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Sleep and Consciousness

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Abstract

Sleep offers a unique opportunity to relate changes in brain activity to changes in consciousness. Indeed, if it were not for sleep, when consciousness fades in and out on a regular basis, it might be hard to imagine that consciousness is not a given but depends somehow on the way our brain is functioning. At the same time as changes in consciousness occur, brain activity undergoes major changes through an orderly progression of sleep stages, which can be identified by recording the electroencephalogram (EEG), eye movements (EOG), and muscle tone (EMG). Within each sleep stage, there are frequent, short-lasting electrophysiological phenomena, such as slow oscillations and spindles representing moments at which brain activity undergoes important fluctuations. There are also orderly spatial changes in the activation of many brain regions, as indicated by imaging studies. Importantly, similar brain activities occur in animals, and this has spear-headed detailed studies of the underlying neural mechanisms.

This chapter will first examine how sleep is traditionally subdivided into different stages that alternate in the course of the night. It will then review the dreaming events we experience across sleep. Next, it will consider the neural

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correlates of sleep and wakefulness – the brain centers that determine whether we are asleep or awake and the mechanisms giving rise to the electrophysiological activities across sleep. It will review functional imaging studies of human sleep including research of regional metabolism using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) correlates of spontaneous brain rhythms, as well as resting-state functional connectivity studies. It will review recent experiments combining transcranial magnetic stimulation (TMS) and EEG that allow perturbing directly cortical neurons and recording with millisecond resolution the response across the cortical mantle in sleep and wakefulness. It will then discuss recent intracranial studies in humans that have provided evidence for the local occurrence of sleep oscillations in both the sleeping and the waking brain. The demonstration of local sleep changes the traditional view of sleep as a monolithic, all-or-none behavioral state and suggests that mixed and dissociated states are not just found in pathological conditions. This chapter ends with some open questions: when and why do we lose consciousness in sleep? Is consciousness in sleep (dreaming) more akin to perception (bottom-up) or imagination (top-down)? And why is sleep consciousness largely disconnected from the external environment?

9.1 Sleep Stages and Cycles

In the course of the night, the EEG, EOG, and EMG patterns undergo coordinated changes that are traditionally used to distinguish among different sleep stages (Fig. 9.1a).

9.1.1 Wakefulness

During wakefulness, the EEG is characterized by waves of low amplitude and high frequency. This kind of EEG pattern is known as low-voltage fast activity or activated. When eyes close in preparation for sleep, EEG alpha activity (8–13 Hz) becomes prominent, particularly in occipital regions. Such alpha activity is thought to correspond to an “idling” rhythm in visual areas. The waking EOG reveals frequent voluntary eye movements and eye blinks. The EMG reveals tonic muscle activity with additional phasic activity related to voluntary movements.

9.1.2 Falling Asleep: Stage N1

Falling asleep is a gradual phenomenon of progressive disconnection from the environment. Sleep is usually entered through a transitional state, stage 1, characterized by loss of alpha activity and the appearance of a low-voltage mixed-frequency EEG pattern with prominent theta activity (3–7 Hz). Eye movements become slow and rolling, and muscle tone relaxes. Although there is decreased

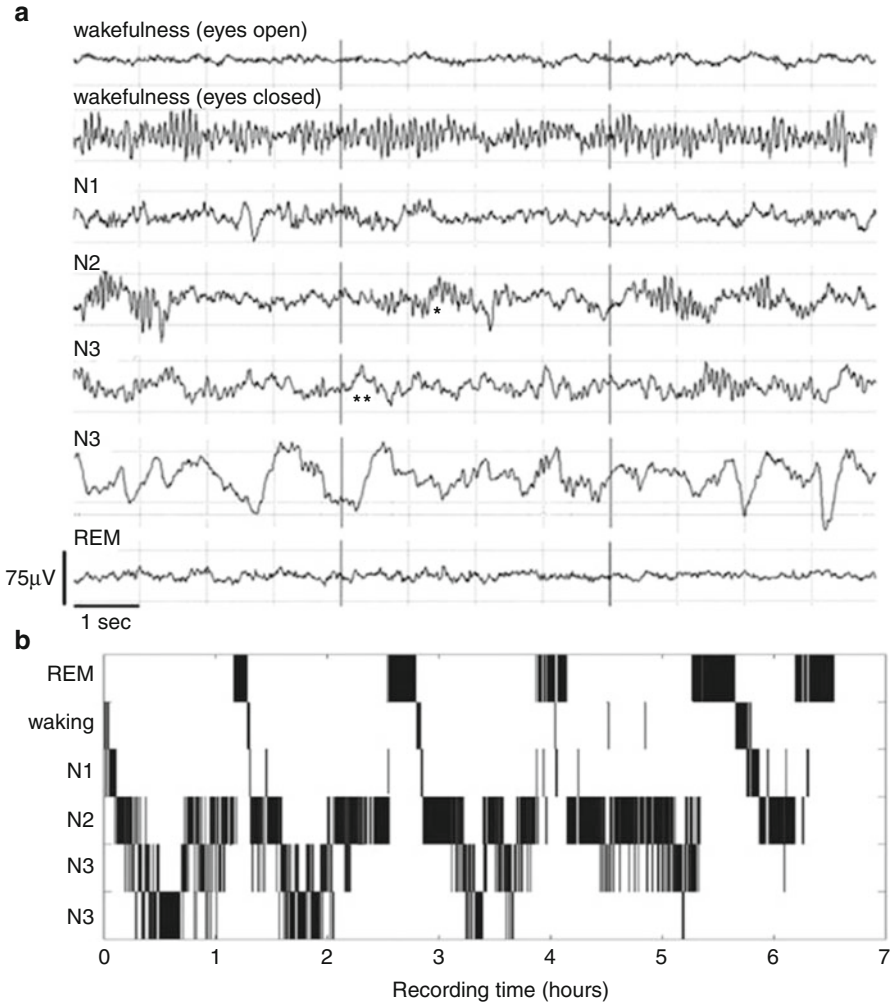


Fig. 9.1 Sleep stages and cycles. (a) EEG wave form during wakefulness with eyes open and closed and during the different stages of sleep. (b) Average times and sequences of sleep cycles during the night

awareness of sensory stimuli, a subject in stage N1 may deny that he was asleep. Motor activity may persist for a number of seconds during stage N1. Occasionally individuals experience sudden muscle contractions (hypnic jerks), sometimes accompanied by a sense of falling and dreamlike imagery. Individuals deprived of sleep often have “microsleep” episodes that consist of brief (5–10 s) bouts of stage 1 sleep; these episodes can have serious consequences in situations that demand constant attention, such as driving a car.

Sleep is traditionally categorized into non-rapid eye movement (NREM) sleep and REM sleep. Human NREM sleep, in turn, is divided into stages N2 and N3.

9.1.3 NREM Sleep: Stage N2

After a few minutes in stage N1, people usually progress to stage N2 sleep. Stage N2 is heralded in the EEG by the appearance of K-complexes and sleep spindles, which are especially evident over central regions. K-complexes are made up of a high-amplitude negative sharp wave followed by a positive slow wave and are often triggered by external stimuli. Sleep spindles are waxing and waning oscillations at around 12–15 Hz that last about 1 s and occur 5–10 times a minute. Eye movements and muscle tone are much reduced. Stage N2 qualifies fully as sleep because people are partially disconnected from the environment, meaning that they do not respond to the events around them – their arousal threshold is increased. If stimuli are strong enough to wake them up, people in stage N2 will confirm that they were asleep.

9.1.4 NREM Sleep: Stage N3

Stage N2 is followed, especially at the beginning of the night, by a period called stage N3, during which the EEG shows prominent slow waves in the delta range (<2 Hz, >75 μ V in humans). Eye movements cease during stage N3 and EMG activity decreases further. Stage N3 is also referred to as slow-wave sleep (SWS), delta sleep, or deep sleep, since the threshold for arousal is higher than in stage N2. The process of awakening from slow-wave sleep is drawn out, and subjects often remain confused for some time.

9.1.5 REM Sleep

After deepening through stages N2 to N3, NREM sleep lightens and returns to stage N2, after which the sleeper enters REM sleep (Aserinsky and Kleitman 1953; Dement and Kleitman 1957a), also referred to as paradoxical sleep (Jouvet 1962, 1965, 1998) because the EEG during REM sleep is similar to the activated EEG of waking or of stage N1. Indeed, the EEG of REM sleep is characterized by low-voltage fast activity, often with increased power in the theta band (3–7 Hz). REM sleep is not subdivided into stages, but is rather described in terms of tonic and phasic components. Tonic aspects of REM sleep include the activated EEG and a generalized loss of muscle tone, except for the extraocular muscles and the diaphragm. REM sleep is also accompanied by penile erections. Phasic features of REM include irregular bursts of rapid eye movements and muscle twitches. Behaviorally, REM sleep is deep sleep, with an arousal threshold that is nearly as high as in slow-wave sleep.

9.1.6 The Sleep Cycle

The succession of NREM sleep stages followed by an episode of REM sleep is called a sleep cycle and lasts approximately 90–110 min in humans. As shown in Fig. 9.1b, there are a total of 4–5 cycles every night. Slow-wave sleep is prominent

early in the night, especially during the first sleep cycle, and diminishes as the night progresses. As slow-wave sleep wanes, periods of REM sleep lengthen and show greater phasic activity. The proportion of time spent in each stage and the pattern of stages across the night is fairly consistent in normal adults. A healthy young adult will typically spend about 5 % of the sleep period in stage N1, about 50 % in stage N2, 20–25 % in stage N3 (slow-wave sleep), and 20–25 % in REM sleep.

9.1.7 Sleep During the Life Span

Sleep patterns change markedly across the life span (Carskadon et al. 2002; Peirano et al. 2003; Carskadon et al. 2004; Jenni and Carskadon 2004; Ohayon et al. 2004). Newborn infants spend 16–18 h/day sleeping, with an early version of REM sleep, called active sleep, occupying about half of their sleep time. At approximately 3–4 months of age, when sleep starts to become consolidated during the night, the sleep EEG shows more mature waveforms characteristic of NREM and REM sleep. During early childhood, total sleep time decreases and REM sleep proportion drops to adult levels. The proportion of NREM sleep spent in slow-wave sleep increases during the first year of life, reaches a peak, declines during adolescence and adulthood, and may disappear entirely by age 60.

9.2 Dreaming Across Sleep

Dreams show that vivid conscious experience is possible despite the sensory and motor disconnection from the environment and the loss of self-reflective thought (see (Nir and Tononi 2010) for review). Studying mental experiences during sleep offers a unique opportunity to explain how changes in brain activity relate to changes in consciousness (Hobson et al. 1998; Rees et al. 2002; Nir and Tononi 2010). In fact, if it were not for sleep, when consciousness fades in and out on a regular basis, it might be hard to imagine that consciousness is not a given but depends somehow on the way our brain is functioning. Traditionally, studies have focused on differences among reports obtained after awakenings from different sleep stages or at different times of night. When REM sleep was initially distinguished from NREM sleep (Aserinsky and Kleitman 1953), it was reported that 74–80 % of REM sleep awakenings produced vivid dream recall, compared to only 7–9 % of awakenings from NREM sleep (Dement and Kleitman 1957a, b). It was only natural to conclude that, compared to NREM sleep, the distinct physiology of REM sleep, and especially its fast, low-voltage EEG resembling that of wakefulness, was the reason why we are conscious in REM sleep, and not in NREM sleep (Hobson et al. 1998). Indeed, for some time, reports of mental activity upon awakenings from NREM sleep were assumed to be recalls of earlier REM sleep dreams, or considered analogous to sleep talking (Hobson 1988), or treated as confabulations made up by subjects confused upon awakening (Rechtschaffen 1973; Nir and Tononi 2010). However, by simply changing the question from “tell me if you had a dream” to “tell me anything that was going through your mind just before you woke up,” reports of

conscious experiences in NREM sleep ranged between 23 and 74 % (Rechtschaffen 1973). Subsequent studies demonstrated clearly that NREM sleep awakenings yielded reports of mental activity (Foulkes 1962; Nielsen 2000).

Specifically, reports from sleep stage N1 are extremely frequent (80–90 % of the time), though they are very short (Foulkes 1966). Usually people report vivid hallucinatory experiences, so-called hypnagogic hallucinations. In contrast to typical dreams, hypnagogic hallucinations are often static – like single snapshots (Hobson et al. 2000; Hobson and Pace-Schott 2002) – and usually do not include a self-character (Foulkes 1985). Some activities performed before sleep (e.g., video games) may influence the content of hypnagogic dreams (Stickgold et al. 2000; Wamsley et al. 2010). Awakenings from NREM sleep stages N2 and N3 yield reports about some experienced content 50–70 % of the time (Nielsen 2000), although there is great variability throughout the night and between subjects. Early in the night, when stage N3 is prevalent and many large slow waves dominate the EEG, awakenings yield few reports (Stickgold et al. 2001). Moreover, these reports are often qualitatively different than typical REM sleep reports, being usually short, thought-like, less vivid, less visual and more conceptual, less motorically animated, under greater volitional control, more plausible, more concerned with current issues, less emotional, and less pleasant (Rechtschaffen 1973; Hobson et al. 2000; Fosse et al. 2001). Also, the average length of REM sleep reports increases with the duration of the REM sleep episode, while this is not true for NREM sleep reports (Stickgold et al. 2001). However, late in the night, NREM sleep reports are considerably longer and more hallucinatory. Indeed, 10–30 % of all NREM sleep reports are indistinguishable by any criteria from those obtained from REM sleep (Monroe et al. 1965; Antrobus et al. 1995). Since NREM sleep accounts for 75 % of total sleep time, this means that full-fledged NREM sleep dreams actually account for a significant portion of all typical dreams.

Thus, the initial equation of a physiological state (REM sleep) with a mental state (dreaming) was incorrect, or at best, an oversimplification. Moreover, neuropsychological evidence indicates that dreaming and REM sleep can be dissociated: forebrain lesions may abolish dreaming and spare REM sleep, whereas brainstem lesions may nearly eliminate overt features of REM sleep without abolishing dreams (Solms 2000; Nir and Tononi 2010). But if dream reports can be elicited during any stage of sleep (Cavallero et al. 1992; Hobson et al. 2000; Nielsen 2000; Hobson and Pace-Schott 2002; Suzuki et al. 2004), and conversely some awakenings may yield no report, no matter in which sleep stage they were obtained (Nielsen 2000), where do we stand today with respect to the relationship between brain activity and consciousness during sleep? The one thing that seems clear is that we need to move beyond the REM/NREM sleep dichotomy and beyond traditional sleep staging. Though staging is useful, it treats brain activity as uniform in space (only a few electrodes are used) and in time (for 30 s epochs). Inevitably, subtler features of brain activity, which may well influence the presence, degree, and reportability of consciousness, are missed both in space and in time.

In the spatial domain, increasing evidence suggests that different brain regions may be in different states at the same time, and this notion will be discussed in

Sect. 9.4 below. Along this line, dreaming in NREM sleep may be related to “covert” REM processes that occur locally (Nielsen 2000). Thus, refined spatial analysis using fMRI or high-density EEG (hd EEG) could potentially identify regionally specific predictors of dreaming and possibly indicate, in real time, whether dream reports will be obtained.

In the temporal domain, some attempts have been made to relate transient, phasic activities to dreaming. For example, various studies have tried to link dream recall to eye movements (Roffwarg et al. 1962; Moskowitz and Berger 1969), PGO waves (Pivik 1991), and EEG power bouts in specific frequency bands (Esposito et al. 2004), but limited success has been achieved, and little has been done for NREM sleep (Hobson et al. 2000; Pivik 2000). We now know that slow waves in NREM sleep reflect a slow oscillation of cortical neurons between UP and DOWN states (Sect. 9.3.2). Perhaps long UP states are necessary for dreaming to occur. This is normally the case in REM sleep since slow waves are absent. As for NREM sleep, we would expect that higher occurrence of recalls, and especially of typical dreams in the morning hours, would reflect longer UP periods upon dissipation of sleep pressure (Vyazovskiy et al. 2009b). In general, focusing on (rather than avoiding) “gray zones” where it is more difficult to predict whether a dream report will be obtained, for example, in early REM sleep or late NREM sleep, may be a promising strategy for identifying psychophysiological correlates that go beyond traditional staging.

9.3 Neural Correlates of Sleep and Wakefulness

9.3.1 Brain Centers Regulating Wakefulness and Sleep

9.3.1.1 Wakefulness System

Maintenance of wakefulness is dependent on several heterogeneous cell groups extending from the upper pons and midbrain (the so-called reticular activating system, RAS) (Lindsley et al. 1949; Moruzzi and Magoun 1949) to the posterior hypothalamus and basal forebrain. These cell groups are strategically placed so that they can release, over wide regions of the brain, neuromodulators and neurotransmitters that produce EEG activation, such as acetylcholine, histamine, norepinephrine, glutamate, and hypocretin (Fig. 9.2, red). Cholinergic cells are located in the basal forebrain and in two small nuclei in the pons: the pedunculopontine tegmental and lateral dorsal tegmental nuclei (PPT/LDT). Both basal forebrain and pontine cholinergic cells fire at high rates in wakefulness and REM sleep and decrease or stop firing during NREM sleep (Hobson et al. 1975; el Mansari et al. 1989; Lee et al. 2005b). Pontine cholinergic cells project to the thalamus, where they help depolarize specific and intralaminar thalamic nuclei. The latter, which are dispersed throughout the thalamus and project diffusely to the cortex, fire at very high frequencies during both wakefulness and REM sleep and help to synchronize cortical firing in the gamma (>28 Hz) range (McCormick 1989; Steriade 2004; Jones 2005a). Cholinergic cells in the dorsal brainstem and nearby non-cholinergic cells also

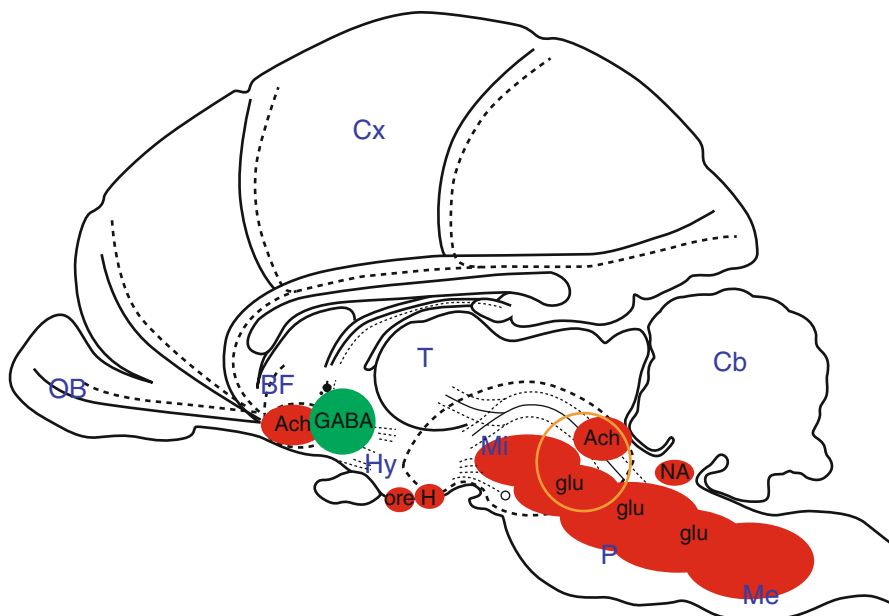


Fig. 9.2 The major brain areas involved in initiating and maintaining wakefulness (*red*), NREM sleep (*green*), and REM sleep (*orange*) (From Tononi 2009)

project to other cholinergic and non-cholinergic cells (many of them glutamatergic) in the basal forebrain, which in turn provide an excitatory input to the entire cortex (Jones 2003, 2005a, b).

Cholinergic neurons in the pons also project to the posterior hypothalamus, where histaminergic neurons are located in the tuberomammillary nucleus (Brown et al. 2001). Histaminergic neurons, which project throughout the cortex, fire at the highest rates during wakefulness and are inhibited during both NREM and REM sleep (Takahashi et al. 2006). Probably the largest contingent of the wakefulness-promoting system is made up by cells dispersed throughout the brainstem reticular formation and the basal forebrain that do not release conventional neuromodulators, but rather the ubiquitous neurotransmitter glutamate. By binding to metabotropic receptors, glutamate can act as a neuromodulator and influence the excitability of target cells. The firing patterns of these glutamatergic cells are not well characterized (Jones 2003, 2005a, b). Noradrenergic cells are concentrated in the locus coeruleus in the upper pons, from where they project throughout the brain (Foote et al. 1980; Aston-Jones and Bloom 1981a, b; Berridge and Abercrombie 1999; Aston-Jones and Cohen 2005). They fire tonically during wakefulness and emit short, phasic bursts of activity during behavioral choices or salient events (Hobson et al. 1975; Foote et al. 1980; Aston-Jones and Bloom 1981a, b; Berridge and Abercrombie 1999; Aston-Jones and Cohen 2005). By contrast, locus coeruleus neurons decrease their firing during NREM sleep and cease firing altogether during REM sleep. Serotonergic cells from the dorsal raphe nucleus also project widely throughout the

brain and, like noradrenergic neurons, fire at higher levels in waking and lower levels in NREM sleep and fall silent during REM sleep. However, in contrast to noradrenergic neurons, serotonergic neurons are inactivated when animals make behavioral choices or orient to salient stimuli and are activated instead during repetitive motor activity such as locomoting, grooming, or feeding (McGinty and Harper 1976; Jacobs et al. 2002). Dopamine-containing neurons located in the substantia nigra and ventral tegmental area, which innervate the frontal cortex, basal forebrain, and limbic structures (Monti and Monti 2007), do not appear to change their firing rate depending on behavioral state, though blocking dopamine reuptake is known to promote arousal (Monti and Monti 2007). Finally, the peptide hypocretin (also known as orexin) is produced by cells in the posterior hypothalamus that provide excitatory input to all components of the waking system (Sakurai 2007). These cells, too, are most active during waking, especially in relation to motor activity and exploratory behavior, and almost stop firing during both NREM and REM sleep (Lee et al. 2005a; Mileykovskiy et al. 2005). Altogether, the main mechanism by which these neuromodulators and neurotransmitters produce cortical activation is by closing leakage potassium channels on the cell membrane of cortical and thalamic neurons, thus keeping cells depolarized and ready to fire.

9.3.1.2 Sleep System

At sleep onset, wakefulness-promoting neuronal groups are actively inhibited by antagonistic neuronal populations located in the hypothalamic and basal forebrain (Fig. 9.2, green). Decreasing levels of acetylcholine and other waking-promoting neuromodulators and neurotransmitters lead to the opening of leak potassium channels in cortical and thalamic neurons, which become hyperpolarized and begin oscillating at low frequencies. Cell groups scattered within the anterior hypothalamus, including the ventrolateral preoptic area (VLPO), (Sherin et al. 1996; Szymusiak et al. 1998) and the median preoptic nucleus (Suntsova et al. 2002), as well as in the basal forebrain, are involved in the initiation and maintenance of sleep. These neurons tend to fire during sleep and stop firing during wakefulness. When they are active, many of them release GABA and the peptide galanin and inhibit most waking-promoting areas, including cholinergic, noradrenergic, histaminergic, hypocretinergic, and serotonergic cells. In turn, the latter inhibit several sleep-promoting neuronal groups (Szymusiak et al. 2001; McGinty and Szymusiak 2003; McGinty et al. 2004; Saper et al. 2005). This reciprocal inhibition provides state stability, in that each state reinforces itself as well as inhibits the opponent state.

9.3.1.3 REM Sleep Generator

This consists of pontine cholinergic cell groups (LDT and PPT) that are part of the wakefulness system and nearby cell groups in the medial pontine reticular formation and medulla (Jouvet 1962; Hobson et al. 1975; McCarley 2004; Siegel 2005). Lesions in these areas eliminate REM sleep without significantly disrupting NREM sleep. Pontine cholinergic neurons produce EEG activation by releasing acetylcholine to the thalamus and to cholinergic and glutamatergic basal forebrain neurons that in turn activate the limbic system and cortex. However, while during wakefulness,

other waking-promoting neuronal groups, such as noradrenergic, histaminergic, hypocretinergic, and serotonergic neurons, are also active, they are inhibited during REM sleep. Other REM active neurons in the dorsal pons are responsible for the tonic inhibition of muscle tone during REM sleep. Finally, neurons in the medial pontine reticular formation fire in bursts and produce phasic events of REM sleep, such as rapid eye movements and muscle twitches.

9.3.2 Spontaneous Neuronal Activity in Sleep: Animal Studies

9.3.2.1 Wakefulness

The waking EEG, characterized by the presence of low-voltage fast activity, is known as activated because most cortical neurons are steadily depolarized close to their firing threshold (Fig. 9.3) and are thus ready to respond to the slightest change in their inputs. The readiness to respond of cortical and thalamic neurons enables fast and effective interactions among distributed regions of the thalamocortical system, resulting in a continuously changing sequence of specific firing patterns. Superimposed on the low-voltage, fast-activity background of wakefulness, one frequently observes rhythmic oscillatory episodes within the alpha (8–13 Hz), beta (14–28 Hz), and gamma (>28 Hz) range, which are usually localized to specific cortical areas. These waking rhythms are due to the activation of oscillatory mechanisms intrinsic to each cell as well as to the entrainment of oscillatory circuits among excitatory and inhibitory neurons.

9.3.2.2 NREM Sleep

The EEG of NREM sleep differs markedly from that of wakefulness because of the occurrence of slow waves (<2 Hz in humans), K-complexes, and sleep spindles. The opening of leakage potassium channels due to the reduced levels of acetylcholine and other neuromodulators draws cortical and thalamic cells toward hyperpolarization and triggers a series of membrane currents that produce the slow oscillation (Fig. 9.3) (Steriade et al. 2001). As shown by intracellular recordings, the slow oscillation is made up of a hyperpolarization phase or down state, which lasts a few 100 ms, and a slightly longer depolarization phase or up state. The down state is associated with the virtual absence of synaptic activity within cortical networks. During the up state, by contrast, cortical cells fire at rates that are as high or even higher than those seen in waking and may even show periods of fast oscillatory activity in the gamma range.

The slow oscillation is found in virtually every cortical neuron and is synchronized across brain regions by corticocortical and thalamocortical connections, which is why the EEG records high-voltage, low-frequency waves. Human EEG recordings using 256 channels have revealed that EEG slow waves behave as traveling waves that sweep across a large portion of the cerebral cortex (Massimini et al. 2004; Murphy et al. 2009). Most of the time, the sweep starts in the very front of the brain and propagates front to back. These sweeps occur very infrequently during stage N1, around five times a minute during stage N2, and more than ten times a minute in stage N3. Thus, a wave of depolarization and intense synaptic activity, followed by a wave of hyperpolarization and synaptic silence, sweeps across the

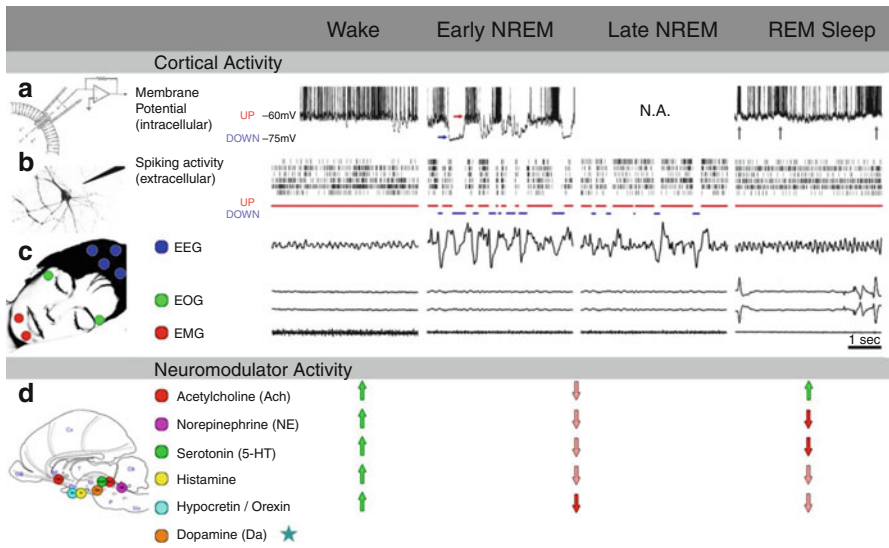


Fig. 9.3 Neurophysiology of wake and sleep states. A comparison of cortical activity (a–c) and neuromodulator activity (d) in wake, early NREM (when sleep pressure is high and dream reports are rare), late NREM (when sleep pressure dissipates and dream reports are more frequent), and REM sleep (when dreams are most common). (a) Intracellular studies. The membrane potential of cortical neurons in both wake and REM sleep is depolarized and fluctuates around -63 and -61 mV, respectively (Steriade et al. 2001). In REM sleep, whenever phasic events such as rapid eye movements and PGO waves occur (gray arrows, events not shown), neurons increase their firing rates to levels that surpass those found in wake (Yamamoto and Nakahama 1983; Steriade et al. 2001). In early NREM sleep, neurons alternate between two distinct states, each lasting tens to hundreds of milliseconds: UP states (red arrow) are associated with depolarization and increased firing, whereas in DOWN states (blue arrow), the membrane potential is hyperpolarized around -75 mV, and neuronal firing fades (Steriade et al. 1993a; Destexhe et al. 2007). Intracellular studies focusing specifically on late NREM sleep are not available (N.A.). (b) Extracellular studies. Spiking of individual neurons in REM sleep reaches similar levels as in active wake. In both wake and REM sleep, neurons exhibit tonic irregular asynchronous activity (Evarts 1964; Noda and Adey 1970; Hobson and McCarley 1971; Destexhe et al. 1999; Steriade et al. 2001). Sustained activity in wake and REM sleep can be viewed as a continuous UP state (Destexhe et al. 2007) (red bars). In early NREM sleep, UP states are short and synchronous across neuronal populations and are frequently interrupted by long DOWN states (blue bars). In late NREM sleep, UP states are longer and less synchronized (Vyazovskiy et al. 2009b). (c) Polysomnography. Waking is characterized by low-amplitude, high-frequency EEG activity (>7 Hz), occasional saccadic eye movements, and elevated muscle tone. In early NREM sleep, high-amplitude slow waves (<4 Hz) dominate the EEG. Neuronal UP (red) and DOWN (blue) states correspond to positive and negative peaks in the surface EEG, respectively (Vyazovskiy et al. 2009b). Eye movements are largely absent and muscle tone is decreased. In late NREM sleep, slow waves are less frequent, whereas spindles (related to UP states and surface EEG positivity) become more common. Eye movements and muscle tone are largely similar to early NREM sleep (Werth et al. 2002). In REM sleep, theta activity ($4\text{--}7$ Hz) prevails, rapid eye movements occur and muscle tone is reduced. (d) Neuromodulator activity. Subcortical cholinergic modulation is active in wake and REM sleep (green arrows) and leads to sustained depolarization in cortical neurons and EEG activation (Steriade et al. 2001). Wake is further maintained by activity of monoamines, histamine, and hypocretin/orexin (green arrows). In sleep, monoaminergic systems, including norepinephrine and serotonin, reduce their activity (pink arrows) and are silent in REM sleep (red arrows). Whereas dopamine levels do not change dramatically across the sleep–wake cycle (asterisks), phasic events and regional profiles can differ (Monti and Monti 2007). Data are pooled across different species for illustration purposes (From Nir and Tononi 2010)

brain more and more frequently just as NREM sleep becomes deeper. Slow waves can originate at short intervals at multiple cortical sites, in which case they superimpose or interfere, leading to EEG waves that are shorter and more fractured. Topographically, slow waves are especially prominent over the dorsolateral prefrontal cortex. K-complexes, which are usually triggered by external stimuli and appear particularly prominent because they are not immediately preceded or followed by other slow waves, are most likely the EEG correlate of global slow oscillations due to the near-synchronous activation of the cortical mantle by the reticular activating system (as opposed to a single cortical source; Riedner et al. 2011).

Sleep spindles occur during the depolarized phase of the slow oscillation and are generated in thalamic circuits as a consequence of cortical firing. When the cortex enters an up state, strong cortical firing excites GABAergic neurons in the reticular nucleus of the thalamus. These in turn strongly inhibit thalamocortical neurons, triggering intrinsic currents that produce a rebound burst of action potentials. These burst percolate within local thalamoreticular circuits and produce oscillatory firing at around 12–15 Hz. Thalamic spindle sequences reach back to the cortex and are globally synchronized by corticothalamic circuits, where they appear in the EEG as sleep spindles.

9.3.2.3 REM Sleep

During REM sleep, the EEG returns to an activated, low-voltage fast-activity pattern that is similar to that of quiet wakefulness or stage 1 (Fig. 9.3). As in wakefulness, the tonic depolarization of cortical and thalamic neurons is caused by the closure of leakage potassium channels. In fact, during REM sleep acetylcholine and other neuromodulators are released again at high levels, just as in wakefulness, and neuronal firing rates in several brain areas tend to be higher.

9.3.3 Metabolism and Functional Brain Imaging in Humans

9.3.3.1 PET Studies

Recently, the data obtained by recording the activity of individual neurons have been complemented by imaging studies that provide a simultaneous picture of neuronal activity over the entire brain, although at much lower resolution.

NREM Sleep

PET studies show that metabolic activity and blood flow are globally reduced in NREM sleep compared to resting wakefulness (Braun et al. 1997; Hofle et al. 1997; Maquet et al. 1997; Kajimura et al. 1999). During slow-wave sleep, metabolic activity can be reduced by as much as 40 %. Metabolic activity is mostly due to the energetic requirements of synaptic transmission, and its reduction during NREM sleep is thus most likely due the hyperpolarized phase of the slow oscillation, during which synaptic activity is essentially abolished. At a regional level, activation is especially reduced in the thalamus, due to its profound hyperpolarization during NREM sleep. In the cerebral cortex, activation is reduced in dorsolateral prefrontal cortex, orbitofrontal, and anterior cingulate cortex (Braun et al. 1997; Hofle et al.

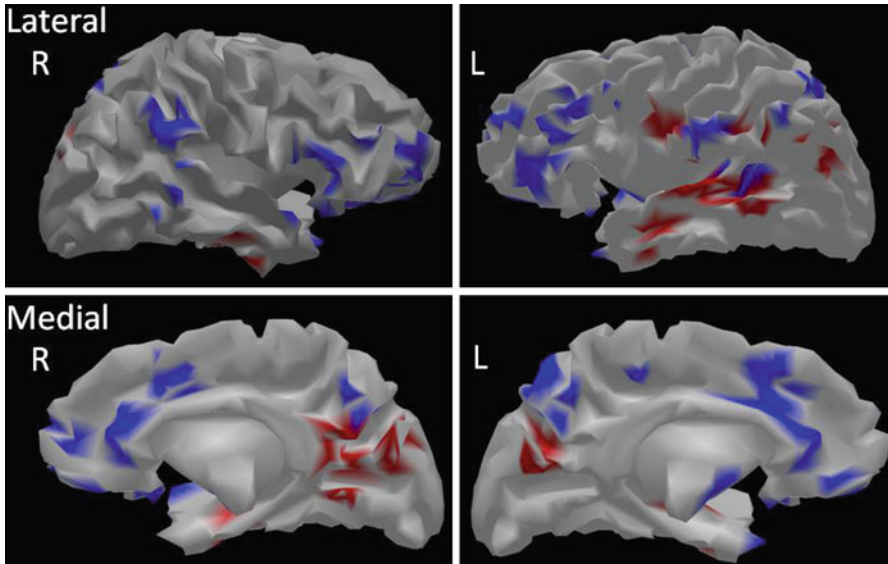


Fig. 9.4 Functional neuroanatomy of human NREM sleep: a meta-analysis of PET results. Meta-analysis of regions showing relatively decreased (*in blue*) and relatively preserved (*in red*) cortical activity during NREM sleep as compared to wakefulness, as seen with PET imaging using $H_2^{15}O$ measurements of regional cerebral blood flow (rCBF) (Maquet et al. 1997; Hofle et al. 1997; Braun et al. 1998; Kajimura et al. 1999). *Top row*: cortical surface, lateral view. *Bottom row*: cortical surface, medial view. Analysis is based on Talairach coordinates of significant foci published in Maquet et al. (1997), Hofle et al. (1997), Braun et al. (1998), and Kajimura et al. (1999). *Blue areas* denote decreased activity in precuneus/posterior cingulate, medial prefrontal cortex/anterior cingulate, superior and inferior parietal gyri, superior and inferior frontal gyri, orbitofrontal cortices, anterior medial and posterior inferior temporal gyri, insula, angular and supramarginal gyri. *Red areas* denote preserved regional activity in calcarine sulcus, fusiform and lateral occipital gyri, superior temporal and anterior middle/inferior temporal gyri, superior temporal sulcus, inferior parietal lobule, and pericentral cortices

1997; Maquet et al. 1997; Kajimura et al. 1999). This deactivation is in line with the observation that slow waves are especially prominent in these areas (Murphy et al. 2009). Parietal cortex, precuneus and posterior cingulate cortex, as well as medial temporal cortex also show relative deactivations (see Fig. 9.4, in blue). As discussed in other chapters, the deactivation of thalamus and associated frontoparietal networks is seen in other conditions characterized by reduced consciousness, such as coma, vegetative states, and anesthesia. By contrast, visual, somatosensory, and auditory cortices are not deactivated compared to resting wakefulness (see Fig. 9.4, in red). Basal ganglia and cerebellum are also deactivated, probably because of the reduced inflow from cortical areas.

REM Sleep

During REM sleep absolute levels of blood flow and metabolic activity are high, reaching levels similar to those seen during wakefulness, as would be expected

based on the tonic depolarization and high firing rates of neurons. There are, however, interesting regional differences (Maquet et al. 1996; Braun et al. 1997; Nir and Tononi 2010). Some brain areas are more active in REM sleep than in wakefulness. For example, there is a strong activation of limbic areas, including the amygdala and the parahippocampal cortex (see Fig. 9.5). Cerebral cortical areas that receive strong inputs from the amygdala, such as the anterior cingulate and the parietal lobule, are also activated, as are high-order visual areas. By contrast, the rest of parietal cortex, precuneus and posterior cingulate, and dorsolateral prefrontal cortex are relatively deactivated. These regional activations and inactivations are consistent with the differences in mental state between REM sleep and wakefulness: REM sleep dream mentation is indeed associated with vivid sensory imagery and emotional content, in the presence of decreased cognitive control and decreased recall (Nir and Tononi 2010).

9.3.3.2 EEG–fMRI Studies: Neural Correlates of Specific Spontaneous Sleep Events

NREM Sleep

By using simultaneous EEG and event-related functional magnetic resonance imaging (fMRI), some recent studies have shed light on brain-wide correlates of phasic activity associated with characteristic sleep electrophysiological events such as slow waves and spindles. Dang-Vu et al. (2008) characterized the transient changes in brain activity consistently associated with slow waves ($>140 \mu\text{V}$) and delta waves ($75\text{--}140 \mu\text{V}$) during NREM sleep in non-sleep-deprived normal human volunteers. Significant increases in activity were associated with these waves in the inferior frontal, medial prefrontal, precuneus, and posterior cingulate areas. Compared with baseline activity, slow waves were also associated with significant activity in the parahippocampal gyrus, cerebellum, and brainstem, whereas delta waves were rather related to frontal activations. No decrease in activity was observed. Schabus et al. (2007) investigated neural correlates of spindle activity in the same cohort of subjects. They showed an activation pattern common to both slow (11–13 Hz) and fast (13–15 Hz) spindles involving the thalamus, anterior cingulate cortex, insular cortices, and superior temporal gyri. No thalamic difference was detected in the direct comparison between slow and fast spindles, although some thalamic areas were preferentially activated in relation to either spindle type. Beyond the common activation pattern, the increases in cortical activity differed significantly between slow and fast spindles. Slow spindles were associated with increased activity in the superior frontal gyrus. In contrast, fast spindles recruited a set of cortical regions involved in sensorimotor processing, as well as the mesial frontal cortex and hippocampus (Schabus et al. 2007). A recent independent EEG–fMRI study likewise showed an involvement of thalamus, posterior cingulate, precuneus, putamen, paracentral cortex, and temporal lobe in sleep spindles (Caporro et al. 2012). The finding of a hippocampal involvement during spindle activity is also in line with a recent EEG–fMRI study showing increased hippocampal/neocortical connectivity during stage N2 sleep spindles (Andrade et al. 2011).

To date, three EEG–fMRI studies investigated neural activity associated with K-complexes evoked by external stimuli. Using an auditory oddball paradigm,

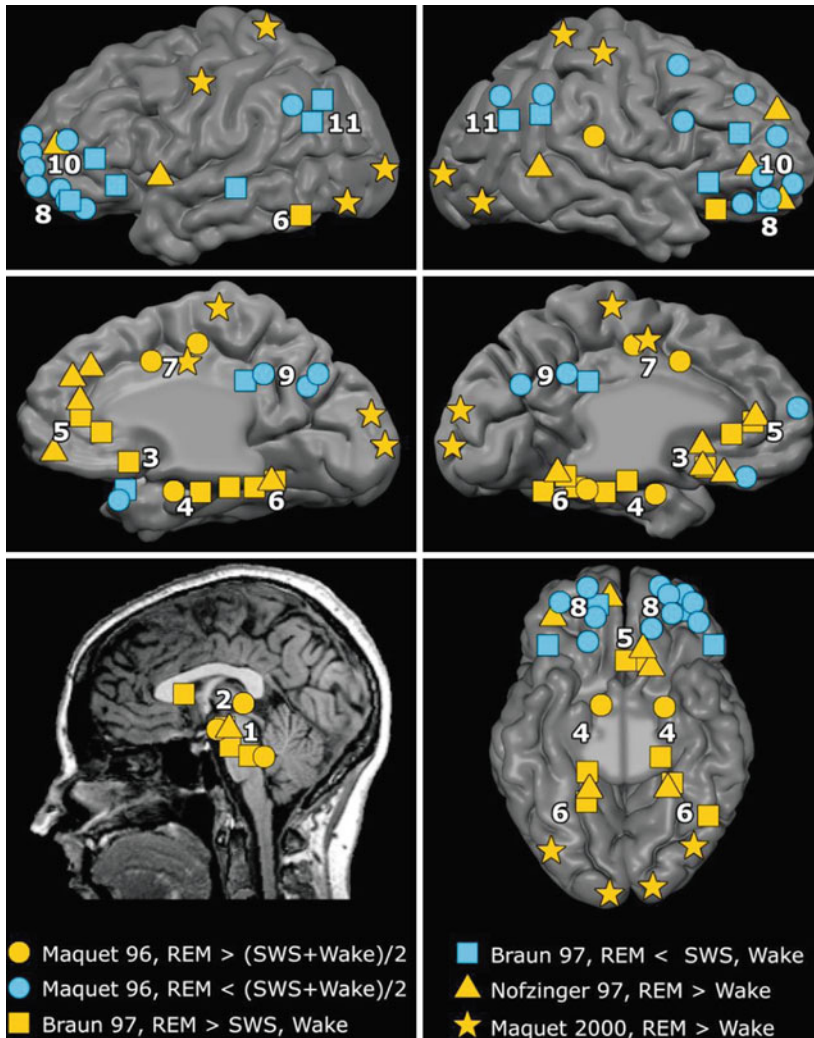


Fig. 9.5 Functional neuroanatomy of human REM sleep: a meta-analysis of PET results. Meta-analysis of relative increases and decreases in neuronal activity during REM sleep as seen with PET imaging using $H_2^{15}O$ measurements of regional cerebral blood flow (rCBF) (Maquet et al. 1996; Braun et al. 1997; Maquet et al. 2000) or [^{18}F]-fluorodeoxyglucose measurements of glucose metabolism (Nofzinger et al. 1997). *Top row*: cortical surface, lateral view. *Middle row*: cortical surface, medial view. *Bottom row*: subcortical foci (*left*) and ventral view of cortical surface (*right*). Analysis is based on published Talairach coordinates of foci whose activity was significant at $p < 0.001$ corrected (Z -score > 3.09). *Circles, squares, triangles, and stars* denote activity as reported in Refs Maquet et al. (1996, 2000), Braun et al. (1997), Nofzinger et al. (1997), respectively. Each symbol marks the center of mass of a region regardless of its spatial extent. *Yellow symbols* denote increased regional activity in the (1) mesopontine tegmentum and midbrain nuclei, (2) thalamus, (3) basal forebrain and diencephalic structures, (4) limbic MTL structures including amygdala and hippocampus, (5) medial prefrontal cortex, (6) occipitotemporal visual cortex, and (7) anterior cingulate cortex. *Cyan symbols* denote decreased activity in the (8) orbitofrontal cortex, (9) posterior cingulate and precuneus, (10) dorsolateral prefrontal cortex, and (11) inferior parietal cortex (From Nir and Tononi 2010)

Czisch et al. (2009) showed that sleep K-complexes evoked by rare tones activated the auditory cortex, hippocampus, superior and middle frontal gyri, and posterior cingulate. Caporro et al. (2012) showed that auditory K-complexes were correlated with increased BOLD signal in thalamus, superior temporal lobes, paracentral gyri, and medial regions of the occipital, parietal, and frontal lobes. Jahnke et al. (2012) found that auditory evoked K-complexes were associated with positive BOLD signal changes in brainstem, thalamus, sensory and motor midline regions, and the default-mode network (DMN). Negative K-complex-related responses were found in the anterior insula. Additionally, connectivity analyses using dynamic causal modeling suggest that the primary auditory cortex may be the first region affected by K-complexes and that midline regions would activate successively from front to back (Jahnke et al. 2012). Using EEG–fMRI, activation of mostly primary cortices (bilaterally in central, precentral, posterior superior temporal, and medial occipital cortex) has also been found during vertex sharp waves (Stern et al. 2011).

REM Sleep

A number of neuroimaging studies are beginning to shed light on the neural correlates of ocular saccades occurring during REM sleep (REMs) as compared to wakefulness. Using H(2)(15)O positron emission tomography, Peigneux et al. (2001) identified activations in the right geniculate body and in the primary occipital cortex in relation to REMs during paradoxical sleep as compared to wakefulness. Using EEG–fMRI, Wehrle et al. (2005) subsequently confirmed fMRI BOLD signal increases in the posterior thalamus and occipital cortex co-occurring with REMs during human paradoxical sleep. Subsequently, several EEG–fMRI studies revealed that not only the posterior thalamus and primary visual cortex but also several other subcortical and cortical areas were activated during paradoxical sleep-associated REMs. Miyachi et al. (2009) found REM-associated activation during sleep in the pontine tegmentum, putamen, anterior cingulate, parahippocampal gyrus, and amygdala. In line with the results of Peigneux et al. (2001), self-paced saccades in total darkness did not produce activity in the visual cortex during wakefulness. Hong et al. (2009) also found additional REM-locked activation in the thalamic reticular nucleus, claustrum, retrosplenial cortex, fusiform gyrus, anterior cingulate cortex, frontal eye field, motor cortex, language areas, and in the ascending reticular activating system, including basal forebrain. In this study, REMs were also associated with BOLD decreases in periventricular subregions matching the distribution of the serotonergic supraependymal plexus.

9.3.3.3 Resting-State fMRI Connectivity Studies

NREM Sleep

A number of studies have investigated changes in functional connectivity, as assessed by BOLD signal correlation techniques, during human NREM sleep as compared to wakefulness. A typical finding is that NREM sleep-induced reduction of consciousness is reflected in altered correlation between DMN components and most notably a reduced involvement of frontal cortex (Horovitz et al. 2009).

This decrease in DMN connectivity is however stage dependent. It was observed that in the transition from wakefulness to light sleep, thalamocortical connectivity is first sharply reduced, whereas corticocortical connectivity is increased; corticocortical connectivity subsequently breaks down mainly in slow-wave sleep (Spoormaker et al. 2010). With increasing sleep depth, contributions of the posterior cingulate cortex, parahippocampal gyrus, and medial prefrontal cortex to the DMN further decrease (Larson-Prior et al. 2011; Samann et al. 2011). Connectivity in task-positive networks, involving lateral parietal and frontal cortices, was also observed to be lower in NREM sleep stages as compared to wakefulness (Spoormaker et al. 2012). Additionally, there is a loss of anti-correlation between the DMN and the “task-positive networks” during NREM sleep as compared to wakefulness (Samann et al. 2011).

EEG–fMRI studies using graph theory tools also show that slow-wave sleep is characterized by a strong hierarchical clustering of brain activity in local sub-modules as compared to wakefulness (Spoormaker et al. 2012). While local clustering values are closest to random values in light sleep, slow-wave sleep is characterized by the highest clustering ratio (Spoormaker et al. 2010). During NREM sleep, brain activity is thus characterized by a modification of the hierarchical organization of the brain’s large-scale networks into smaller independent modules (Boly et al. 2012). This reorganization is however independent from markers of the slow oscillation, as far as can be inferred from scalp EEG. An increase in delta power per se is rather associated with a further breakdown of connectivity in DMN and lateral frontoparietal cortices (Boly et al. 2012). Recently, an fMRI-based multivariate classification approach has been applied to differentiate between NREM sleep and wakefulness. Inputs to the classifier were the BOLD signal correlation values between 20 cortical regions and two regions in the thalamus. This classification approach achieved accuracies over 0.8 in the binary classification between NREM sleep and wakefulness, based on changes in functional connectivity values obtained for epochs as short as 60s (Tagliazucchi et al. 2012). Taken altogether, these results support a marked reorganization of brain connectivity architecture between NREM sleep and wakefulness.

REM Sleep

A recent EEG–fMRI study investigated DMN resting-state functional MRI connectivity during REM sleep as compared to NREM sleep (Koike et al. 2011). Results showed that during REM sleep, the connectivity between the anterior cingulate cortex, the dorsomedial prefrontal cortex, and the inferior parietal lobule on one hand and the medial temporal cortex on the other hand was significantly stronger than in NREM sleep. In contrast, functional connectivity between the dorsomedial prefrontal and the precuneus was significantly weaker in REM sleep as compared to NREM sleep. The authors suggest that such lack of co-activation between the precuneus and medial prefrontal cortex in REM sleep could prevent autobiographic memory from being incorporated into dream content (Koike et al. 2011). To shed further light on this question, additional studies of functional connectivity changes in REM sleep as compared to wakefulness are warranted.

9.3.4 TMS–EEG Studies

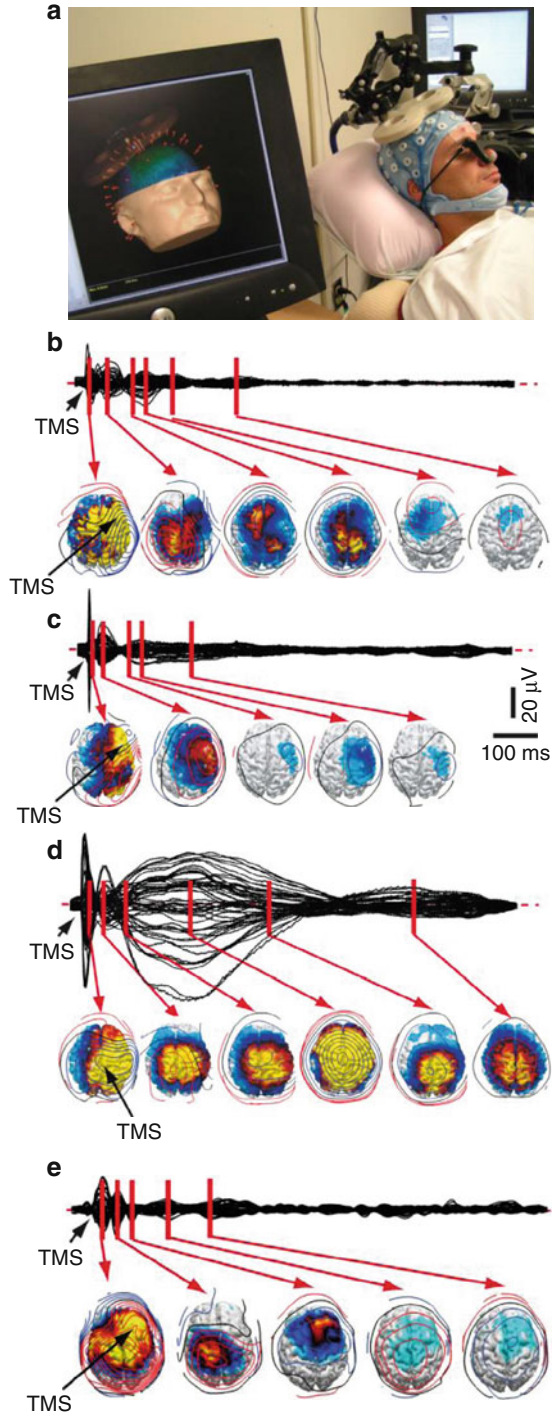
9.3.4.1 NREM Sleep

As was discussed above, the level and quality of conscious experience can vary dramatically across the sleep–wake cycle. For example, during NREM sleep early in the night, consciousness can nearly vanish (Pivik and Foulkes 1968; Hobson and Pace-Schott 2002; Suzuki et al. 2004) despite periods of persistent neural activity in the thalamocortical system (Steriade et al. 2001) and despite preserved levels of neuronal synchronization (Bullock et al. 1995; Duckrow and Zaveri 2005). In order to better understand how information transmission/processing within thalamocortical changes across the sleep–wake cycle, a series of recent experiments employed a combination of transcranial magnetic stimulation and electroencephalography (TMS/EEG) (Fig. 9.6a). This technique allows perturbing directly a subset of cortical neurons and recording with millisecond resolution the response of this initial activation in the rest the brain. Therefore, TMS/EEG represent a suitable method to evaluate directly the ability of different areas of the cerebral cortex to engage in complex patterns of causal interactions (effective connectivity), a theoretical requirement for information integration and consciousness (Tononi 2004).

In a first set of experiments, TMS/EEG measurements were carried out during the transitions from wakefulness into NREM sleep early in the night (Massimini et al. 2005, 2007). Figure 9.6b shows the typical response obtained after direct cortical stimulation (rostral premotor cortex) in an awake subject. During wakefulness, TMS triggers a series of low-amplitude, high-frequency (25–30 Hz) waves associated with cortical activations that propagate along long-range ipsilateral and transcallosal connections. Remarkably, the exact same stimulation, applied 15 min later during sleep stage N3, results in a very different picture (Fig. 9.6c). In this case, TMS elicits a larger, lower-frequency wave, associated with a strong initial cortical activation, which does not propagate to connected brain regions and dissipates rapidly. This finding was extremely reproducible, could be generalized to any cortical area, and suggested that during sleep stage N3 thalamocortical networks – despite being active and reactive – lose their ability to sustain long-range causal interactions.

TMS/EEG measurements not only indicate that during slow-wave sleep the thalamocortical system tends to break down into isolated modules, but they also show that the ability of thalamocortical circuits to produce differentiated responses is impaired. Indeed, while during wakefulness different cortical areas react to TMS with a pattern of activation which has a characteristic shape and frequency content (Rosanova et al. 2009), this distinction is clearly obliterated during sleep; the local response to TMS becomes, in all cases, a simple positive–negative wave (Massimini et al. 2007). Interestingly, this positive–negative component resembles a full-fledged sleep slow wave when TMS is delivered at high intensities in a scalp region around the vertex. Also in this case, the complexity of the response obtained during wakefulness is lost; indeed, while the pattern of cortical activation associated with the full-fledged slow waves is global, it is also simple and stereotypical (Fig. 9.6d). In summary, TMS/hd–EEG measurements suggest that during NREM sleep early in the night, when consciousness vanishes, the only way the brain can react to a direct

Fig. 9.6 Spatiotemporal cortical current maps of TMS-induced activity during wakefulness, NREM, and REM sleep. **(a)** The experimental setup including the TMS coil, a 60-electrode EEG cap, and an MRI-based neuronavigation system. From the EEG data, current sources corresponding to periods of significant activations were plotted on the subject's MRI. **(b)** TMS during wakefulness elicits rapidly changing patterns of activation, lasting up to 300 ms and involving several different areas (right premotor cortex stimulation is shown, but similar results are observed for other stimulation sites, including midline centroparietal regions). **(c)** TMS during NREM sleep elicits either a brief activation that remains localized to the area of stimulation (right premotor cortex stimulation) or **(d)** a global wave of activation that affects indiscriminately and stereotypically the entire cortex (midline centroparietal stimulation) **(e)** for TMS during REM sleep; a balanced pattern of activation and a significant resumption of effective connectivity are observed (From Massimini et al. 2005, 2007, and Tononi and Massimini, unpublished data)



cortical perturbation is by producing a slow wave that is either local or global but nonspecific and stereotypical. Hence, the thalamocortical system, despite being active and reactive, either breaks down in causally independent modules (producing a local slow wave) or bursts into an explosive and nonspecific response (a full-fledged, global slow wave). In no case, during NREM sleep, did TMS result in a balanced, long-range, differentiated pattern of activation. The possible mechanisms for this apparent breakdown of complex interactions within the thalamocortical system will be discussed in Sect. 9.5.

9.3.4.2 REM Sleep

As was also mentioned, complete loss of consciousness during sleep is the exception rather than the rule, and many awakenings yield dream reports (Casagrande et al. 1996; Stickgold et al. 2001; Fagioli 2002; Nir and Tononi 2010), suggesting that during much of sleep thalamocortical circuit may retain a high capacity to integrate information. In a recent study TMS/EEG was employed to evaluate intracortical communication during REM sleep (Massimini et al. 2010), when dreaming is most frequently reported upon awakening. In this case, TMS-evoked EEG potentials were recorded during the first REM sleep episode. These measurements showed that during the transition from NREM to REM, while subjects were still behaviorally asleep, the brain's response to TMS recovered fast oscillatory components and became similar to the one obtained during wakefulness, especially during the first 100–150 ms post-stimulus. Source modeling revealed that, as in wakefulness, the resumption of fast oscillations during REM sleep was associated with a pattern of activation that was more complex and widespread compared to one of NREM sleep (Fig. 9.6e). This observation corroborates the hypothesis that cortical effective connectivity may play a role in the shifts of conscious experience that occur during sleep. Notably, the persistence, to some degree, of long-range corticocortical effective connectivity has been also reported during stage 1 (see Fig. S2 in Massimini et al. 2005), another sleep stage associated with frequent dream reports (Foulkes 1966). In future work, it would be interesting to systematically collect TMS/EEG measures of thalamocortical effective connectivity during the whole night and to correlate them with dream reports. This approach may help to clarify the neural correlates of consciousness during sleep on a finer timescale, beyond the REM/NREM sleep dichotomy and beyond traditional sleep staging.

9.3.5 Intracranial Recordings in Humans

Until recently, our understanding of neuronal activity in sleep reflected a massive gap between functional imaging and behavioral studies in humans and electrophysiological investigations typically carried out in cats and rodents. Direct brain recordings during sleep in patients with intractable epilepsy, implanted with depth electrodes for potential surgical treatment, constitute an invaluable opportunity for bridging this gap. Such studies permit the investigation of simultaneously recorded neuronal activity from multiple brain areas bilaterally and provide sampling of

activity across cortical and subcortical structures that is rarely achieved in animal studies. Naturally, recording sites are dictated by clinical considerations and usually encompass mostly medial limbic structures. Fortunately, these brain regions play a pivotal role in supporting many activity patterns in sleep such as slow waves (Murphy et al. 2009; Nir et al. 2011) and sleep spindles (Andrillon et al. 2011).

9.3.5.1 Sleep Slow Waves

The most prominent electrophysiological events in sleep are slow waves and related K-complexes – isolated high-amplitude waves that are triggered by external or internal stimuli (Colrain 2005). Animal studies established that such waves reflect a bistability of thalamocortical neurons undergoing a slow oscillation (<1 Hz) between active (“UP”) and inactive (“DOWN”) states and that these waves group and modulate other neuronal oscillations (Steriade et al. 1993b; Contreras and Steriade 1995; Destexhe et al. 2007; Crunelli and Hughes 2010). Recently, microelectrode studies confirmed that, in humans, slow waves are similarly associated with underlying neuronal bistability (Fig. 9.7) oscillating between active and inactive states (Cash et al. 2009; Csercsa et al. 2010; Le Van Quyen et al. 2010; Nir et al. 2011), as was found in natural sleep of rodents (Vyazovskiy et al. 2009b) and cats (Chauvette et al. 2011).

Importantly, such studies also revealed some important features of sleep slow waves that had not been evident in previous work. While slow oscillations are remarkably synchronous when examined in brain slices (Sanchez-Vives and McCormick 2000) and in animals under anesthesia (Chauvette et al. 2011), human studies focusing on natural sleep and recording in many regions in parallel revealed that most sleep slow waves and the underlying active and inactive neuronal states occur locally (Fig. 9.7e, f), where some regions can be active while others are silent (Nir et al. 2011). It was also found that slow waves have a tendency to propagate along typical paths (Fig. 9.3d), from medial prefrontal cortex to the medial temporal lobe (MTL) through the cingulate gyrus and neighboring structures (Nir et al. 2011), which constitute an anatomical backbone of anatomical fibers (Hagmann et al. 2008). Such propagation was previously suggested by high-density EEG and animal studies (Massimini et al. 2005; Volgushev et al. 2006; Murphy et al. 2009; Vyazovskiy et al. 2009a; Riedner et al. 2011). Slow waves also exhibit complex propagation patterns at a local scale (Hangya et al. 2011).

In addition, important insights were gained about slow-wave propagation *within* the MTL, where noninvasive imaging is limited. By and large, cortical slow waves precede hippocampal waves, revealing a sequential propagation from the parahippocampal gyrus, through entorhinal cortex, to hippocampus (Nir et al. 2011), in line with previous animal studies (Sirota et al. 2003; Isomura et al. 2006; Hahn et al. 2007; Ji and Wilson 2007) and with a recent study of human depth EEG (Wagner et al. 2010). As for the direction of cortico-hippocampal dialogue in sleep (Buzsaki 1998), it was found that at times of hippocampal ripples (associated with the “replay” of activity in cell assemblies during sleep in rodents (Diekelmann and Born 2010)), local effects of hippocampal output can be observed within the MTL in terms of increased unit activity (Nir et al. 2011) as well as gamma bursts in parahippocampal

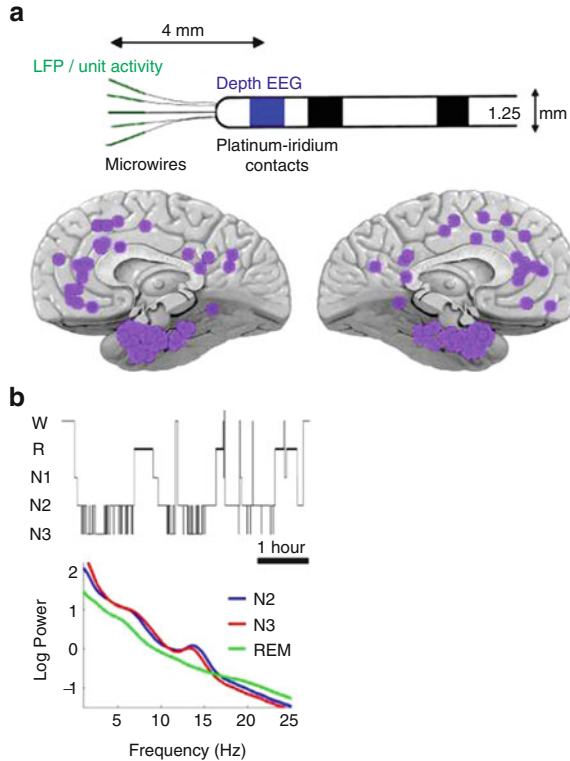


Fig. 9.7 (a) (Top) Diagram of flexible probes used for concomitant recording of depth EEG (platinum contacts, blue) and unit activity (microwires, green) in microelectrode studies of human sleep. (Bottom) Overview of depth electrode locations in 13 individuals encompassing multiple brain regions seen from medial view. (b) Hypnogram (top) and average power spectra of scalp EEG (bottom) in one representative individual indicate that sleep measures in epilepsy patients are in general agreement with typical findings in healthy young adults (*W* wake, *R* REM sleep; N1–N3, NREM sleep, stages 1–3). (c) Neuronal activity underlying slow waves in human sleep. Electrical brain activity across 15 s of deep NREM sleep. Top (red), scalp EEG; bottom (blue), intracranial depth EEG in entorhinal cortex. Green dots, individual slow waves that are automatically detected and separated from pathological events. Black, MUA and action potentials of six neurons. Vertical green bar, OFF periods of inactivity. Orange green bar, ON periods of neuronal silence. Bottom insets, an analysis across 600 units confirms that neurons increase and decrease their activity in concert with local electrical fields. (d) Slow waves have a tendency to propagate along typical paths. Left, each circle denotes a depth electrode and its color marks the typical slow-wave timing at that location. Right, average unit activity in frontal cortex (top, $n=76$) and MTL (bottom, $n=155$), triggered by the same scalp slow waves. Note that on average slow waves and underlying neuronal activity occur earliest in the frontal lobe, about 200 ms later in the temporal lobe and finally in the hippocampus. (e) An example of local sleep slow waves occurring at different times in left and right posterior cingulate cortices. Rows (top to bottom) depict activity in scalp EEG (Cz, red), left and right posterior cingulate. Blue, depth EEG; green, MUA; black lines, single-unit spikes. White shadings mark local OFF periods. (f) The vast majority of slow waves occur locally. Distribution of slow-wave involvement (percentage of monitored brain structures expressing each wave) shows that global slow waves are quite rare (From Nir et al. 2011)

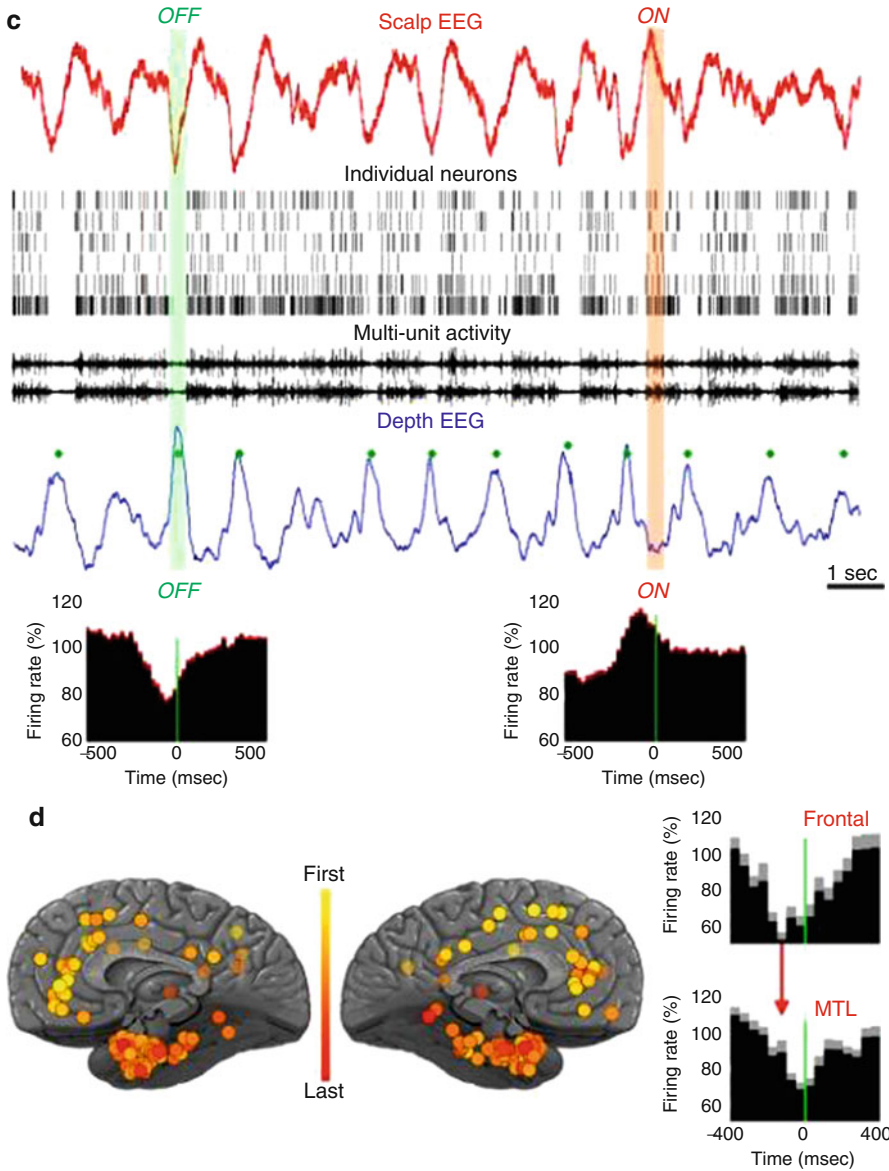


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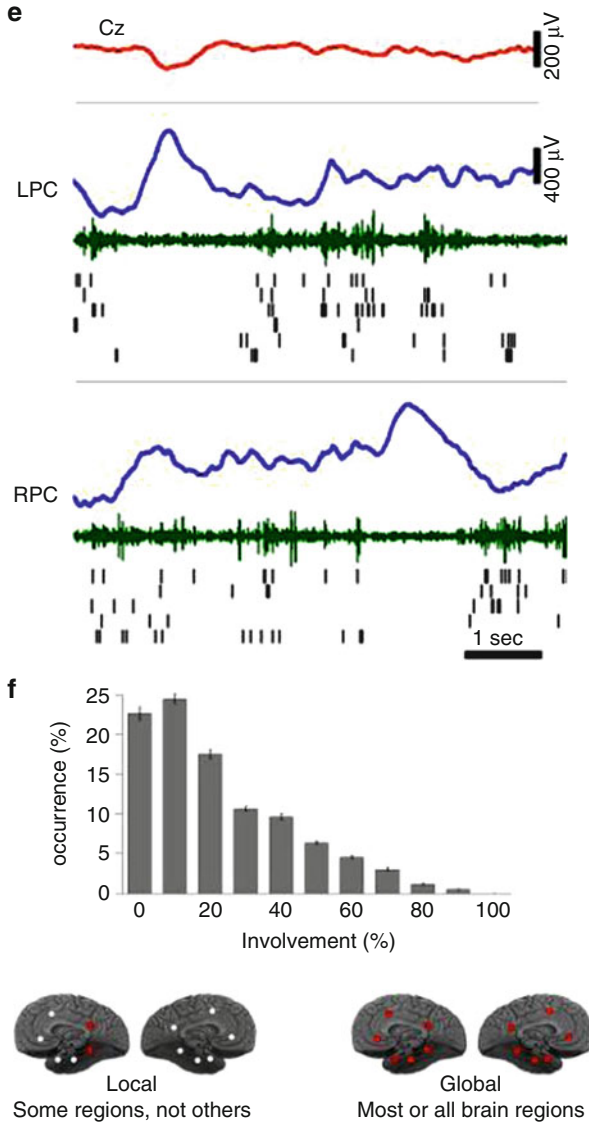


Fig. 9.7 (continued)

gyrus (Le Van Quyen et al. 2010). However, ripples were not associated with detectable effects in the medial prefrontal cortex (Nir et al. 2011), a primary projection zone of hippocampal output in primates. On the whole, during NREM sleep neural activity propagates predominantly from the neocortex to the hippocampus. Future studies are needed to determine whether within this robust cortico-hippocampal broadcast, there may be islands of hippocampo-cortical transmission that may be functionally relevant for memory consolidation.

9.3.5.2 Sleep Spindles

Sleep spindles are the other hallmark oscillation of NREM sleep; they are waxing-and-waning 10–16 Hz oscillations lasting 0.5–2 s and are believed to mediate many sleep-related functions (De Gennaro and Ferrara 2003). Recent intracerebral human studies (Andrillon et al. 2011; Peter-Derex et al. 2012) revealed that spindle frequency is topographically organized with a sharp transition between fast (13–15 Hz) centroparietal spindles and slow (9–12 Hz) frontal spindles occurring 200 ms later on average (Fig. 9.8). Moreover, like slow waves, most spindles occur locally, thereby showing that constrained intracerebral communication is an important feature of NREM sleep. It was also found that spindle frequency changes along with sleep depth, reflecting the level of thalamocortical hyperpolarization at any given time and that robust firing rate modulations were surprisingly weak during sleep spindles (Andrillon et al. 2011). On the whole, patient studies revealed changes in spindle occurrence, frequency, and timing between regions and across sleep (Andrillon et al. 2011; Peter-Derex et al. 2012). Some of this heterogeneity (e.g., slow frontal vs. fast centroparietal spindles) was observed also with noninvasive scalp measurements (Anderer et al. 2001; De Gennaro and Ferrara 2003; Schabus et al. 2007; Ferrarelli et al. 2010), whereas several other novel aspects such as timing differences between brain regions, frequency changes across sleep, and the lack of robust firing rate modulations (Andrillon et al. 2011) were previously unknown.

9.3.5.3 Gamma and Ripple Oscillations During Slow-Wave Sleep

Gamma oscillations (40–120 Hz) are usually associated with waking functions such as sensory binding (Singer and Gray 1995), attention (Fries et al. 2001), or encoding/retrieval of memory traces (Montgomery and Buzsaki 2007) and have been shown to be closely related to correlated neuronal activity in humans during wakefulness (Nir et al. 2007). These oscillations are also present during SWS, as shown by extensive evidence from in vivo (Steriade et al. 1996; Grenier et al. 2001; Isomura et al. 2006; Mena-Segovia et al. 2008) and in vitro recordings of the rodent and feline cortex (Dickson et al. 2003; Compte et al. 2008). These experiments have shown that gamma oscillations occur preferentially during the active (UP) component of the slow wave – characterized by rhythmic cycles of synaptically mediated depolarization – and disappear during the hyperpolarized (DOWN) phase. Recent microelectrode studies in the human cortex during sleep have confirmed that gamma oscillations are reliably associated with EEG slow waves and with a marked increase in local cellular discharges (Cash et al. 2009; Le Van Quyen et al. 2010). Also, coincident firings with millisecond precision between cells within the same cortical area were shown to be strongly enhanced during gamma oscillations (Le Van Quyen et al. 2010). Cortical gamma patterns in sleep have been suggested to briefly restore “micro-wake” activity (Destexhe et al. 2007; Haider and McCormick 2009) and may be important for consolidation of memory traces acquired during previous wakefulness. Along this line, coupling between parahippocampal gamma oscillations and hippocampal ripple/sharp-wave complexes has been reported in humans (Le Van Quyen et al. 2010; Fig. 5C). Ripple oscillations (80–160 Hz) are known to coincide with reactivation of hippocampal activity patterns (Wilson and McNaughton

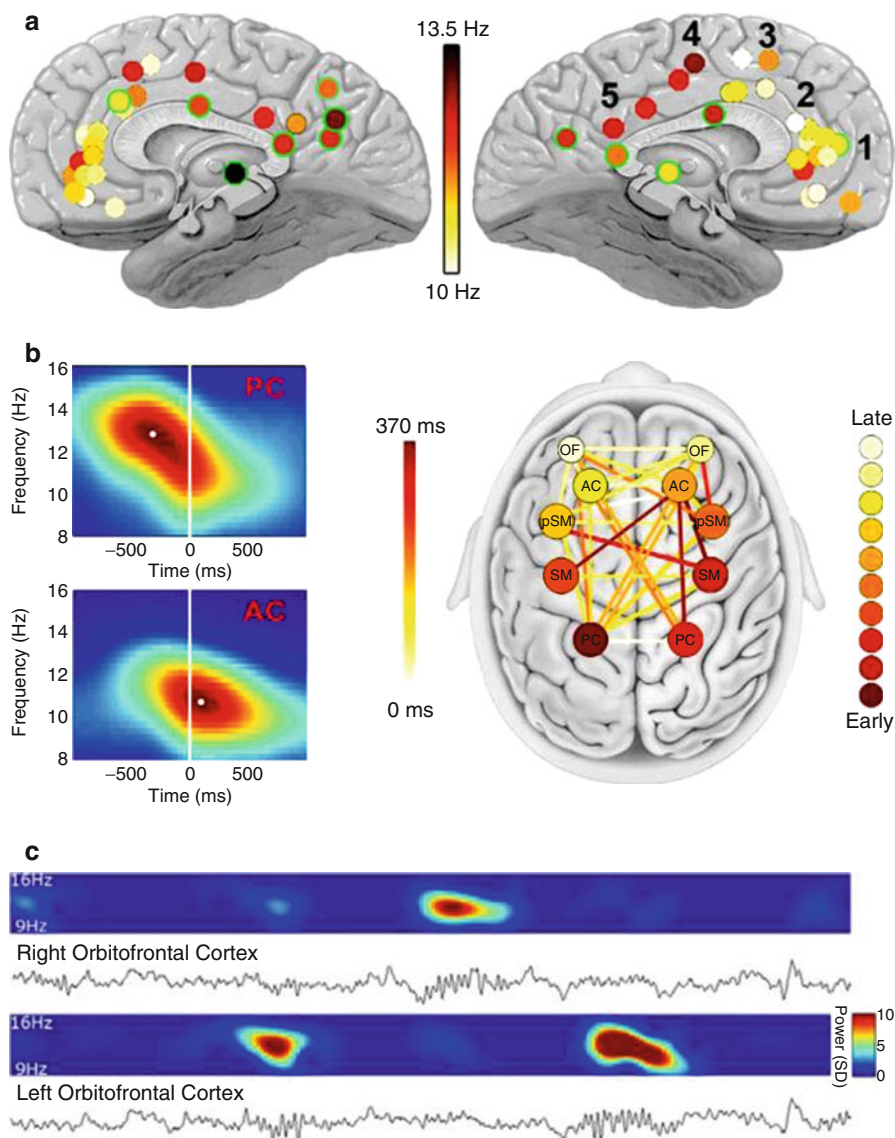


Fig. 9.8 (a) Average frequency of spindles across the medial brain; note the contrast between slow (9–12 Hz) frontal spindles and fast (13–16 Hz) centroparietal spindles. (b) Fast centroparietal spindles precede slow frontal spindles by 200 ms on average; (*left*) an example of differences in timing and frequency between early, fast spindles in posterior cingulate (PC) and late, slower spindles in anterior cingulate (AC). (*Right*) a graph showing a quantitative analysis of the order in which spindles are detected across multiple regions (*node color*) and the mean temporal delays between each pair of regions (*edge color*). (c) Example of a local sleep spindle as seen in depth EEG across bilateral orbitofrontal cortex along with corresponding spectrograms in the spindle frequency range (9–16 Hz) during 15 s of slow-wave sleep. (d) Spindle frequency reflects sleep depth. Representative time course of slow-wave activity (SWA) and spindle frequency dynamics throughout sleep in the anterior cingulate of one individual. Note that spindle frequency is lowest in deep sleep when SWA is highest and increases toward transitions to REM sleep (From Andrillon et al. 2011)

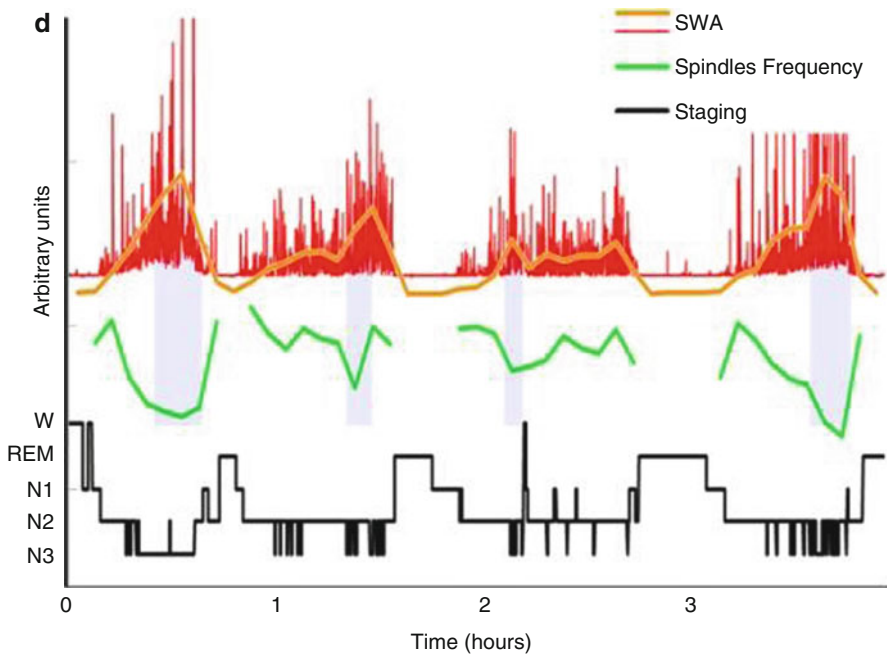


Fig. 9.8 (continued)

1994) which could reflect information flow from the hippocampus to the cortex. In the human hippocampus and entorhinal cortex, ripples are similar to those described in non-primate CA1 and CA3 in terms of duration and spectral frequency, bilateral occurrence in hippocampal areas, highest probability of occurrence during NREM sleep, and minimal occurrence during REM sleep (Buzsaki et al. 1992; Staba et al. 2004; Le Van Quyen et al. 2008). Thus, human microelectrode studies show that high-frequency gamma and ripple oscillations robustly occur and modulate single neuron firing during sleep. Moreover, slower fluctuations such as slow waves group and modulate faster “nested” oscillations such as cortical spindles, gamma events, and hippocampal ripples (Clemens et al. 2007; Le Van Quyen et al. 2010; Andrillon et al. 2011; Nir et al. 2011) confirming findings in animal studies (Sirota et al. 2003; Battaglia et al. 2004; Steriade 2006).

9.3.5.4 Ultraslow Resting-State Fluctuations in Sleep and Wakefulness

Although perception and action occur on the sub-second timescale, it has long been recognized that cortex also shows fluctuations in electrical activity with slower dynamics. As discussed in Sect. 9.3.3, resting-state ultraslow fluctuations (<0.1 Hz, at the timescale of tens of seconds) in blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signals have gained attention as a powerful tool to study functional brain networks in health and disease (Fox and Raichle 2007). However, the extent to which such waves reflect neuronal activity or may stem from nonneuronal sources (e.g., cardiac, respiratory) remained unclear. Recent intracerebral recordings (He et al. 2008; Nir et al. 2008) established that spontaneous

ultraslow neuronal activity can indeed be detected in direct cortical recordings and that it exhibits significant correlations between nodes within the same functional system. An important open question in this field is whether such resting-state waves may reflect cognitive processes such as mind wandering, shifts in attention or mental imagery, or whether they may be more closely related to basic maintenance of synaptic contacts (Balduzzi et al. 2008). Interestingly, ultraslow waves in humans were found to persist and grow stronger in sleep. They are also present in anesthesia (Vincent et al. 2007) and to some extent in vegetative patients (Ovadia-Caro et al. 2012) thus arguing against involvement of such waves in conscious processes.

In summary, by analyzing simultaneous activity across multiple brain regions, microelectrode studies of human sleep demonstrated that slow waves and sleep spindles (Nir et al. 2011) as well as gamma bursts (Le Van Quyen et al. 2010) are mostly local. The local nature of sleep slow waves has recently been confirmed in animal studies (Vyazovskiy et al. 2011; see also Sirota and Buzsaki 2005; Mohajeri et al. 2010). Thus, an important new theme that has emerged from single-unit human studies is that sleep oscillations are much more heterogeneous than initially assumed (Magnin et al. 2010; Andrillon et al. 2011; Hangya et al. 2011; Nir et al. 2011). Regional diversity in occurrence, spectral, and temporal aspects of sleep oscillations were hardly observable with noninvasive human imaging, when recording from a limited number of brain regions in rodents or when using anesthesia as a model for sleep.

9.4 Local Sleep and Dissociated States

9.4.1 Local Sleep: Mixed States, Sleep Onset, and Sleep Inertia

The main new finding put forward by recent intracranial studies of human sleep is that most sleep slow waves and the underlying active and inactive neuronal states occur locally, and this is also the case for sleep spindles (Nir et al. 2011). The demonstration that sleep oscillations typically occur in a local manner highlights the notion that at a fundamental level, electrophysiological features associated with particular vigilance states such as sleep or wakefulness may regularly occur independently in different brain regions. This finding in normal sleep adds to several lines of evidence supporting the notion of mixed states and their underlying local activities and offers a new emerging perspective on behavioral states and underlying brain activities (Nobili et al. 2012).

While mammalian sleep is typically associated with distinct electrophysiological markers, it is important to note that sleep is first and foremost defined as a reversible state of reduced behavioral responsiveness (Carskadon and Dement 2005). Given the primacy attributed to behavior, the global changes in neuromodulation (Jones 2005a), and the clear-cut changes in the EEG (driven in large part by central subcortical arousal networks such as the reticular activating system (Moruzzi and Magoun 1949)), sleep has been traditionally regarded as a global phenomenon.

However, it has been proposed that sleep may be fundamentally a local property of neuronal ensembles and that behavioral sleep emerges only when local sleep

emerges over sufficiently large cortical regions (Krueger et al. 2008; Rattenborg et al. 2012). Along this line, there is evidence that electrophysiological signatures of sleep and wakefulness can be restricted to small populations such as individual cortical columns (Pigarev et al. 1997; Rector et al. 2005). Along this line, naturally occurring sleep patterns in dolphins (Mukhametov and Rizzolatti 1970), seals (Siegel 2009), and birds (Rattenborg et al. 2001) suggest that parts of the brain can be awake while others are asleep, a condition that may have evolved in those species in order to facilitate continuous flying or swimming in the face of dissipating sleep need.

Furthermore, slow waves can be locally regulated so that their intensity varies among cortical regions. Prolonged waking induces an increase in slow-wave activity (SWA; EEG power <4 Hz), which is largest over the frontal cortex (Werth et al. 1997; Finelli et al. 2001). Sleep slow waves can be locally regulated as a function of prior use and plastic processes (Vyazovskiy et al. 2000; Huber et al. 2004, 2006). Local gradients of SWA intensity and SWA regulation are also coherent with the spatiotemporal dynamics of slow waves during full-fledged NREM sleep. As we have seen (Fig. 9.3d), slow waves originate more frequently at anterior cortical regions and tend to propagate from medial prefrontal cortex to the MTL through the cingulate gyrus and neighboring structures (Massimini et al. 2004; Volgushev et al. 2006; Murphy et al. 2009; Vyazovskiy et al. 2009a; Nir et al. 2011; Riedner et al. 2011).

In further support of mixed states consisting of coexisting wake-like and sleep-like activity patterns, recent intracranial studies of human sleep demonstrated long-lasting (10–120 s) local awakenings within the sleeping brain. For example, local activation as indicated by abrupt increases in high-frequency EEG power within the motor cortex occurs synchronously with deep-sleep EEG patterns in the dorsolateral prefrontal cortex and scalp EEG (Nobili et al. 2011). As noted in the earlier sections, primary cortices are often reported to be the least deactivated brain regions in NREM sleep (Braun et al. 1997; Dang-Vu et al. 2005), and it has been hypothesized that this pattern may have been evolutionary selected to increase the probability of survival by facilitating motor behaviors in case of sudden awakenings (Nobili et al. 2012). Such local cortical awakenings could also underlie confusional arousals (Terzaghi et al. 2009), as discussed in more detail below in the section on dissociated states.

Conversely, sleep-like activities may occur during wakefulness. During prolonged wakefulness, the EEG gradually shows a progressive increase in slow frequency activities reflective of increased homeostatic sleep pressure (Finelli et al. 2000; Vyazovskiy and Tobler 2005). Indeed, it was noted that sleep-deprived monkeys may be able to activity control behavior with some neural circuits, while others are idle (Pigarev et al. 1997). More recently, it was demonstrated directly that in freely behaving rats, after a long period of wakefulness, cortical can go briefly “off-line” exactly as in sleep (i.e., showing brief OFF periods resembling those of the sleep slow oscillation) in one cortical area but not in another (Vyazovskiy et al. 2011). The incidence of such local OFF periods increases with the duration of the awake state, while rats are active and display an “awake” EEG. However, they are progressively impaired in a sugar-pellet-reaching task.

Another condition where mixed states seem to be particularly prevalent is during sleep onset. Magnin et al. (2010) showed that when falling asleep, the emergence of slow waves is highly asynchronous across brain regions, such that the thalamic deactivation precedes that of the cortex by several minutes. Moreover, several minutes before sleep onset, sleep spindles emerge in the hippocampus along with early slow-wave activity in the anterior thalamic nuclei (Nobili et al. 2012). Within cortex, anterior frontal regions are the first to show synchronized sleep EEG signatures (De Gennaro et al. 2001). Interestingly, frontal cortex shows the strongest slow-wave activity throughout sleep (Werth et al. 1997). Since SWA is an established marker of sleep intensity, it seems that frontal cortex possesses the strongest sleep need and consequently “falls asleep” before other regions do. Interestingly, many subjects awakened from early stage N1 sleep claim that they had been awake. Such mismatch between subjective reports of sleep onset and the electrophysiological markers of scalp EEG may not be surprising given that sleep does not seem to begin simultaneously in all cortical and subcortical areas. In addition, such sleep onset asynchrony may help explain in part the long sleep latency in patients with insomnia and paradoxical insomnia (Nobili et al. 2012).

Mixed patterns of activities reflecting local wakefulness and sleep could also be related to the phenomenon of sleep inertia (Ferrara et al. 2006; Marzano et al. 2011) – the subjective feeling of grogginess accompanied by decreased levels of cognitive and behavioral performance which typically follows the awakening. For example, a PET study (Balkin et al. 2002) demonstrated that post-sleep waking patterns of regional CBF were reestablished at different rates in different brain areas, most rapidly in centrencephalic regions (e.g., brainstem and thalamus) and then in the anterior cortical regions (prefrontal association cortices) across the ensuing 15 min of wakefulness. In an EEG study (Ferrara et al. 2006), the first 10 min after awakening was characterized by increased EEG power in the 1–9 Hz range especially over parieto-occipital range and decreased power in the beta range (18–24 Hz) especially over occipital areas, suggesting that posterior brain areas may take longer to become fully “awake.”

9.4.2 Dissociated States

The next section will consider a number of conditions that lie in between waking and sleep: They partake of some features typical of waking consciousness as well as of some characteristic of consciousness in sleep – that is, they represent dissociated states (Mahowald and Schenck 2005). Some of these conditions, such as daydreaming and lucid dreaming, are perfectly normal and can even be learned; others occur in the context of sleep disorders that provide further striking examples that sleep and wakefulness might be simultaneously present in different cerebral regions. These clinical conditions, known as parasomnias, include some of the most remarkable examples of pathological dissociation between consciousness, awareness of the environment, reflective consciousness, and behavior.

9.4.2.1 Daydreaming

A common definition of daydreaming is “a dreamlike musing or fantasy while awake, especially of the fulfillment of wishes or hopes.” For experimental purposes, daydreaming can be defined as “stimulus independent mentation,” that is, as waking images and thoughts that are independent of the task at hand (Singer 1993). Daydreaming is extremely common. Indeed, no matter how hard one concentrates on the task at hand, a surprising amount of time is spent drifting off into fantasies and interior monologues of one kind or another. If subjects are periodically interrupted for thought sampling during a signal-detection task, they report stimulus-independent mentation at least 35 % of the time, even under heavy processing loads. Their reports also indicate discontinuities and scene changes that are more frequent than in REM sleep. There have been attempts at further categorizing waking mental activities and validating such categories using questionnaires and factor analysis. Relevant dimensions are (1) directed or operant vs. non-directed or respondent thought (the former voluntarily directed toward accomplishing a task), (2) stimulus bound vs. stimulus independent, (3) realistic vs. fanciful, (4) well integrated (orderly, connected, coherent) vs. degenerated, and (5) vivid vs. non-vivid. A prototypical daydream would be non-directed, stimulus independent, fanciful, and non-integrated. Recall of waking images and thoughts experienced while daydreaming can be as poor as dream recall, possibly because, just as dream images, daydreaming images cannot be referenced by external events.

The neural circuits involved in daydreaming are beginning to be studied. For instance, using both thought sampling and brain imaging (Mason et al. 2007), a recent study showed that mind wandering is associated with activity in the same default network of cortical regions that are active when the brain is not actively engaged in a task (Raichle et al. 2001). Regions of the default network that exhibited greater activity during mind wandering included bilateral medial prefrontal cortex, anterior cingulate, posterior cingulate, precuneus, insula, left angular gyrus, as well as superior temporal cortex. In addition, individuals’ reports of the tendency of their minds to wander were correlated with activity in this network (Mason et al. 2007). Based on these results, however, it would seem that the circuits activated during daydreaming may actually be different from those involved in dreaming, given that, for instance, posterior cingulate, precuneus, and lateral parietal cortex are relatively deactivated during REM sleep (Maquet et al. 1996; Braun et al. 1997; Nir and Tononi 2010).

9.4.2.2 Lucid Dreaming

Dreams usually involve loss of self-reflection and of reality testing. Hallucinations and delusions in dreams are typically thought to be real rather than dreamt up. Sometimes, however, a dreamer can become aware that he is dreaming (LaBerge 2000). Under such circumstances, the dreamer is able to remember the circumstances of waking life, to think clearly, and to act deliberately upon reflection all while experiencing a dream world that seems vividly real. Lucid dreaming can be cultivated, typically by a pre-sleep autosuggestion procedure: the key is to remember that if one is experiencing something bizarre, such as floating in space, it must

be a dream rather than a waking experience. In fact, lucid dreamers often attempt to fly: If they succeed, they know they are probably dreaming. Lucid dreaming has been extensively studied in the laboratory by asking trained subjects to carry out distinctive patterns of voluntary eye movements when they realize they are dreaming. The prearranged eye movement signals appear on the polygraph records during REM sleep, proving that the subjects had indeed been lucid during uninterrupted REM sleep. This strategy has been used to demonstrate that time intervals estimated in lucid dreams are very close to actual clock time, that dreamed breathing corresponds to actual respiration, and that dreamed movements result in corresponding patterns of muscle twitching. Stable lucid dreams apparently only occur out of REM sleep, especially in the early morning, when REM sleep is accompanied by intense phasic phenomena. A recent EEG study (Voss et al. 2009) has shown that during lucid dreaming, gamma activity is higher than in typical REM sleep, especially over frontal cortex. Moreover, EEG coherence throughout the frequency spectrum in lucid dreaming is significantly higher than in REM sleep, even higher than in wake for the delta and theta band (but lower for the alpha band), especially over frontal areas. Thus, lucid dreaming may indeed be a distinctive state in its own right.

9.4.2.3 Sleepwalking

Sleepwalking refers to various complex motor behaviors, including walking, that are initiated during deep NREM sleep, typically during stage N3 (Bassetti 2009). Some episodes may be limited to sitting up, fumbling, picking at bedclothes, and mumbling. Patients usually stand up and walk around quietly and aimlessly. Sleepwalkers walk around with open eyes and sometimes speak, though slowly and often inarticulately. They behave as if they were wide awake though their awareness of their actions is very restricted. Occasionally, sleepwalkers become agitated, with thrashing about, screaming, running, and aggressive behavior. A highly publicized case is that of Ken Parks, a sleepwalker who, after falling asleep at home, arose to drive to his in-laws, strangled his father-in-law into unconsciousness, and stabbed his mother-in-law to her death.

Sleepwalking is frequent in children, but it can persist in up to 1 % of adults. In predisposed individuals, attacks can be precipitated by forced arousals, e.g., by placing the subject afoot. Sleepwalking is regarded as a disorder of arousal with frequent but incomplete awakening from slow-wave sleep. If awakened during an episode, sleepwalkers typically do not report any dreamlike mental activity, although in a few cases hallucinations have been reported. There is almost never any memory of the behaviors carried out while sleepwalking. The episodes begin while the EEG shows high-amplitude slow waves. During the episodes, the EEG decreases in amplitude and increases in frequency, usually leading to the appearance of mixed-frequency patterns typical of stage N1. There may also be rhythms resembling the alpha rhythm of waking, but slower by 1–2 Hz and not abolished by eye opening or visual stimulation. During short episodes of sitting up with eyes open and moving around, the EEG may show slow waves throughout – providing a clear-cut dissociation between observable behavior, brain activity, and consciousness.

A recent study has succeeded in performing neuroimaging during a sleepwalking episode using single-photon emission computed tomography, a variant of PET (Bassetti et al. 2000; Bassetti 2009). The patient, a 16-year-old man, stood up with his eyes open and a scared facial expression. After a few seconds, he sat down, pulled on the EEG leads, and spoke a few unintelligible words. The EEG showed diffuse, high-voltage rhythmic slow-wave activity. Compared to waking, regional cerebral blood flow was decreased during sleepwalking in frontoparietal associative cortices, just as it is in slow-wave sleep. This deactivation of prefrontal cortices during normal sleep and sleepwalking is consistent with the lack of self-reflective consciousness and recall that characterize both conditions. However, blood flow was higher during sleepwalking than in slow-wave sleep in the posterior cingulate cortex and anterior cerebellum, and the thalamus was not deactivated as it is during normal slow-wave sleep. Thus, at least in this patient, sleepwalking seems to arise from the selective activation of thalamo-cingulate circuits and the persisting deactivation of other thalamocortical systems. Normally, the entire forebrain is either awake or asleep. Sleepwalking thus appears to constitute a dissociated state where some brain areas are “awake” while others are “asleep.” It is likely that, in different patients or at different times in the same patient, different areas may be awake or asleep. This interpretation is supported by a recent intracranial study (Terzaghi et al. 2009) in an epileptic patient suffering from confusional arousals – an NREM sleep parasomnia closely related to sleepwalking. During an episode of confusional arousal, the motor and cingulate cortices were precociously activated and displayed the same fast activity seen during wakefulness, while the frontoparietal associative cortices displayed an enhancement of delta activity.

Sleeptalking is a more frequent occurrence than sleepwalking, and it can occur both in NREM and REM sleep. The majority of sleep speeches contain at least a few words, but they range from a single, mumbled utterance to several minutes of perfectly intelligible talk, the latter more frequently associated with REM sleep. Sometimes sleeptalk is clearly a soliloquy; at other times, it may resemble telephone conversation. While there is some correspondence between sleeptalking and dream content, more often one has the impression of multiple, concurrent stream of mental activity that occur independently and in parallel. Such instances suggest that the speech-production system may be active in relative isolation from dream consciousness, thereby constituting another example of dissociation.

9.4.2.4 REM Sleep Behavior Disorder

This disorder, which affects mostly elderly males, is characterized by vigorous, often violent episodes of dream enactment, with punching, kicking, and leaping from bed (Mahowald and Schenck 2005). Patients often injure themselves or their spouses. For example, a male subject would dream of defending his wife, but in enacting his dream he would actually forcefully strike her in bed. In rare cases there can be well-articulated speech. Polysomnographic recordings demonstrate that such episodes occur during REM sleep. Unlike sleepwalkers, who usually have no recollection of what they were thinking or dreaming at the time of their actions, people with REM sleep behavior disorder can usually recall their dreams in detail.

Conscious experience during an episode is extremely vivid, as in the most animated dreams, and is fully consistent with the motor activity displayed.

Much before the clinical syndrome was recognized in humans, sleep researchers had observed that if certain regions of the pons that are normally responsible for inhibiting muscle tone and motor programs during REM sleep are lesioned, cats seem to “enact their dreams” of raging, attacking, fleeing, or eating while not responding to external stimuli (Sastre and Jouvet 1979; Morrison 1988). In humans, the disorder most often occurs without an obvious cause, but it is sometimes associated with neurological conditions. It may indeed result from minute lesions in the pons, it may anticipate the development of Parkinson’s disorder, and it may be triggered acutely by certain drugs (certain antidepressants) or by withdrawal (ethanol).

9.4.2.5 Narcolepsy and Cataplexy

Narcolepsy is characterized by daytime sleepiness (sleep attacks), cataplexy (muscle weakness attacks), hypnagogic hallucinations, and sleep paralysis (Mahowald and Schenck 2005). Narcolepsy usually begins with excessive sleepiness and unintentional naps in the teens and 20s. Sleepiness is especially strong during periods of inactivity and may be relieved by short naps. When narcoleptics fall asleep, they usually go straight into REM sleep. Not surprisingly, patients complain that they have a short attention span, have poor memory, and sometimes behave in an automatic, uncontrolled way. The sleepiness seems to be due to a problem staying awake rather than to an increased need for sleep, since narcoleptics generally get enough sleep at night. In more than half of the cases, narcolepsy is accompanied by cataplexy. This is a sudden loss of muscle tone, typically brought on by strong emotions such as laughter or anger. The sudden weakness may be generalized and force the patient to collapse to the ground, or it may be localized to the voice, the chin, or a limb. Each episode generally lasts only a few minutes. Consciousness and awareness of the environment are preserved during cataplectic attacks, unless sleep intervenes. Hypnagogic hallucinations are dream-like hallucinations, mostly visual, that occur at sleep onset or when drowsy. Sleep paralysis is a frightening feeling of not being fully conscious but unable to move, which may occur on awakening or falling asleep, like a temporary version of the locked-in syndrome (Gosseries et al. 2009). Healthy individuals can experience hypnagogic hallucinations, especially when sleep deprived, and may also experience sleep paralysis. However, while laughter and other emotional stimuli can produce muscle relaxation in healthy individuals, cataplexy is definitely an abnormal phenomenon. Sleep paralysis and cataplexy are probably due to the inappropriate activation of the brainstem mechanisms responsible for abolishing muscle tone during REM sleep. Narcolepsy–cataplexy are known to be associated with a defect in the hypocretin/orexin system (Dauvilliers et al. 2007). Narcoleptic dogs and mice have a mutation in the gene for hypocretin or its receptors and, in the brain of narcoleptic patients, there is a loss of hypocretin cell groups in the posterior hypothalamus.

9.5 When and Why Do We Lose Consciousness in Sleep?

Sleep highlights several interesting paradoxes about the relationship between consciousness and the brain. For instance, it was first thought that the fading of consciousness during sleep was due to the brain shutting down. However, while metabolic rates decrease in some cortical areas (see Sect. 9.3.3), thalamocortical neurons may remain active also during slow-wave sleep, with mean firing rates comparable to those of quiet wakefulness (see Sect. 9.3.5.1; (Steriade et al. 2001; Nir et al. 2011)). It was also hypothesized that sensory inputs are blocked during sleep and that they are necessary to sustain conscious experience. However, we now know that, even during deep sleep, sensory signals continue to reach the cerebral cortex (Kakigi et al. 2003) where they are processed subconsciously (Portas et al. 2000). Gamma activity and synchrony have been viewed as possible correlates of consciousness, and some studies found them to be low in slow-wave sleep (Cantero et al. 2004; He et al. 2008). However, they may be equally low in REM sleep, when subjective experience is usually vivid, and they can be high in anesthesia (Vanderwolf 2000). On the other hand, intracellular recordings show that gamma activity and gamma coherence (Bullock et al. 1995) persist during slow-wave sleep. Interestingly, similar paradoxes, where neural activity levels, access to sensory information, and the degree of neural synchrony do not correlate with the level of consciousness, can be found in other conditions such as anesthesia, epilepsy, and brain-injured patients. In this sense, sleep may represent a physiological model to investigate why consciousness fades, transforms, and reappears in the brain.

The rapid succession of differentiated, unified conscious scenes that characterizes subjective experience is thought to rely on the ability of multiple, functionally specialized cortical areas to interact rapidly and effectively to form an integrated whole. Hence, an emerging idea in theoretical neuroscience is that consciousness depends on the ability of distributed cortical areas to engage in complex activity patterns that are, at the same time, spatially extended (integrated) and information rich (differentiated). As described in Sect. 9.3.4, TMS/EEG measurements show that, while in wakefulness TMS triggers a balanced response where different cortical areas become activated at different times giving rise to a complex pattern, during early NREM sleep cortical responses become a positive–negative wave that is either local or global and stereotypical, depending on stimulation intensity (Massimini et al. 2005). This finding suggests that this ability to integrate information is lost during NREM sleep early in the night, when reports of conscious experience upon awakening are least likely.

What prevents the emergence of a long-range, differentiated pattern of activation during sleep? It is possible that the mechanism underlying the impaired capacity of the sleeping brain to engage in complex activity patterns is the same mechanism that underlies the occurrence of spontaneous sleep slow waves, that is, bistability in thalamocortical circuits (Massimini et al. 2009). Upon falling asleep, brainstem activating systems reduce their firing rates, thus increasing the influence of depolarization-dependent K⁺ currents in thalamic and cortical neurons (McCormick et al.

1993). These hyperpolarizing K⁺ conductances become stronger after neurons have become depolarized and have fired action potentials. Due to these currents, neurons become bistable and tend to fall into a silent, hyperpolarized state (down state) after a short period of activation (up state), such as the one induced by TMS. As suggested by modeling studies, a shift in the balance of synaptic excitation and inhibition toward inhibition due to changes in the neuromodulatory milieu may also contribute to bistability (Esser et al. 2009). As a consequence, any local activation, whether occurring spontaneously or induced by a stimulus (like TMS), will converge into a silent neuronal down state and into a stereotypical EEG slow wave (Hill and Tononi 2005). Thus, the intense bistability with frequent and prolonged OFF periods during early NREM sleep (Vyazovskiy et al. 2009b) is likely to prevent the occurrence of sustained depolarization, a precondition for the establishment of sustained, complex thalamocortical interactions. Moreover, given the recent evidence that OFF periods in NREM sleep are mostly local, i.e., they occur asynchronously, especially in distant cortical areas (Nir et al. 2011), then interactions among distant cortical areas are particularly vulnerable to disruption by bistability, because longer reentrant loops involving multiple nodes can be interrupted by an OFF period in any node. If information integration among distributed cortical regions is indeed necessary for consciousness, then, it follows that consciousness during sleep should be maximally impaired when OFF periods are frequent and longer-lasting, as in early NREM sleep, and minimally so when OFF periods are largely absent, as in REM sleep, or rare and short, as in late NREM sleep (Vyazovskiy et al. 2009b).

Future studies, possibly employing intracranial perturbations and recordings in humans, are warranted in order to evaluate the role of bistability and cortical down states in reducing the information-processing capability of thalamocortical networks during NREM sleep. Is the breakdown of corticocortical effective connectivity actually associated with a neuronal down state as indicated by an actual suppression of neuronal discharge? Is the rebound of activation that follows the down state uncorrelated to the stimulus, suggesting a loss of causality in the temporal domain? Are the local slow waves revealed by intracranial recordings (Nir et al. 2011) preventing the propagation of activity to specific regions of the brain, resulting in functional disconnections? Are these roadblocks specific for different stages of sleep? What are the spatial relationships between spontaneous slow waves and covert bistability, as revealed by slow waves evoked by cortical stimulation? Hopefully, some of these questions may be answered in the next few years.

9.6 Is Consciousness During Sleep More Akin to Perception or Imagination?

Whether dreams are generated in a “bottom-up” or a “top-down” manner is a question that has been asked since at least Aristotle (350 B.C.). To put the question in a modern context, do dreams start from activity in low-level sensory areas, which is then interpreted and synthesized by higher-order areas, as is presumably the case in waking perception? Or do they begin as wishes, abstract thoughts, and memories

deep in the brain, which are then enriched with perceptual and sensory aspects, as in imagination? Of course, it is possible that such a dichotomy is misguided, and dreams may be best conceptualized as global attractors that emerge simultaneously over many brain areas. However, as we shall see, the available data do indeed suggest that there may be a privileged direction of dream generation (Nir and Tononi 2010).

In the nineteenth century, sensory experience was often regarded as the source of dreams, which were considered to be an attempt of the mind to interpret somatic nerve stimuli. A similar notion was later adopted by Allan Hobson (Hobson et al. 2000; Hobson and Pace-Schott 2002; Hobson 2009; Nir and Tononi 2010). According to his AIM model, internally generated signals originating in the brainstem during REM sleep, such as PGO waves, excite visual cortex and are later processed and synthesized by higher-order areas. High levels of acetylcholine in the absence of aminergic neuromodulation may enhance feed-forward transmission and suppress back-propagation (Hobson 1988; Hasselmo 1999). By contrast, Freud and some of his followers asserted that dreams originate from psychic motives that are later instantiated as sensory percepts, much like mental imagery (Freud 1900).

Deciding between these alternative views will most likely require difficult experiments in which the direction of signal flow during dreaming sleep is evaluated and compared to that during waking perception and imagery (Buzsaki 1996; Nir and Tononi 2010). However, various lines of evidence already suggest that dreaming may be more closely related to imagination than to perception. From lesion studies, we know that dreaming requires an intact temporo-parieto-occipital junction (Solms 1997, 2000), and lesions in this region also affect mental imagery in wakefulness (Kerr and Foulkes 1981). Cognitive studies indicate that the skill that maximally correlates with dream recall in adults is visuospatial imagery (Butler and Watson 1985). In children, dream recall develops hand in hand with visuospatial imagery (Nir and Tononi 2010). In epileptic patients, direct electrical stimulation in high-order regions such as the medial temporal lobe, rather than in visual cortex, can elicit “dreamlike” experiences (Penfield and Jasper 1954), although such patients are simultaneously aware of their surroundings. Other evidence comes from lucid dreamers (LaBerge 2000) who report that it is impossible to focus on fine-grain details of visual objects, as is the case in mental imagery (Finke and Kurtzman 1981). Perhaps top-down connections lack the anatomical specificity to support detailed representations. The rare occurrences of smells or pain in dreams may also be related to our difficulty in imagining them vividly when awake. However, one important difference between dreaming and mental imagery is that while imagining we are aware that the images are internally generated (preserved reflective thought).

If the flow of brain activity during dreaming were shown to be largely backward, as one would expect in imagery, rather than forward, as in perception, many of the seemingly bizarre properties of dreams, such as blended characters and scene switches, would be easier to explain, as they are standard features of our imagination. Such a top-down mode may disrupt the encoding of new memories and thus underlie dream amnesia. In addition, top-down mental imagery could obstruct the processing of incoming stimuli and disconnect us from the environment (see final section below). If this view is correct, waking consciousness is more like watching

the news in real time, while dreaming is more like watching a movie created by an imaginative director (Tononi 2009). As in some B-movies, the director is not particularly choosy and any actor, dress, means of transportation, or object that is readily available will do. Albert Einstein said that “imagination points to all we might yet discover and create,” and indeed, dreaming may turn out to be the purest form of our imagination.

9.7 Why Is Sleep Consciousness Disconnected from the Environment?

The most obvious difference between consciousness during sleep and wakefulness is the profound disconnection from the environment. Such disconnection, of course, is a key feature of sleep: By definition a sleeping person shows no meaningful responses to external stimuli, unless they are strong enough to cause an awakening as may happen with the sound of an alarm clock. Such a high “arousal threshold” gradually increases with the succession of NREM sleep stages and persists also in REM sleep (Rechtschaffen et al. 1966; Neckelmann and Ursin 1993). Moreover, stimuli largely fail to be incorporated in the content of dreams (Rechtschaffen 1978; Nir and Tononi 2010), though some stimuli such as a spray of water, pressure on the limbs, and meaningful words have a slightly higher chance of incorporation (Dement 1958; Berger 1963; Koulack 1969). For example, if we are to sleep all night in front of the television, our dreams will have little, if anything, to do with the contents of the surrounding stream of sounds. This striking disconnection occurs even when subjects sleep with their eyes taped open and objects are illuminated in front of them (Rechtschaffen and Foulkes 1965). By and large, consciousness in sleep is remarkably disconnected from the external environment, posing an intriguing paradox – especially if one considers that it persists in REM sleep along with strong cortical activation and along with dreams involving vivid sensory experiences.

It has been suggested that during NREM sleep and anesthesia, disconnection is due to “thalamic gating” where a burst-silence mode of activity in the thalamus does not relay peripheral sensory inputs effectively to the cortex (McCormick and Bal 1994; Steriade 2003). Along this line, attenuated single-unit responses in NREM sleep have been reported in thalamic sensory relay nuclei (Mukhametov and Rizzolatti 1970; Livingstone and Hubel 1981; Mariotti et al. 1989; Edeline et al. 2001) and primary visual and somatosensory cortices (Evarts 1963; Gucer 1979; Livingstone and Hubel 1981). However, several lines of evidence suggest that thalamic gating can not sufficiently explain sleep disconnection. First, recent studies in the auditory system demonstrate that neuronal responses in primary auditory cortex (A1) are comparable in sleep and wakefulness (Pena et al. 1999; Edeline et al. 2001; Issa and Wang 2008; Nir et al. 2012). Second, functional imaging in humans reported comparable activation in wakefulness and NREM sleep at the level of A1 (Portas et al. 2000) although some challenge this view (Czisch et al. 2002). Third, event-related potential (ERP) studies in humans suggest that potentials that are attributed to sensory cortices are largely preserved during sleep (Colrain and Campbell 2007)

and that some semantic analysis of auditory stimuli remains possible in the sleeping human brain (Bastuji et al. 2002). Fourth, olfactory stimuli are not directly incorporated in dreams (Schredl et al. 2009) suggesting that we remain disconnected also from these stimuli, though they are not routed through the thalamus.

A related notion is that of a cortical “gate” leading to diminished inter-cortical propagation (Esser et al. 2009), as seems to be the case in the dissociation of primary visual cortex (V1) from high-order visual cortex in REM sleep (Braun et al. 1998). As discussed earlier, regional NREM sleep oscillations (Nir et al. 2011) may promote a state of functional disconnection that could prevent activity in primary sensory regions from effectively driving that in high-order cortical nodes (Massimini et al. 2005). Indeed, in those cases that reported comparable auditory responses in thalamus and A1 across sleep and wakefulness (Portas et al. 2000), sounds could not drive the activity of high-order (frontoparietal) networks as effectively in sleep.

Recent EEG–fMRI studies emphasize that the processing of auditory stimuli in sleep may also be largely dependent on momentary changes in underlying activity. Along this line, Dang-Vu et al. (2011) showed that acoustic responses in thalamus and A1 present during wakefulness persisted in NREM sleep except during spindles, during which responses became less consistent. When sounds induced a K-complex, activity in the auditory cortex was enhanced and responses in distant frontal areas were elicited, similar to the stereotypical pattern associated with slow oscillations. Schabus et al. (2012) also showed that responses to sounds outside A1 (at higher cortical levels) decreased when their presentation co-occurred with the negative going phase of the scalp EEG slow oscillation. Thus, in deep NREM sleep, the brain may be more responsive between spindles and during the positive going slope of the slow oscillation. Wehrle et al. (2007) found that auditory responses during phasic periods of REM sleep (with bursts of rapid eye movements and muscle twitches) were correlated with a lack of reactivity to sensory stimuli compared with tonic REM sleep. These findings are in line with the observation of a higher arousal threshold during phasic as compared to tonic REM sleep in humans (Ermis et al. 2010). Taken together, such recent findings highlight the significant heterogeneity in brain responsivity that exists during sleep, even during epochs occurring within the same sleep stage.

Another important consideration with regard to sleep disconnection is that the neuromodulatory milieu changes drastically in sleep (Fig. 9.3). Specifically, the levels of norepinephrine, serotonin, histamine, and hypocretin are greatly reduced in REM sleep compared to wake, so the presence of one or more of these neuromodulators may be necessary for external stimuli to be incorporated into our stream of consciousness. Two particularly relevant candidates are histamine – whose levels are correlated with our ability to incorporate sensory stimuli into conscious experience in the context of cataplexy (John et al. 2004; Nir and Tononi 2010) – and phasic activities of the locus coeruleus–norepinephrine (LC-NE) system which may be strongly tied to orienting to external stimuli and their subsequent processing (Nieuwenhuis et al. 2005). For instance, it could be that in wakefulness such neuromodulatory tone facilitates transmission of feed-forward sensory inputs in cortical layer 4, at the expense of backward signal propagation.

Other possibilities that could mediate sleep disconnection are the dominance of internally oriented, default-mode networks at the expense of externally oriented cortical networks (Fox et al. 2005; Golland et al. 2007) (see (Nir and Tononi 2010) for further discussion), and alterations in attention (analogous to states such as extreme absorption, hypnosis, and neglect). While the underlying mechanisms are unclear, frontoparietal cortices and the reticular thalamic nucleus are both important for directing and sustaining attention, and both undergo dramatic changes in activity in sleep (Guillery et al. 1998; Zikopoulos and Barbas 2007).

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