 1997 Oxford University Press.

Sleep and the basis of conscious experience

A cognitive neuroscience of conscious experience is gradually emerging from the three sources that we review in this section. When focusing on formal features of mentation, one can no longer either equate REM sleep with dreaming or say that REM sleep is the exclusive substrate of dream-like mentation. When we measure hallucinosis, thinking or bizarreness, all conscious states — including waking — might have some quantifiable aspects of dream-like mental activity, although such activity is minimal in waking and even lower in active waking. Mentation becomes more dream-like at sleep onset[18,60]; the dream-like state increases further in NREM and peaks in REM sleep[60]. Our working hypothesis is that, because REM sleep provides the most favourable brain conditions for dreaming, we can focus on its neurophysiology in our attempt to model the brain basis of dreaming.

The activation–synthesis model of dreaming. When the reciprocal-interaction model of sleep-cycle control was formulated[61], it was natural to speculate about the significance of the unique neuromodulatory conditions of REM sleep for the mental experience of dreaming. In the 'activation–synthesis hypothesis'[2], our initial concept was that ascending cholinergic activation of the off-line, aminergically demodulated brain during REM sleep provided the best physical substrate for such distinctive formal features of dreaming as visual hallucinosis, the delusional loss of self-reflective awareness, bizarreness, emotional intensification and memory loss.

When the theory was first formulated, the data supporting it were restricted to the mechanisms of forebrain activation by the brainstem, as elucidated by the

BASAL GANGLIA
A group of interconnected subcortical nuclei in the forebrain and midbrain that includes the striatum (putamen and caudate nucleus), globus pallidus, subthalamic nucleus, ventral tegmental area and substantia nigra.

LIMBIC/PARALIMBIC SYSTEM
Definitions vary, but usually encompass brain regions that are involved in emotion, instinct, memory and the integration of autonomic functions with conscious awareness. Includes subcortical structures such as the amygdala, hippocampus, hypothalamus and basal forebrain, as well as cortical areas such as the parahippocampal, entorhinal, insular, caudal medial orbitofrontal and anterior cingulate cortices.

PGO WAVES
REM-associated phasic potentials that are recorded sequentially in the pons, thalamic lateral geniculate body and occipital cortex of the cat and are thought to be one way in which pseudosensory information from the brainstem might be transmitted to the cortex during human dreaming.

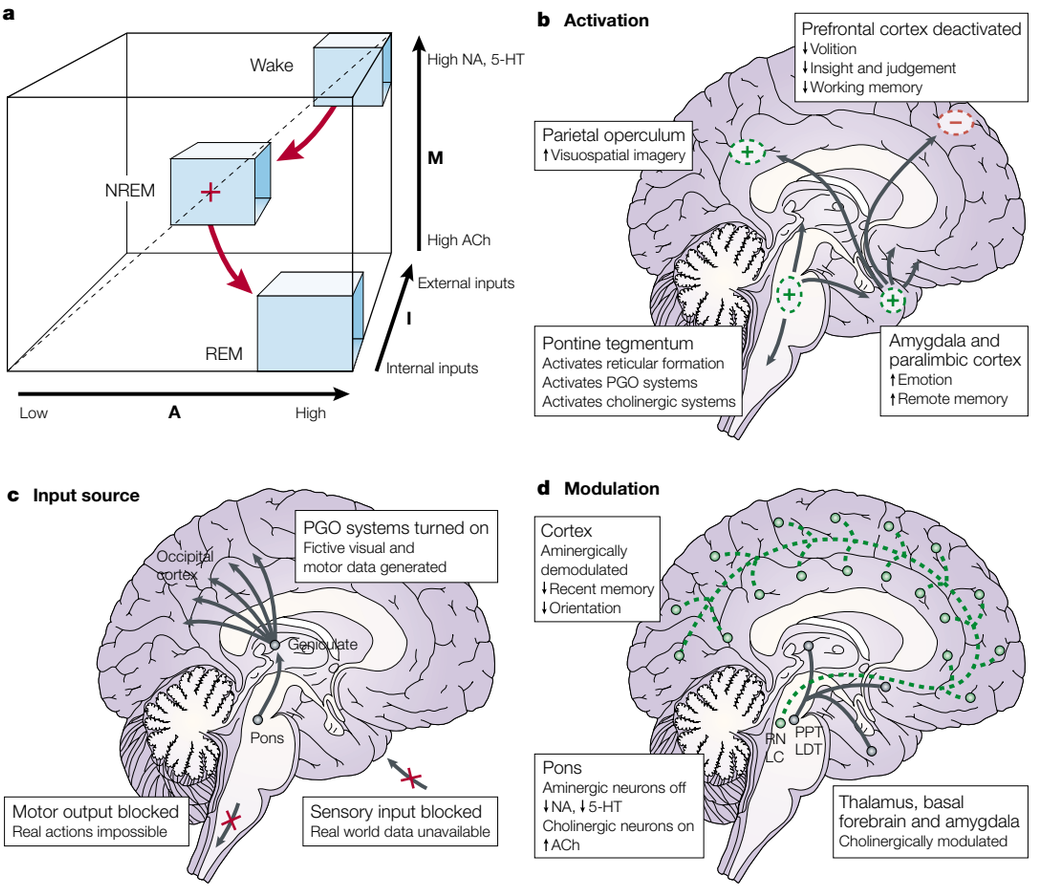


Figure 5 | **The updated AIM formulation of the activation synthesis model of dreaming. a** | The three-dimensional AIM (activation, input source, modulation) state-space model showing normal transitions within the AIM state space from wake to non-rapid eye movement (NREM) and then to REM sleep. REM occupies the lower right-hand front corner in which activation (A) is high, input (I) is entirely internal, and the forebrain is cholinergically activated and aminergically demodulated (M). **b**–**d** | Physiological signs and regional brain mechanisms of REM sleep dreaming separated into the activation (**b**), input source (**c**) and modulation (**d**) functional components of the AIM model. Dynamic changes in activation, input and modulation during REM sleep dreaming are described. Note that these are highly schematized depictions that illustrate global processes; no attempt has been made to provide comprehensive details of all the brain structures and their interactions that might be involved in REM sleep dreaming. 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; NA, noradrenaline; PGO, ponto-geniculo-occipital; PPT, pedunculopontine tegmental nucleus; RN, raphe nuclei. Anatomical images adapted, with permission, from REF. 129 © 1996 Appleton & Lange.

integration of findings in cats with PSG data from humans[2]. Neuroimaging data in humans now complement phenomenological studies of mental states that focus on hallucinatory imagery, thinking and memory loss, and we can say more about the synthesis side of the theory — that is, the consequences in the forebrain of activation by the brainstem in REM sleep. FIGURE 5 shows our current formulation of this hypothesis as the AIM (activation, input source, modulation) model of conscious states[3].

Portable, home-based recording devices such as the 'Nightcap' (FIG. 6a) have made it possible to access the formal characteristics of mental activity in waking and sleep over prolonged time periods in the same subjects[62,63]. Home-based study has three main advantages over the sleep lab. First, it allows repeated sampling of waking and sleep in the same subjects. Second, the increased sample size makes possible quantitative analyses of formal features such as hallucinosis and thinking (FIG. 6) in both waking and sleep. Third, it has shown that the differences between the physiologically and behaviourally defined states are much more robust than the laboratory studies of the past 50 years have suggested. In particular, there can no longer be any doubt that NREM and REM sleep support quantitatively different states of consciousness.

In one example, the mental activity of 16 normal young subjects was studied for 16 consecutive days by combining home-based sleep recording with beeper-based experience sampling of waking. A computer-controlled beeper or wake-up stimulus elicited 1,803 useful reports from the five states shown in FIG. 6b[60,63]. Reports of hallucinatory activity increased exponentially as subjects proceeded from waking to sleep onset and NREM sleep to a peak in REM sleep[60], whereas reports of directed thinking decreased rapidly. So, waking

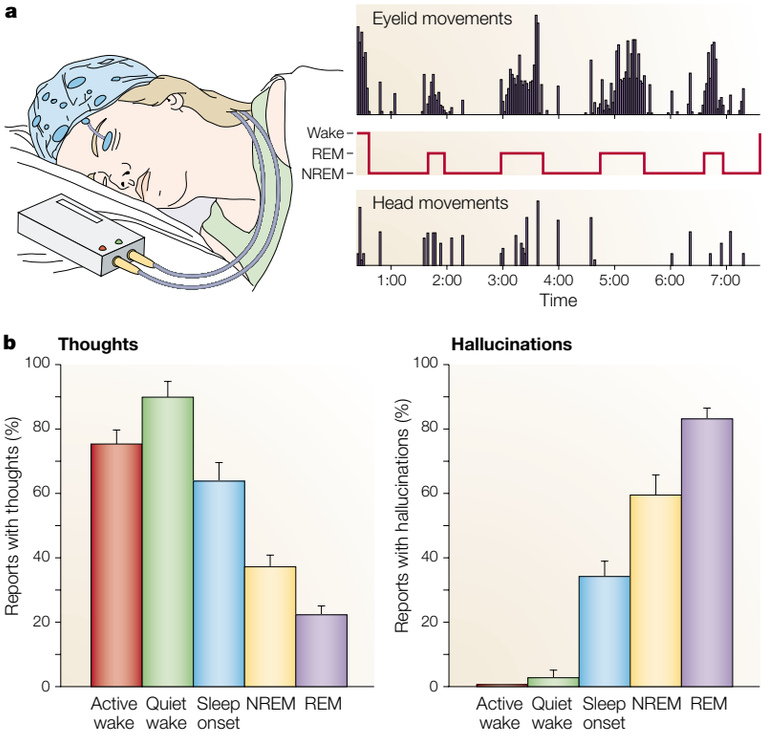


Figure 6 | **State-related changes measured using the Nightcap system. a** | Central arousal accompanying the activated states of rapid eye movement (REM) sleep and waking can be measured using the 'Nightcap' — a simple ambulatory monitor[62,63,131]. The Nightcap is a two-channel recording device that distinguishes waking, REM sleep and non-REM (NREM) sleep. One channel of the Nightcap monitors eye movement and the other monitors body movements. The Nightcap eyelid-movement readout is thought to reflect activity in portions of the brainstem oculomotor nucleus that innervate the eyelid and are adjacent to portions of the medial brainstem ascending reticular system, the activity of which, in turn, generates forebrain activation. **b** | Decline in directed thought and reciprocal increase in hallucinations during progression from active waking through sleep onset and NREM sleep to REM sleep. Modified, with permission, from REF. 60 © 2001 American Psychological Society.

suppresses hallucinosis in favour of thought, and REM sleep releases hallucinosis at the expense of thought. This contrast in mental activity corresponds to shifts in the activation pattern from waking to REM at both the molecular/cellular and brain-regional levels. We propose that this correlation represents a deep causality: as the brain goes, so goes the mind.

Freud believed that dream content was determined by a daytime experience that triggered the emergence of related memories. But does dreaming really depend on the memory of recent experience, and does it consist of the activation of episodic memories? We asked subjects to assess their dream reports, paying special attention to identifiable memory sources, and to provide confidence ratings of their identifications[10,64]. The results revealed that dream content does not accurately represent the narrative or episodic memories that are available to awake subjects. Instead, discrete and incomplete fragments of narrative memory are assembled to create the new synthetic scenarios of dreams. So, the synthesis that we proposed in the first formulation of the activation–synthesis dream theory proceeds without access to episodic memory. This helps to explain the plot discontinuities and incongruities of dream content[3,10].

Stickgold *et al.*[10] have suggested that the absence of episodic memory in dreams reflects the inaccessibility of hippocampally stored information to the dreaming brain. Elevated levels of acetylcholine, which suppresses the flow of information from the hippocampus to the cortex both in waking and in REM, might particularly restrict such outflow in the absence of aminergic neuromodulation during REM sleep[65].

Other formal aspects of dream consciousness that now seem to be clearly brain-based are the lack of self-reflective awareness, the inability to control dream action voluntarily, and the impoverishment of analytical thought. These cognitive deficits have inspired our diagnosis of dreaming as a 'normal delirium', sharing with the clinical syndrome all of its defining features: visual hallucinosis, disorientation, memory loss and confabulation[66].

In REM sleep, the activated forebrain is aminergically demodulated compared with waking and NREM sleep. Different regions are also hyperactivated (the amygdala, paralimbic cortices and certain multimodal association areas) and deactivated (the dorsolateral prefrontal cortex). We propose that findings at these different levels of analysis are causally linked and that they conspire to cause the robust shifts in formal mental-state features that distinguish waking and dreaming consciousness. Neuropsychological (as opposed to purely psychological) models of dreaming are increasingly being put forward by sleep scientists. In particular, Solms[67] has generated a large database on the dream effects of cerebral lesions and has advanced a psychoanalytically based neuropsychological model of dreaming that is quite different from the one described below.

Brain activation. Distributed networks of brain structures, not strictly localized 'centres', control waking cognitive skills, perception and consciousness[68]. So, explanations of sleep mentation that are based on correlations of regional brain activation with waking experience are inherently risky; the network's output might be affected by state-related changes in regions other than those being observed. Nevertheless, we can cautiously seek parallels between the wake–sleep differences in regional brain activation and in cognition to see whether they covary in the manner predicted from studies of waking. Our current model of the possible neurobiological instantiation of REM sleep dream phenomenology refers to each specific brain area depicted in FIG. 7.

As in waking, activation of the forebrain in REM occurs through ascending arousal systems (areas 1 and 2 in FIG. 7) in the brainstem reticular activating system[4,14,15] and the basal forebrain[69]; however, unlike in waking, activation is aminergically deficient and cholinergically driven[1,3]. During REM sleep, activated thalamic nuclei (area 6 in FIG. 7), which occupy key sites in sensory-relay and other brain circuits, transmit endogenous stimuli that lead to the sensory phenomena of dreaming. In NREM sleep, intrinsic thalamocortical

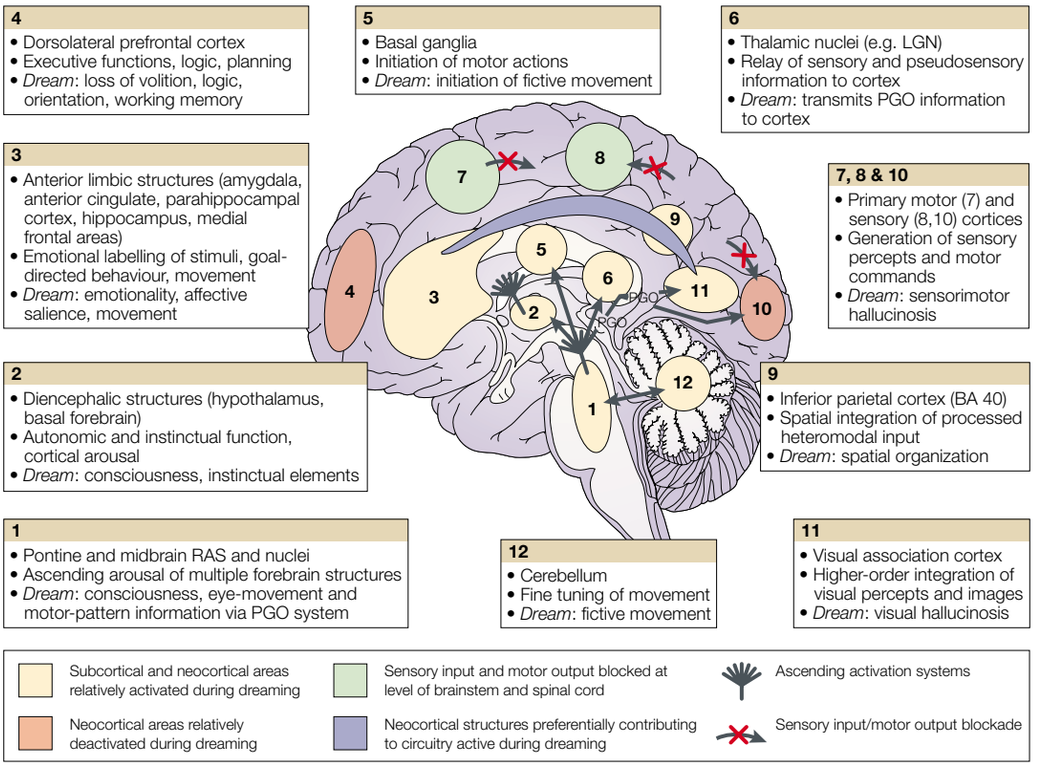


Figure 7 | **Forebrain processes in normal dreaming — an integration of neurophysiological, neuropsychological and neuroimaging data.** Regions 1 and 2, ascending arousal systems; 3, subcortical and cortical limbic and paralimbic structures; 4, dorsolateral prefrontal executive association cortex; 5, motor initiation and control centres; 6, thalamocortical relay centres and thalamic subcortical circuitry; 7, primary motor cortex; 8, primary sensory cortex; 9, inferior parietal lobe; 10, primary visual cortex; 11, visual association cortex; 12, cerebellum. BA, Brodmann area; LGN, lateral geniculate nucleus; PGO, ponto-geniculo-occipital; RAS, reticular activating system. Anatomical image adapted, with permission, from REF. 129 © 1996 Appleton & Lange.

oscillations suppress, but do not completely extinguish, perception and mentation.

Medial forebrain structures, especially limbic and paralimbic areas of the cortex and subcortex (area 3 in FIG. 7), are selectively activated during REM dreaming[46,47,52,53]. This activation could underlie dream emotionality[3,46,58] and the highly social nature of dreaming[70–72]. Activated limbic structures include the amygdala, which, among other functions, mediates anxiety[73] — a prevalent dream emotion[3,74–76]. They also include the anterior cingulate, the roles of which include emotion-related cognition such as conflict monitoring, as well as affect-related premotor functions[77]. Parts of the medial orbitofrontal and insular cortices are also activated[46,53]. Disruption of such anterior limbic areas by strokes and other brain lesions can cause dream-like confabulatory syndromes[67]. In addition, these areas are particularly recruited by emotion and social cognition[78,79], which are important phenomenological aspects of dream experience[70–72,80]. The hippocampus collaborates with the amygdala to mediate the storage of emotional memories in waking[81]; reactivation of these areas could allow the readout of emotionally salient memory fragments in REM sleep.

Strong activation of the basal ganglia[46] (area 5 in FIG. 7) might mediate the fictive motion of dreams[82]. The basal ganglia are extensively connected with REM-regulatory areas in the mesopontine tegmentum[83], where they are coextensive with gait circuitry[84]. Notably, the cerebellar vermis, which is involved in motor control and is increasingly implicated in emotion, cognition and psychopathology[85], is also activated during REM[46]. Similarly, Jouvet[86] and Revonsuo[87] propose that dreaming constitutes instinctively salient behaviour rehearsal.

According to our theory, areas of the medial occipital and temporal cortices that mediate higher visual processing (area 11 in FIG. 7) generate the visual imagery of dreams[47,67]. As in waking, specific areas of the visual association cortex process specific visual features in dreaming. For example, the fusiform gyrus mediates waking face recognition[88] and is selectively activated in REM[46,47,53]. Braun *et al.*[47] suggest that REM constitutes a unique cortical condition of internal information processing (between extrastriate and limbic cortices) that is functionally isolated from external input (from the striate cortex) or output (to the frontal cortex). The inferior parietal lobe (area 9 in FIG. 7), especially BRODMANN AREA 40, generates the perception of a fictive dream space that is necessary for the organized hallucinatory experience of dreaming[67]. Destruction of only this area is sufficient to prevent dreaming[67,89].

Deactivation of executive areas in the dorsolateral prefrontal cortex (area 4 in FIG. 7) during NREM sleep[45–48],

BRODMANN AREAS (BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains subdivisions, including BA 46, BA 9 and others). Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

followed by their failure to reactivate during REM[46,47,52], might underlie the prominent executive deficiencies of dream mentation, including disorientation, illogic, impaired working memory and amnesia for dreams[3]. REM sleep dreaming constitutes a normal physiological state of the brain that shares both its physiological substrate and psychological experience with psychopathological conditions, such as schizophrenia, in which limbic hyperactivation is combined with frontal hypoactivation (see REFS 80,90).

Component subsystems of states of consciousness (such as memory or visual processing) are physically instantiated in networks, each of which consists of several discrete brain regions[68]. In relation to networks, some generalizations about dreaming can be made. First, ascending arousal systems activate the many forebrain regions that are involved in dream construction in a manner that is chemically and anatomically different from waking arousal processes. Second, REM dreaming preferentially activates more medial cortical circuits that link posterior association and paralimbic areas (depicted by the central crescent in FIG. 7), rather than circuits that include the primary sensory cortex and/or frontal executive regions, which are not activated in REM[47]. This explains why dreaming is so emotionally salient and social, but also shows profoundly deficient working memory, orientation and logic. Third, subcortical circuits involving the limbic structures, STRIATUM, diencephalon and brainstem regions are selectively activated in REM. So, dreaming often involves a suite of emotional (limbic subcortex), motoric (striatum) and instinctual (diencephalon) elements.

Cognition and behaviour

Within the past decade, a sea-change in theory and practice has revolutionized our thinking and experimental approaches to the new cognitive neuroscience of sleep and dreaming. In this section, we emphasize direct and experimental work. The theme that ties all these parts together is, of course, plasticity. Ultimately, we must know how sleep promotes plasticity, and how this presumed enhancement of plasticity influences the phenomenology of sleep and the cognitive capacities of subsequent waking.

The concept that neuroplastic changes are consolidated in sleep, especially REM, is controversial. Some investigators point to animal studies that show increases in REM after learning, learning decrements after REM deprivation, and neuronal replay during sleep, and to specific correlations with procedural learning in humans[8–10,70]. Others argue that the effects of REM deprivation on learning might be epiphenomena of stress, and offer more general homeostatic and ecological explanations for the adaptive value of sleep and its stages[91,92]. Here, we adopt the working hypothesis that sleep does contribute to plasticity, and we describe the growing evidence in support of this theory.

Developmental plasticity and sleep. It has been suggested that sleep provides state-dependent facilitation of plastic processes in the early development of the mammalian nervous system[93,94]. Neonatal humans not only sleep much more than adults do, but they also devote more of that sleep to REM (~50% versus ~25% in adults). The proportion of REM sleep declines rapidly over the first year of life, and reaches adult levels by ~10 years of age[94]. Brain activity *in utero* and in premature infants consists almost entirely of REM-sleep-like states[95]. These findings have led many to attribute a developmental role to infant sleep states in mammals[93,94,96,97], but some question whether the desynchronized activity of the immature brain can be identified as REM sleep, or even likened to it.

Sleep has been shown to enhance cortical plasticity induced by monocular deprivation in the kitten during a critical period of development (~30 days of age)[98]. Brief monocular deprivation of an awake kitten in a lighted environment increases the percentage of neurons in its primary visual cortex that respond to stimuli delivered to the non-occluded eye — a process termed 'ocular dominance plasticity'. When the kittens were allowed to sleep for six hours after monocular deprivation, this plasticity was enhanced, but this enhancement did not occur if the kitten spent the additional six hours in the dark but was kept awake. Interestingly, the enhancement of ocular dominance plasticity was due entirely to NREM sleep[98].

Plasticity of the rat visual cortex shows a similar interaction with REM sleep[25]. Stimulation of underlying white matter reliably produces LTP in layers II/III of visual cortex slice preparations from rats younger than 29–30 days, but not after this age. This LTP is thought to reflect developmentally based plasticity of the visual cortex that is present during, but not after, a postnatal critical period. REM sleep deprivation extends the age at which such stimulation evokes LTP by up to a week[25] — an effect that is also produced by rearing rats in total darkness[99]. This led to the idea that REM might provide an endogenously based cortical stimulation that is analogous to stimulation of the visual cortex by normal visual input[25].

Cheour *et al.*[100] have shown that neonatal humans can distinguish changes in speech sounds. Measurement of EVENT-RELATED POTENTIALS showed that sleeping neonates could discriminate deviant from standard sounds following training during sleep. As such sleep learning does not occur in adults, the neonatal brain might be better able to assimilate auditory information.

Memory processing during sleep. Observations of replay during sleep of neuronal firing patterns recorded during previous waking (see below), along with evidence for specific outflow of information from the hippocampus to the neocortex during sleep[7], have prompted theories that interactions between the neocortex and the hippocampus during sleep promote the storage and consolidation of information acquired during previous waking[7,9,65]. One such model of state-dependent, hippocampal–neocortical information exchange[9] is illustrated in FIG. 8. On the basis of data collected in the rat, Buzsáki[7] posits that the cortex transfers experiential data that are acquired during waking to the

STRIATUM
A subset of the basal ganglia that is often differentiated into the dorsal striatum (caudate nucleus and putamen) and the ventral striatum (for example, nucleus accumbens).

EVENT-RELATED POTENTIALS
Electrical potentials that are generated in the brain as a consequence of the synchronized activation of neuronal networks by external stimuli. These evoked potentials are recorded at the scalp and consist of precisely timed sequences of waves or 'components'.

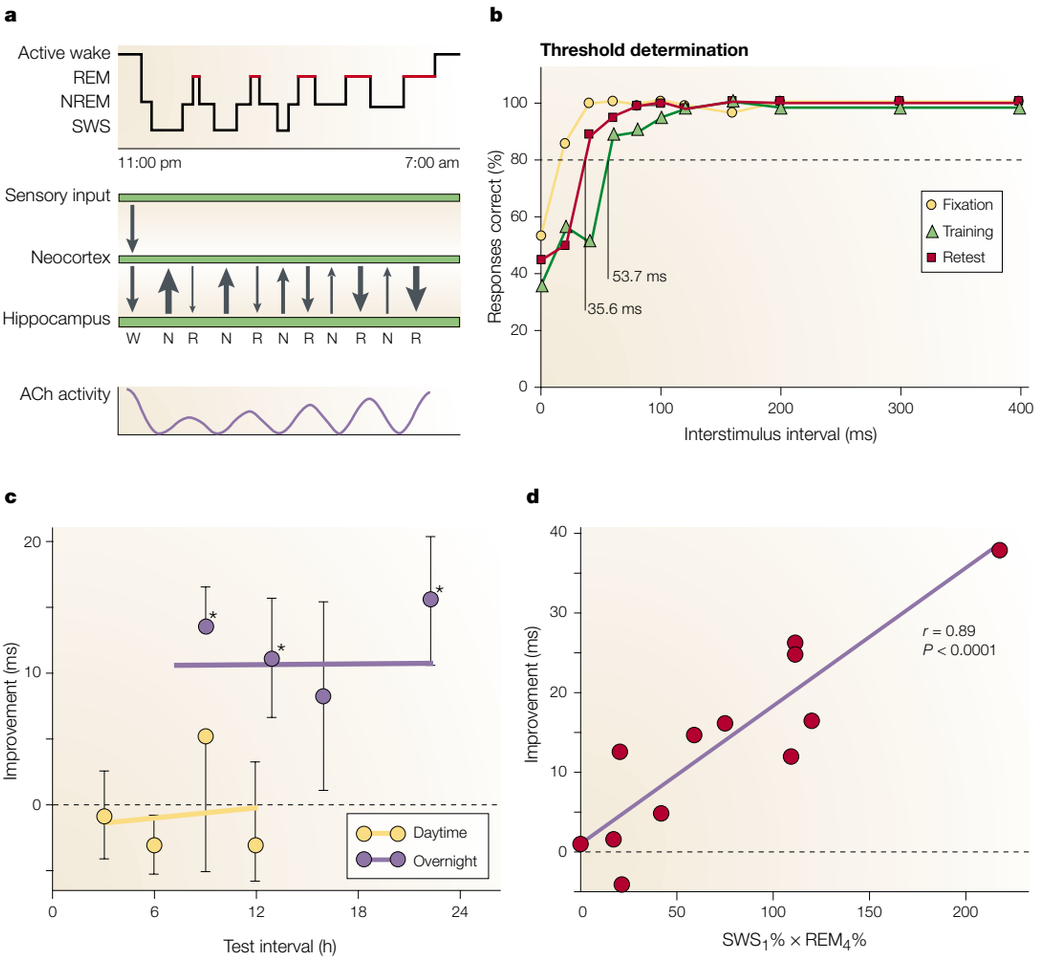


Figure 8 | **A model of sleep-dependent memory consolidation.** Supportive results are from the texture-discrimination task (TDT) of Karni and Sagi[9,117–122]. **a** | State-related changes in hippocampal–neocortical information flow. Changes in cholinergic (acetylcholine, ACh) neuromodulation (bottom) and hippocampal–neocortical communication (middle) are aligned with the human rapid eye movement (REM)–non-REM (NREM) cycle (top). Cholinergic levels are maximal in waking and REM, and minimal in NREM. During waking, environmental input to the primary sensory neocortices proceeds through association cortices to the entorhinal cortex and into the hippocampus. Reverse flow from the hippocampus to the cortex is attenuated. During NREM, information is conveyed primarily from the hippocampus to the neocortex, where, over time, the memories that this information represents are permanently stored. During REM, as in waking, this hippocampal outflow to the neocortex is blocked, but wake-like flow of information from neocortex to hippocampus might again be possible. Changing levels of acetylcholine favour this pattern of state-dependent information flow by augmenting feedforward (cortical–hippocampal) transmission circuits in the hippocampal formation, and by blocking feedback (hippocampal–cortical) circuits during cholinergic maxima in wake and REM[65]. During cholinergic minima in NREM, such feedback circuits are released to allow flow of information from the hippocampus to the cortex. N, non-REM; R, REM; W, waking. **b** | The Karni and Sagi TDT. Subjects view a textured pattern that is composed of short lines on a computer screen while keeping their vision focused on a central fixation point. In each trial, they are briefly presented with a stimulus to detect at the fixation point, while being asked to decide whether three short lines in one quadrant of their peripheral visual field are aligned in a vertical or horizontal pattern. After an interstimulus interval (ISI), they are presented with a masking computer screen that is composed of multiple lines that effectively extinguish any afterimage of the stimulus screen. The ISI is then progressively shortened over successive trials of a training or testing block (see below). The dependent variable, derived by interpolation, is the minimal ISI at which they are 80% correct in their decision on the vertical-versus-horizontal alignment of the bars (53.7 ms in this figure). Subjects first complete a 60–75-min training session, and are then retested in an identical testing session after a period of time in which experimental manipulations (varying duration, sleep deprivation) can be performed. **c** | Time course of improvement on the TDT. Subjects were tested either on the day of training with no intervening sleep (yellow circles) or on the day after training following a night's sleep (blue circles). Only subjects who slept for six or more hours between the training and testing sessions showed improvement in TDT performance[117,119]. Asterisks indicate individual groups showing significant improvement. **d** | A two-step model of memory consolidation in TDT performance. Improvement in TDT performance was found to correlate with the percentage of slow-wave sleep in the first quarter of the night (SWS_1) and the percentage of REM sleep in the last quarter (REM_4), but not with sleep-stage variables from other parts of the night. Most notably, the product of percentage SWS_1 and REM_4 further improved the correlation with TDT improvement when compared with either measure individually, indicating a two-stage process for the consolidation of improvement on this task[117]. Part **a** modified, with permission, from REF. 9 © 1998 Elsevier Science; parts **c** and **d** modified, with permission, from REF. 117 © 2000 Massachusetts Institute of Technology.

hippocampus, in association with specific wake-related EEG frequencies (theta and gamma), subcortical neuromodulatory inputs (such as acetylcholine) and entorhinal cortex–hippocampal pathways.

During NREM sleep and quiet waking, the hippocampus consolidates these unstable memory traces and transfers the information to the cortex for long-term storage[7]. Such NREM-related hippocampal output is associated with specific NREM-related EEG frequencies (sharp waves with associated fast 'ripples') and the attenuation of subcortical neuromodulatory input. It proceeds through hippocampal–entorhinal output pathways that can be distinguished from waking entorhinal–hippocampal input pathways. Unlike wake-related rhythms, the highly synchronized hippocampal output during such NREM oscillations provides favourable conditions for LTP and resultant synaptic plasticity in the cortical targets of hippocampal output[7].

In contrast to cortical–hippocampal information flow during active waking, and the hippocampal–cortical flow of information during quiet waking and NREM[7], it has been suggested that, during REM, new associative links are formed between memory traces already stored in the neocortex[9,10]. Stickgold *et al.*[10] suggest that the REM sleep state might specifically enhance cortical plasticity involved in procedural memory[101] or high-level cognitive processing[102], but not in hippocampal episodic-memory processes.

Sleep-dependent memory-consolidation processes would require a representation of waking experience to be instantiated in neuronal pathways during sleep. Evidence for such a representation comes from replay during sleep of neuronal firing patterns recorded in the rat hippocampus during previous waking[103–105]. Such replay is noted particularly in hippocampal 'place cells', which, during waking, fire reliably when the rat enters specific places in familiar environments and are therefore presumed to encode spatial location[104,106,107].

This presumed plasticity-related process occurs during both NREM[105,108] and REM sleep[106,107]. Correlated firing of hippocampal place cells is stable across waking and subsequent NREM and REM sleep unless other stimuli are introduced[109]. This confirms the sensitivity of sleep-dependent firing to previous experience, and is consistent with the NREM sleep reiteration and transfer portion of the above models. In NREM, the temporal correlation between fast (200 Hz) hippocampal EEG ripples and cortical sleep spindles is consistent with the proposed readout of hippocampal information to the cortex in NREM sleep[110]. The correlation of the ripples with hippocampal cell firing is strengthened by repeated experience, as if a memory trace were being established as a network 'attractor state'[111]. The specificity of this information is indicated by a 180° shift of firing in relation to the phase of the REM hippocampal theta rhythm that occurs in place cells over time after learning, which indicates a possible shift from LTP to LONG-TERM DEPRESSION of the system once learning has been established[107]. During NREM sleep, firing patterns are replayed on a condensed timescale[108], whereas, during REM sleep, the timescale of the replay of hippocampal neural firing is similar to that of the original waking experience[106].

It has been suggested that plasticity-related processes during sleep occur in other brain systems, such as thalamocortical[4,14] (see above) and brainstem–forebrain circuits[112]. For example, pontine P-waves (the rodent equivalent of the feline PGO wave) increase in frequency after training on an avoidance task[112]. In this paradigm, P-wave density correlates with degree of learning, indicating that the intrinsic phasic activation of P-waves promotes consolidation of learning in the forebrain structures that are targeted by such waves. Fear conditioning increases the amplitude of elicited PGO waves during REM sleep in cats[113], supporting a role for PGO waves in experience-dependent neuroplasticity.

Such findings have been extended to other models. For example, learning-related neuronal replay in sleep is also proposed to occur in the brain of the zebra finch[114]. The activity of song-related neurons in premotor regions of the brain is replayed during sleep in a manner that is identical to their patterns during song production in waking[114]. Such replay might reinforce the complex sensorimotor interactions needed for reliable song production[114]. As a result of studies such as these, the importance of sleep-dependent changes in brain state for plasticity is becoming more widely recognized[10].

Waking cognitive performance and sleep. The interaction of sleep and its component stages with the consolidation of learning and memory has become an arena for many exciting discoveries[8–10,13,102], as well as for vigorous scientific controversy[10,70,91,92]. Peigneux *et al.*[8] have conceptualized two distinguishable but overlapping theoretical stances.

In the first, termed the 'dual-process hypothesis', NREM and REM sleep facilitate different memory processes. For example, NREM sleep is proposed to facilitate declarative or explicit memory, whereas REM facilitates procedural and non-declarative learning[101,115]. This is supported by work showing that deprivation of early-night (SWS-rich) sleep selectively impairs performance on declarative-memory tasks such as paired-word associates or spatial-task memory, whereas deprivation of late-night (REM-rich) sleep impairs performance on procedural-memory tasks such as mirror drawing or word-stem priming[101,115]. However, further studies are needed to clarify the accuracy of this model for the variety of procedural- and declarative-memory skills in humans[8].

In the second stance — the 'sequential hypothesis' — different sleep stages consolidate a memory trace in a complementary, sequential manner[116,117]. This theory is supported by studies[117] using a unique texture-discrimination task (TDT), in which performance can improve with time after training[118]. This improvement requires sleep during the first night after training (FIG. 8c), and subsequent nights of sleep produce additional improvement even without further training[119]. Subjects who were deprived of sleep on the night after training, but

LONG-TERM DEPRESSION (LTD). An enduring weakening of synaptic strength that is thought to interact with long term potentiation (LTP) in the cellular mechanisms of learning and memory in structures such as the hippocampus and cerebellum. Unlike LTP, which is produced by brief high-frequency stimulation, LTD can be produced by long-term, low-frequency stimulation.

were then allowed two nights of unrestricted recovery sleep, did not improve.

At first glance, the sleep-stage-specific requirements for improvement on this task seem to be contradictory. For example, Karni *et al.*[120] showed that REM rather than NREM sleep was required, whereas Gais *et al.*[121] found that early-night (mainly NREM) sleep was needed. These findings could be resolved if TDT learning were a two-step process requiring both early-night SWS and late-night REM[10,117]. In fact, TDT improvement significantly correlates with both the amount of SWS in the first quarter and the amount of REM in the last quarter of the night[117]. Most strikingly, the product of early-night SWS and late-night REM accounted for 79% of the variance in TDT improvement[117] (FIG. 8d). Recently, it has been found that sleep, in the form of naps, prevents the decline in TDT performance seen when this task is given repeatedly without an intervening sleep bout[122]. A sleep-mediated improvement has also been shown for another procedural-learning task[123].

The idea of a hippocampal–neocortical exchange of information in sleep has been supported in humans by a study of visual imagery. Control subjects and amnesic patients with hippocampal damage experienced visual imagery while falling asleep and in early, light sleep[124]. Experience-related hypnogogic hallucinations were reported after extensive practice of a video game by the normal subjects and by amnesic patients long after they had forgotten having played the game. This study showed the key role of cortical structures in the short-term retention of perceptual memory.

Cognition during sleep. Attempts to study sleep-related changes in conscious experience are frustrated by the impossibility of gaining direct access to mental content without performing state-disruptive awakenings. Fortunately, there is a 5–10-min lag time, caused by sleep inertia, in achieving a spontaneous or forced state transition, and sleep-state carryover effects can be studied during this period[37].

In the semantic-priming task, subjects can detect a word (against a non-word) more rapidly if the target word is strongly or weakly associated with the prime word they have just seen. By taking advantage of this sleep inertia, it has been shown that REM sleep enhances weak but not strong semantic priming[125]. This finding seems to mean that semantic networks that instantiate weakly associated elements are activated in REM. This finding and its interpretation are consistent with the claim that dreaming is hyperassociative, an idea that was first proposed by David Hartley in 1791 (REF. 126). It is also compatible with the idea that associations are loosened during REM and that such loosening is linked to dream bizarreness[127].

Regional activity and plasticity. As in the EEG studies of NREM sleep, neuroimaging studies have begun to reveal the human cortical and subcortical networks that might be involved in the sleep-associated consolidation of learning and memory[8]. For example, a PET study[128] found reactivation during human REM sleep of the brain areas that were activated during previous waking performance of a cognitive task, as well as experience-dependent changes in parieto-frontal functional connectivity during REM sleep after training[12]. Such findings are similar to the REM sleep hippocampal replay that is seen in the rat[106].

Conclusions

The relationship between cellular and network-level changes in thalamic and cortical systems provides an increasingly clear picture of how the EEG signatures of waking, NREM and REM sleep are generated. Activation of the thalamocortical system by ascending arousal systems in waking and REM suppresses the autonomous slow oscillation, spindle and delta activity of NREM. This activation underlies the consciousness of both states, whereas the gating of external input in sleep keeps the dreaming brain–mind off-line. When such activation is withdrawn, spontaneous cortical slow oscillatory activity triggers and synchronizes EEG spindles and delta waves.

Changes in sensorimotor gating, regional activation and neuromodulation produce the marked changes in posture, stimulus threshold and conscious experience that differentiate waking, NREM and REM sleep. Widespread deactivation characterizes the wake-to-NREM-sleep transition, whereas selective reactivation is seen in REM sleep. Compared with waking, REM sleep activation is greater in the limbic lobe and in certain cortical association areas, but the dorsolateral prefrontal cortex remains conspicuously deactivated. There is also a progressive decrease in output from the noradrenergic, serotonergic and histaminergic neurons, all of which shut off in REM, leaving the selectively activated forebrain aminergically unmodulated.

In waking, the brain is activated to allow behaviours that can interact with conditions of the outside world, and it is modulated to capture important information. In NREM sleep, the brain is actively off-line, allowing stereotyped endogenous activation to be instantiated in the forebrain. This mechanism could allow recent inputs to be reiterated in a manner that promotes plasticity processes that are associated with memory consolidation. In REM sleep, the brain is reactivated but the microchemistry and regional activation patterns are markedly different from those of waking and NREM sleep. Cortically consolidated memories, originally stored during NREM by iterative processes such as corticopetal information outflow from the hippocampus, would thus be integrated with other stored memories during REM. In this view, dreaming is the conscious experience of hyperassociative brain activation that is maximal in REM sleep. The emotional salience of our conscious experience in dreaming and the unconscious changes in memory are related to the regional activation patterns and specific neurochemistry of REM. This means that the formal psychological features of dreaming are determined by the specific regional activation patterns and neurochemistry of sleep.

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