10 Microelectrode Studies of Human Sleep

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Sleep is a pervasive, universal, and fundamental behavior and is present in every animal species where it has been studied (Cirelli & Tononi, 2008). All available evidence indicates that sleep is restorative for brain function and has a vital role for supporting cognition (Hobson, 2005; Banks & Dinges, 2007). For example, memory consolidation may be optimally performed offline when we are disconnected from the environment (Stickgold & Walker, 2007; Diekelmann & Born, 2010). While significant progress has been made in understanding cellular (Gilestro et al., 2009; Liu et al., 2010; Bushey et al., 2011) and behavioral effects of sleep (Banks & Dinges, 2007; Stickgold & Walker, 2007; Killgore, 2010), the contribution of specific activity patterns in sleep to cognitive restoration remains unclear (Wilson & McNaughton, 1994; Nadasdy et al., 1999; Tononi & Cirelli, 2006; Stickgold & Walker, 2007; Diekelmann & Born, 2010). In addition, sleep brings about dramatic changes in consciousness—we remain largely disconnected from external sensory stimuli; at times our perceptual awareness reduces to impoverished fragments that cannot be recalled and reported while at other times intrinsic activity gives rise to rich dream representations (Hobson & Pace-Schott, 2002; Nir & Tononi, 2010). Despite sleep's being a basic behavior occupying a third of our life and affecting cognition, mood, and health, the mechanisms underlying the interplay between sleep and cognition remain unclear.

At present, our understanding of sleep and the manner by which it affects cognition and perception reflects a massive gap between human behavioral studies and electrophysiology investigations, typically in rodents. While such a gap is inherent to many fields of cognitive neuroscience, it is especially evident in sleep research, where technical difficulties have precluded extensive use of functional imaging studies in humans (Nofzinger, 2005; Dang-Vu et al., 2010). In addition, although sleep was an important research focus of early single unit primate studies (Evarts, 1964; Steriade & Deschenes, 1973), such studies have become increasingly rare. Thus, patient studies offer a unique opportunity to bridge the gap between human behavior and rodent electrophysiology. In fact, the value of such sleep recordings goes beyond understanding sleep itself. Spontaneous brain activity in sleep offers a unique window into the activity of functional networks that transcends the ability of patients and healthy individuals to follow elaborate tasks during daytime. It is also possible to record continuously over many hours in which noise and movement play a minimal role and address many questions in systems

neuroscience such as the relation between various brain oscillations and neuronal activity (Buzsáki, 2006).

Direct brain recordings during sleep in patients with epilepsy, and single unit studies in particular, constitute an invaluable opportunity for elucidating the relation between sleep and cognition. 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. By recording simultaneously from multiple brain regions, patient studies have the potential to reveal regional diversity in the properties of sleep oscillations such as their spatial topography, spectral characteristics, precise timing and propagation, and phase coherence. Naturally, in patients with suspected temporal lobe epilepsy, 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) and could provide important information about hotly debated issues such as corticohippocampal "dialogue" in sleep (Buzsáki, 1998). From a practical standpoint, recordings carried out during sleep are well tolerated by patients and do not interfere with visits and other activities as can be the case with daytime recordings.

Another important and intriguing aspect is the close link between sleep and epilepsy (Dinner & Lüders, 2001). Any investigator who embarks on patient sleep recordings should be well aware of this intimate and complex relationship. On one hand, sleep data are an exceptional opportunity for understanding epileptogenesis, and in some presurgical cases changes in the rate of interictal epileptiform discharges (IEDs) from waking to sleep can provide important diagnostic information on the location of the seizure onset zone (Lieb et al., 1980; Sammaritano et al., 1991). However, special care must be exerted when using patient sleep data for making inferences about normal sleep physiology. These considerations will be discussed in the "Epilepsy and Sleep" section.

Overall, single unit patient sleep studies have already given rise to important discoveries about sleep neurophysiology, and important experience has been gained in terms of how to approach sleep data and minimize technical challenges and confounds of epilepsy. However, there is much to be done yet, and exciting future directions await this field.

Patient Sleep Studies: Technical Considerations

Patient sleep studies are best conducted as continuous full-night recordings that combine microelectrodes and wideband electroencephalography (EEG) intracerebral data with standard polysomnography (PSG; see figure 10.1). While data acquisition using intracerebral depth electrodes is described in detail in chapters 3–6, PSG refers to a set of noninvasive measures that are used for standardized scoring of sleep–wake stages. Such scoring is indispensable for comparing sleep recordings across nights, across patients, and in relation to benchmark findings in healthy populations. Ideally, PSG should include electrooculogram (EOG), electromyogram (EMG),

electrocardiogram, video monitoring, and scalp EEG from multiple derivations in consistent locations. Whenever possible, PSG data should be perfectly synced with intracerebral depth EEG/microwire recordings. It is highly advantageous to be able to use PSG data not only for sleep staging in 30-s intervals but to relate more precisely intracerebral activities to noninvasive measures such as EEG graphoelements, eye movements, and behavior (see figure 10.1).

Detailed established guidelines for PSG setup and analysis are widely available (Iber et al., 2007). In brief, signals should be acquired at a sampling rate of 500 Hz or higher and referenced to electrodes with minimal brain activity contribution (mastoids or electrodes pasted on earlobes). EEG should be obtained from multiple derivations since different elements (e.g., slow waves, sleep spindles, and alpha activity) are best detected in different locations (frontal, centroparietal, and occipital, respectively). Two EOG electrodes should be pasted, below the left and above the right canthi, and referenced to contralateral reference electrodes. EOG signals are important to delineate sleep onset (often associated with slow eye movements), periods of rapid eye movement (REM) sleep, and brief awakenings that may be associated with blinks and rapid/irregular eye movements. At least two EMG electrodes are placed to record chin muscle activity and are typically referenced to each other. EMG helps detect brief arousals, and it is indispensable in separating periods of REM sleep from those of wakefulness with closed eyes. It is recommended to calibrate and verify EOG and EMG signals by asking the patient to move his or her eyes in all directions, blink, and clench teeth before beginning data acquisition.

Basic research involving presurgical patients with epilepsy conducted on a hospital ward constitutes a challenging and potentially inhospitable environment for consolidated sleep that could influence when and how sleep recordings are carried out. During the clinical evaluation, microelectrode single unit studies performed shortly after surgical depth electrode implantation could benefit from greater signal-to-noise ratio and lower occurrence of seizures that can disrupt sleep (Mendez & Radtke, 2001; Foldvary, 2002). By contrast, a longer postoperative recovery interval often corresponds with greater patient comfort and consolidated sleep due to habituation to the hospital room that might be advantageous to the sleep study. Investigators must consider the anticipated duration of the clinical evaluation that can last between one and two weeks, which typically provides sufficient opportunity to schedule sleep recording(s). In studies that seek to generalize sleep findings to healthy populations, it is important to consider tapering of antiepileptic drugs (AEDs) and sleep deprivation that are often prescribed clinically in depth patients who have low seizure frequency. Both are intended to increase the occurrence of seizures and other epileptiform discharges that may interrupt habitual sleep patterns (Peled & Lavie, 1986). Accordingly, optimal timing for sleep studies in our experience at UCLA is 48–72 hours after electrode implantation and prior to tapering of AEDs or sleep deprivation. In addition, it is important to avoid sleep studies in close proximity (<12 hours) to daytime seizures that can affect sleep architecture (Foldvary, 2002), as well as carefully document medication, seizures, and sleep history (e.g., naps). Up to one third of patients with refractory seizures have sleep-related breathing disorders, for example, obstructive sleep apnea syndrome (OSAS), that are associated with midsleep arousals and sleep fragmentation that should also be taken into

consideration (Malow et al., 2000). Finally, ambient noise, unexpected visitors, and routine clinical procedures (e.g., nursing staff taking vital signs) may lead to poor sleep hygiene. Therefore, a successful sleep study often hinges on managing these details and coordination among clinical and research personnel.

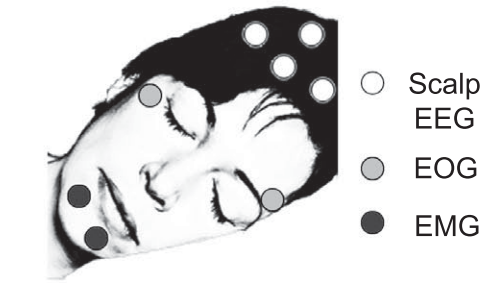
Routine data preprocessing includes filtering (EEG, above 0.3 Hz; EOG, 0.3–35 Hz; EMG, 10–100 Hz) and sleep scoring upon visualization of EEG, EOG, EMG, and video (Iber et al., 2007). Ideally, spike sorting should be done on entire full-night recordings as a whole, so that the activity of the same neuron or small neuronal populations can be compared and analyzed throughout sleep and possibly also in surrounding intervals of wakefulness. In practice, more than half a million putative action potentials could be detected in individual channels in such recordings, and existing clustering algorithms often use template matching to simplify computational load (Quian Quiroga et al., 2004). At any rate, the stability of unit recordings throughout long sleep recordings should not be taken for granted; rather, it is necessary to carefully inspect the consistency of waveforms and interspike interval distributions (see, e.g., figure S3B in Nir et al., 2011).

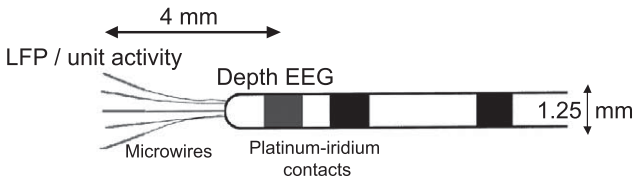
Epilepsy and Sleep

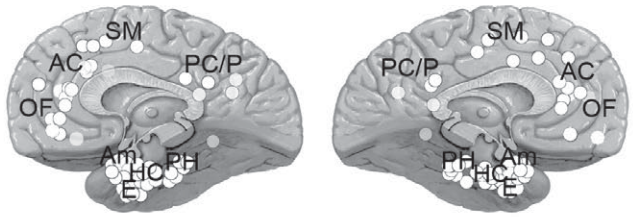
Effects of Epilepsy, Medication, and Comorbidity on Sleep

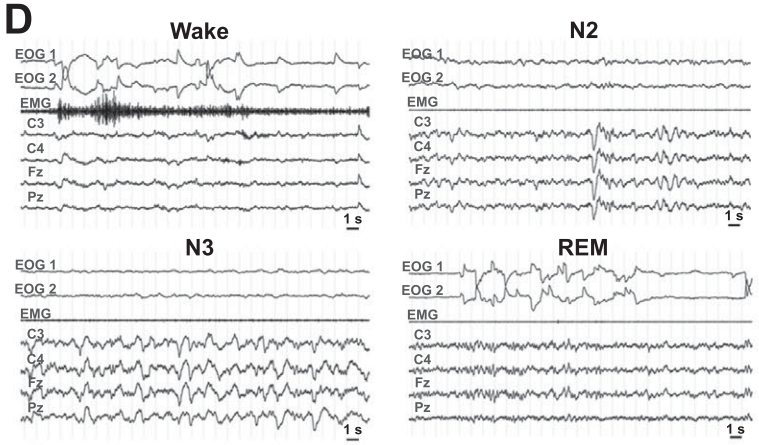
Patients with epilepsy, compared to healthy controls, are two times more likely to complain of sleep disturbances, chiefly excessive daytime sleepiness (EDS) and insomnia that can have a negative influence on quality of life measures (de Weerd et al., 2004; Piperidou et al., 2008). Furthermore, with respect to type of epilepsy, patients with nocturnal frontal lobe epilepsy report greater tiredness after awakening and more frequent spontaneous midsleep awakenings (Vignatelli et al., 2006). Refractory temporal lobe epilepsy is associated with similar sleep disturbances and in some cases abnormal sleep efficiency and microarchitecture (Crespel et al., 2000). Other studies show that sleep disruptions are more pronounced on nights with seizures compared

Figure 10.1
Experimental setup for patient sleep studies. (A) Setup for polysomnography (PSG) includes electrooculogram (EOG), electromyogram (EMG), scalp electroencephalogram (EEG) from multiple derivations, and video monitoring. (B) Diagram of flexible probes used for concomitant recording of depth EEG (platinum contacts) and local field potential (LFP)/unit activity (microwires) synced with PSG data. (C) Overview of typical depth electrode locations in encompassing multiple brain regions seen from medial view. Abbreviations: OF, orbitofrontal cortex; AC, anterior cingulate; SM, supplementary motor; PC/P, posterior cingulate/parietal cortex; PH, parahippocampal gyrus; HC, hippocampus; E, entorhinal cortex; Am, amygdala. (D) Representative examples of 30-s PSG data used for sleep scoring in wake stages, N2, N3, and rapid eye movement (REM) sleep. (E) Representative PSG-based sleep; sleep efficiency corresponds to total sleep time per time in bed. Sleep latency is to stage 2. WASO refers to waking after sleep onset; SWS, slow-wave sleep (N2 + N3); NREM, non–rapid eye movement. (F) Representative hypnogram (time course of sleep–wake stages across sleep in one individual). (G) Representative average power spectra of scalp EEG computed separately in stages N2, N3, and REM sleep; note high power in slow-wave (<4 Hz) and spindle (10–16 Hz) range in NREM sleep. (H) example of data acquired during 6 s of NREM sleep. Rows (top to bottom) show activity in scalp EEG (Cz), depth EEG (entorhinal cortex), multiunit activity (MUA) in one microwire, and spiking activity in six isolated single units (black bars). Modified from Nir et al. (2011).









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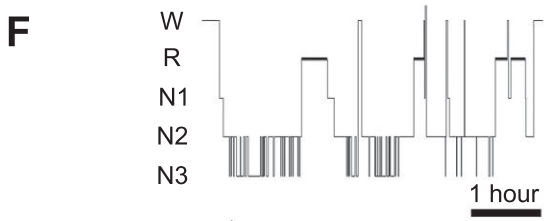
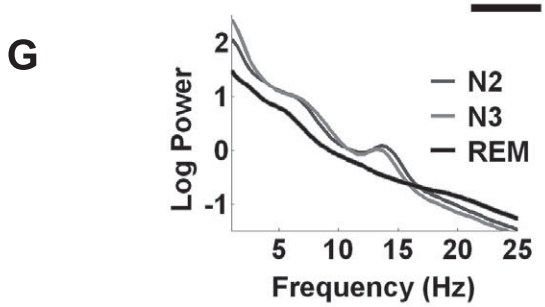
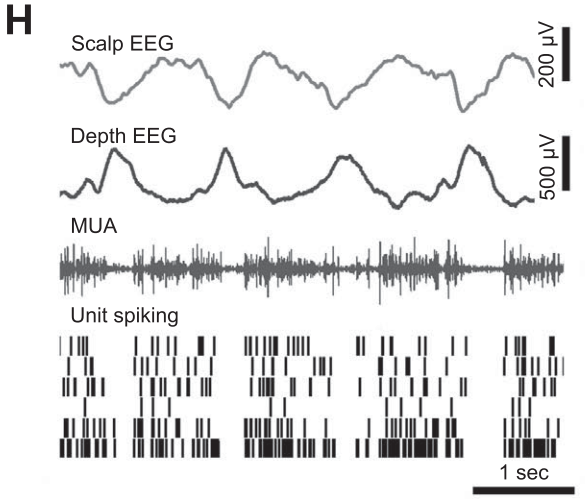
Recording time (min)	403	±	23.5
Sleep time (min)	323	±	19
Sleep latency (%)	76.3	±	16.5
Sleep efficiency (%)	81	±	2
WASO (%)	13.9	±	2.2
N1 (%)	15.3	±	3.9
N2 (%)	41.5	±	3.5
N3 (%)	16.4	±	1.71
NREM (%)	73.2	±	2.58
REM (%)	13	±	2.07







to seizure-free nights (Foldvary-Schaefer & Grigg-Damberger, 2009; Carrion et al., 2010), but importantly, EDS decreases and quality of sleep improves in patients with good postsurgical seizure outcome (Carrion et al., 2010). Results from these studies suggest seizures can disrupt sleep and highlights the importance of seizure control in restoration of normal sleep.

Other factors affecting sleep include AEDs and comorbidities. First-generation AEDs such as barbiturates and benzodiazepines facilitate sleep onset but can reduce the amount of REM sleep, increase daytime somnolence, and lower sleep quality compared to second-generation AEDs (Bazil, 2003). Compared to healthy controls, patients with poorly controlled seizures have a higher prevalence of depression and anxiety (Stefanello et al., 2010), which can have detrimental effects on sleep (van Mill et al., 2010). OSAS and corresponding complaint of EDS is also associated with epilepsy. OSAS associated with epilepsy could be due to AED-related weight gain, prescribed barbiturates or benzodiazepines that reduces upper airway rigidity, or in some cases the use of vagal nerve stimulation that can effect respiration and exacerbate OSAS. The link between EDS and OSAS does not appear to be due to sleep apnea or sleep disruption (Roure et al., 2008) although treatment of OSAS reduces the rate of overnight respiratory disturbances and increases sleep stability as well as improving EDS (Sforza & Krieger, 1992; Conradt et al., 1998). Patients with epilepsy receiving therapy for OSAS had a reduction of IEDs (Oliveira et al., 2000), while other studies noted that some patients had a 50% or greater reduction in seizures frequency (Vaughn et al., 1996; Malow et al., 1997; Malow et al., 2003).

Effects of Sleep on Epileptogenicity

Some seizures and IEDs occur more frequently during sleep and particularly during episodes of non-REM (NREM) compared to REM sleep. For example, seizures associated with autosomal-dominant nocturnal frontal lobe epilepsy occur only during sleep whereas seizures associated with benign epilepsy with centrotemporal spikes occur up to 80% of the time during sleep. In addition, epileptic encephalopathy with continuous spike-and-wake during sleep is defined by the occurrence of diffuse electrical status epilepticus that occupies up to 85% of NREM sleep. In general, focal seizures arising from frontal lobe occur more frequently during sleep than temporal lobe seizures (Bazil & Walczak, 1997; Crespel et al., 2000) while the latter type of seizures are more likely to secondarily generalize during NREM sleep compared to REM sleep (Herman et al., 2001).

In most types of epilepsy IEDs occur more frequently during NREM sleep than REM sleep. It is hypothesized that during NREM sleep, synchrony of neuronal discharges within thalamo-cortical networks increases cortical excitability and facilitates the spread of focal IEDs to remote brain areas (Steriade et al., 1994). By contrast, transition to REM sleep or arousal from NREM sleep is associated with a reduction in thalamocortical synchronization and spatial restriction of IEDs. Consistent with the presumed sleep-related changes in cortical excitability, studies of human hippocampal single neurons found interictal firing rates and propensity for bursting are highest during NREM sleep and lowest during REM sleep (Staba et al., 2002c). In relation to epileptogenicity, single neurons in the medial temporal lobe (MTL) ipsilateral to the seizure

onset have higher firing and burst rates as well as greater synchrony of discharges than neurons in contralateral MTL sites (Staba et al., 2002b). In this same study the greatest differences in firing properties and synchrony with respect to sites of seizure onset were associated with NREM and REM sleep. This latter finding could reflect the relatively greater autonomy of primary epileptogenic brain areas compared to remote sites that do not support seizure genesis (Gentilomo et al., 1975; Lieb et al., 1980).

Interictal bursts of pathological high-frequency oscillations (HFOs; 200–500 Hz) are also found in human MTL ipsilateral to seizure onset (see figure 10.2A, B; Bragin et al., 1999a; Bragin et al., 1999b; Staba et al., 2002a) and in neocortical sites capable of generating seizures although often of lower spectral frequency (Worrell et al., 2004). Single neuron discharges increase significantly during pathological HFOs, and there is evidence to suggest pathological HFOs reflect spontaneous bursts of abnormally synchronous unit discharges that appear as local population spikes (figure 10.2C, D; Bragin et al., 2002; Bragin et al., 2011). Similar to the sleep-related changes in MTL single neuron discharges described in the preceding paragraph,

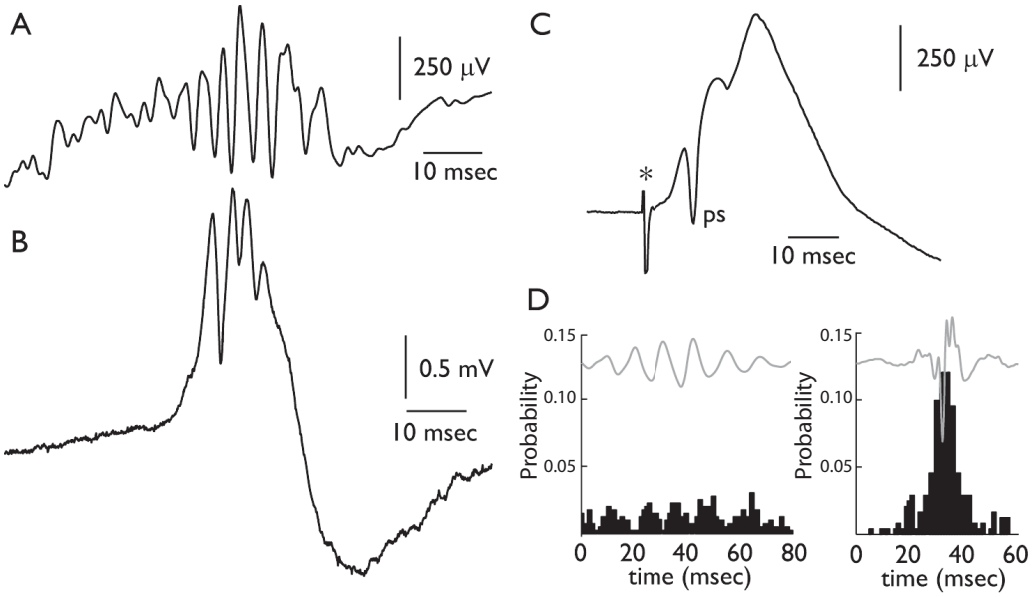


Figure 10.2
High-frequency oscillations (HFOs) in epileptic hippocampus. (A) Pathological HFO (~333 Hz) recorded from a microelectrode positioned in hippocampus ipsilateral to seizure onset of a patient with medial temporal lobe epilepsy and hippocampal sclerosis. (B) Spontaneous interictal electroencephalography spike with superimposed pathological HFO (~300) recorded from microelectrode in entorhinal cortex. (C) Average (n = 12) evoked response recorded from microelectrode positioned in hippocampus during electrical stimulation (indicated by asterisk) from adjacent clinical electrode in entorhinal cortex. Note population spike (ps) superimposed on large-amplitude postsynaptic potential. (D) Peri-event histogram of multiunit discharge during ripple-frequency HFO (left) and pathological HFO (right) in entorhinal cortex. Averaged HFOs (n = 10) recorded from same distal microwire and neuronal discharges recorded from adjacent microwires spaced 0.5 mm apart in entorhinal cortex. Modified from Staba (2012).

pathological HFOs occur more frequently during NREM sleep and rates remain elevated during REM sleep compared to waking, which contrasts with the occurrence of presumably normal ripple-frequency HFOs (80–160 Hz) in human MTL and ripples in normal nonprimate hippocampus associated with REM sleep episodes (Buzsáki et al., 1992; Staba et al., 2004). Overall, NREM sleep facilitates the occurrence of epileptiform discharges whereas mechanisms governing REM sleep that typically restrict neuronal synchrony are less effective inside primary epileptogenic brain areas.

Neurophysiology of Human Sleep

Patient studies of human sleep, and microelectrode recordings in particular, have significantly furthered our understanding of sleep electrophysiology by investigating different sleep oscillations such as slow waves, sleep spindles, gamma and ripple oscillations, and ultraslow neuronal fluctuations. The manner in which such sleep oscillations may contribute to memory consolidation is an area gaining increasing attention.

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 have 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., 1993; Contreras & Steriade, 1995; Destexhe et al., 2007; Crunelli & Hughes, 2010). Recently, microelectrode studies confirmed that in humans slow waves are similarly associated with underlying neuronal bistability (see figure 10.3A, plate 10) 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 exciting findings that were not expected based on the noninvasive studies and animal literature. While slow oscillations are remarkably synchronous when examined in brain slices (Sanchez-Vives & 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 (see figure 10.3C, D, plate 10) where some regions can be active while others are silent (Nir et al., 2011). Furthermore, in some cases wake-like and sleep-like activity patterns can coexist for longer durations in different cortical areas, and such activities may underlie NREM parasomnias such as sleepwalking (Terzaghi et al., 2009; Nobili et al., 2011).

It was also found that slow waves have a tendency to propagate along typical paths (see figure 10.3B, plate 10), 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

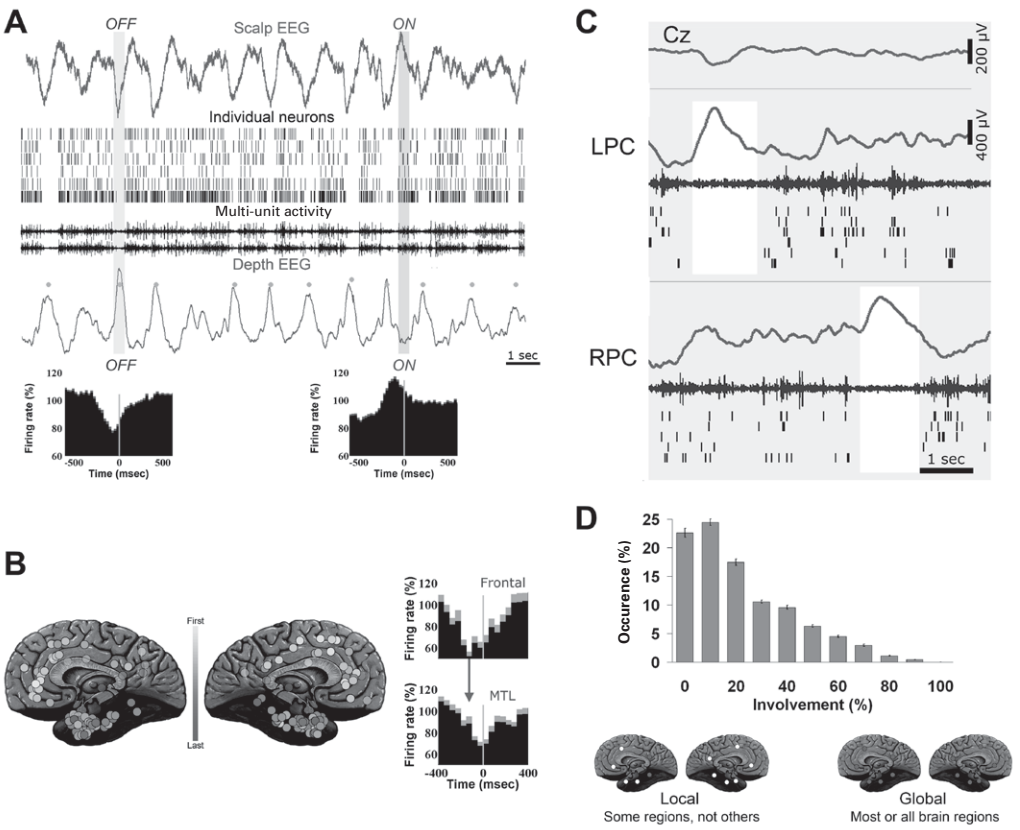


Figure 10.3 (plate 10)
Regional slow waves in human sleep. (A) Neuronal activity underlying slow waves in human sleep. Electrical brain activity across 15 s of deep non–rapid eye movement (NREM) sleep. Top (red), scalp electroencephalography (EEG); bottom (blue), intracranial depth EEG in entorhinal cortex. Green dots, individual slow waves that are automatically detected and separated from pathological events. Black, multiunit activity (MUA) and action potentials of six neurons. Vertical green bar, OFF periods of inactivity. Vertical orange 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. (B) 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 medial temporal lobe (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. (C) An example of local sleep slow waves occurring at different times in left posterior cingulate cortex (LPC) and right posterior cingulate cortex (RPC). 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. (D) 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. Modified from Nir et al. (2011).

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 & Wilson, 2007) and with a recent study of human depth EEG (Wagner et al., 2010). As for the direction of corticohippocampal dialogue in sleep (Buzsáki, 1998), it was found that at times of hippocampal ripples (associated with the "replay" of activity in cell assemblies during sleep in rodents; Diekelmann & 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 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 corticohippocampal broadcast there may be islands of hippocampocortical transmission that may be functionally relevant for memory consolidation.

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 & 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 (see figure 10.4). As was the case for slow waves, most spindles occur locally, thereby showing that constrained intracerebral communication is an important feature of 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 & 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.

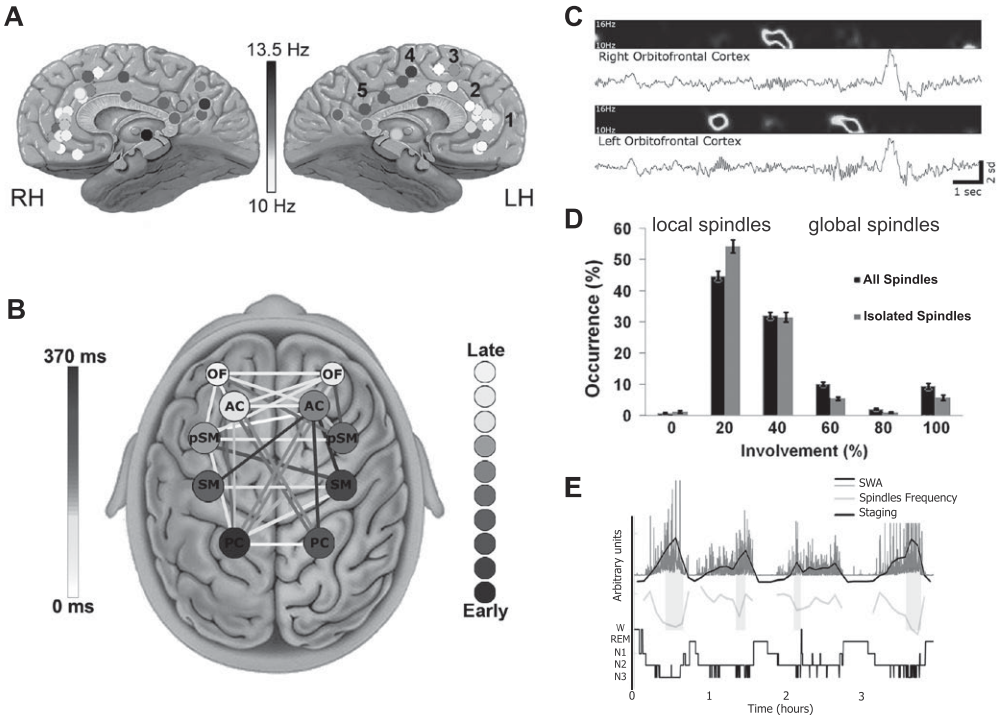
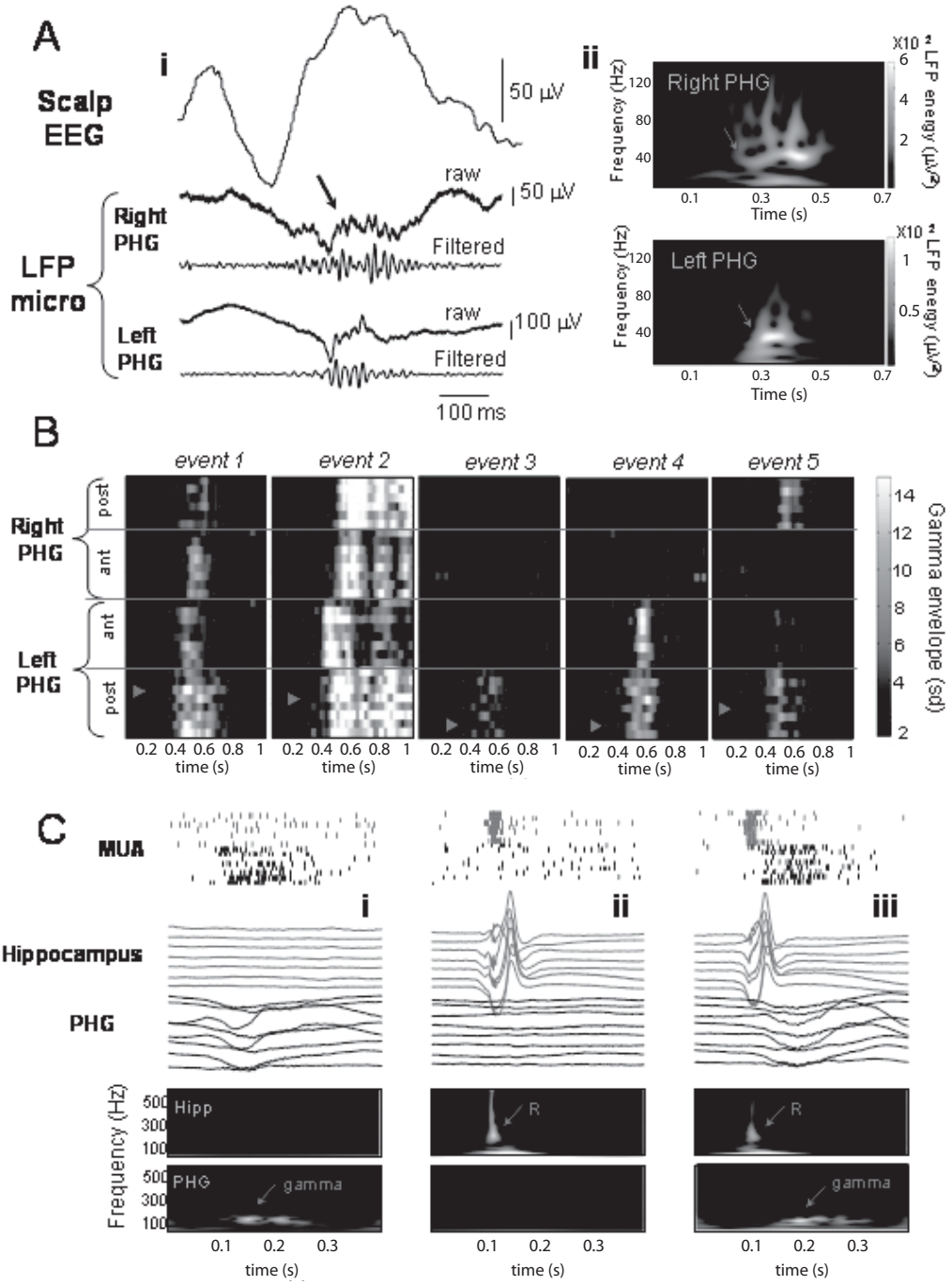


Figure 10.4
Human sleep spindles. (A) Average frequency of spindles across the medial brain; note the contrast between slow (9–12 Hz) frontal spindles and fast (13–16 Hz) centroparietal spindles. RH, right hemisphere; LH, left hemisphere. (B) Fast centroparietal spindles precede slow frontal spindles by 200 ms on average: 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) Most sleep spindles are local. Distribution of involvement (percentage of monitored brain structures expressing each spindle) for all spindles (dark bars) and for isolated spindles (lighter bars). Note that 73% of spindles are observed in 50% of electrodes, indicating that most spindles are local. (E) 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 rapid eye movement (REM) sleep. Modified from Andrillon et al. (2011).

Gamma and Ripple Oscillations during Slow-Wave Sleep

Gamma oscillations (40–120 Hz) are usually associated with waking functions such as sensory binding (Singer & Gray, 1995), attention (Fries et al., 2001), or encoding/retrieval of memory traces (Montgomery & Buzsáki, 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 slow-wave sleep, 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 (Dickson et al., 2003; Compte et al., 2008) recordings of the rodent and feline cortex. Such experiments demonstrated 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; figure 10.5A). These gamma oscillations frequently appeared at about the same time in different cortical areas, including homotopic regions, forming large spatial patterns (see figure 10.5B). Similar sleep gamma oscillations were also recently reported using intracranial macroelectrodes (Valderrama et al., 2012), suggesting a strong local synchronization of the cellular activities. Indeed, 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 "microwake" activity (Destexhe et al., 2007; Haider & 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; figure 10.5C). Ripple oscillations (80–160 Hz) are known to coincide with reactivation of hippocampal activity patterns (Wilson & McNaughton, 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 nonprimate CA1 and CA3 in terms of duration and spectral frequency, bilateral occurrence in hippocampal areas, highest probability of occurrence during NREM sleep, and

Figure 10.5
Gamma oscillations during slow-wave sleep. (A) (i) Display of a single gamma episode (black arrow) appearing simultaneously, in either the raw signals or those filtered between 40 and 120 Hz, in the right and left posterior parahippocampal gyri (PHG) during slow-wave sleep. Note that gamma activities were temporally correlated with positive peaks (i.e., up deviations) of slow waves in scalp electroencephalography (EEG). LFP, local field potential. (ii) Corresponding wavelet transforms of two homotopic sites revealing nearly simultaneous gamma oscillations with distinct narrow band frequencies around 40 Hz (white arrows). (B) Examples of gamma events simultaneously recorded with 30 microelectrodes in the right and left parahippocampal gyri (PHG, ant: anterior part and post: posterior part). Note the complex spatiotemporal distribution of these activities, often involving both homotopic sides, the strong variability of involved electrodes and variable location of the starting site (triangles). (C) In individual events i and ii, hippocampal ripple/sharp-wave complexes (R) and parahippocampal gamma oscillations (gamma) were not coincident within a time window of 100 ms. In event iii, parahippocampal gamma oscillations immediately followed hippocampal ripple/sharp-wave complexes, suggesting a temporal coupling between both oscillations. MUA, multiunit activity; Hipp, hippocampal. Modified from Le Van Quyen et al. (2010).



minimal occurrence during REM sleep (Buzsáki et al., 1992; Staba et al., 2004; Le Van Quyen et al., 2008; figure 10.2). 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). Future human microelectrode studies at the large-scale level are necessary to further characterize the full details of these local and long-range coupling of oscillations across vast cortical territories.

Ultraslow Resting-State Fluctuations in Sleep and Wakefulness

Although perception and action occur on the subsecond timescale, it has long been recognized that cortex also shows fluctuations in electrical activity with slower dynamics. Recently, resting-state ultraslow fluctuations (<0.1 Hz, at the timescale of tens of seconds) in blood oxygen level–dependent functional magnetic resonance imaging signals have gained attention as a powerful tool to study functional brain networks in health and disease (Fox & Raichle, 2007). However, the extent to which such waves reflect neuronal activity or may stem from nonneuronal sources (e.g., cardiac, respiratory) remained unclear until very recently. 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 (see figure 10.6). 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.

Sleep and Memory Consolidation

A promising research direction is to clarify the role sleep may have in offline consolidation of memories (Diekelmann & Born, 2010). An important postulated mechanism for such consolidation involves hippocampal sharp-wave ripples accompanying reactivation of neuronal ensembles that were active during preceding wake experience (Wilson & McNaughton, 1994; Nadasdy et al., 1999; Girardeau et al., 2009). Importantly, such high-frequency MTL events can be routinely recorded in patient sleep studies (Staba et al., 2002a). Indeed, some studies are beginning to link sleep activities with those recorded during cognitive tasks in wakefulness. Intracranial EEG studies have found that successful learning is correlated with NREM sleep oscillations including MTL ripples (Axmacher et al., 2008a; Axmacher et al., 2008b) and slow waves (Bodizs et al., 2002; Moroni et al., 2008). Future work focusing on single unit activities should further clarify the contribution of sleep to memory. Ideally, one would try to relate activity that is

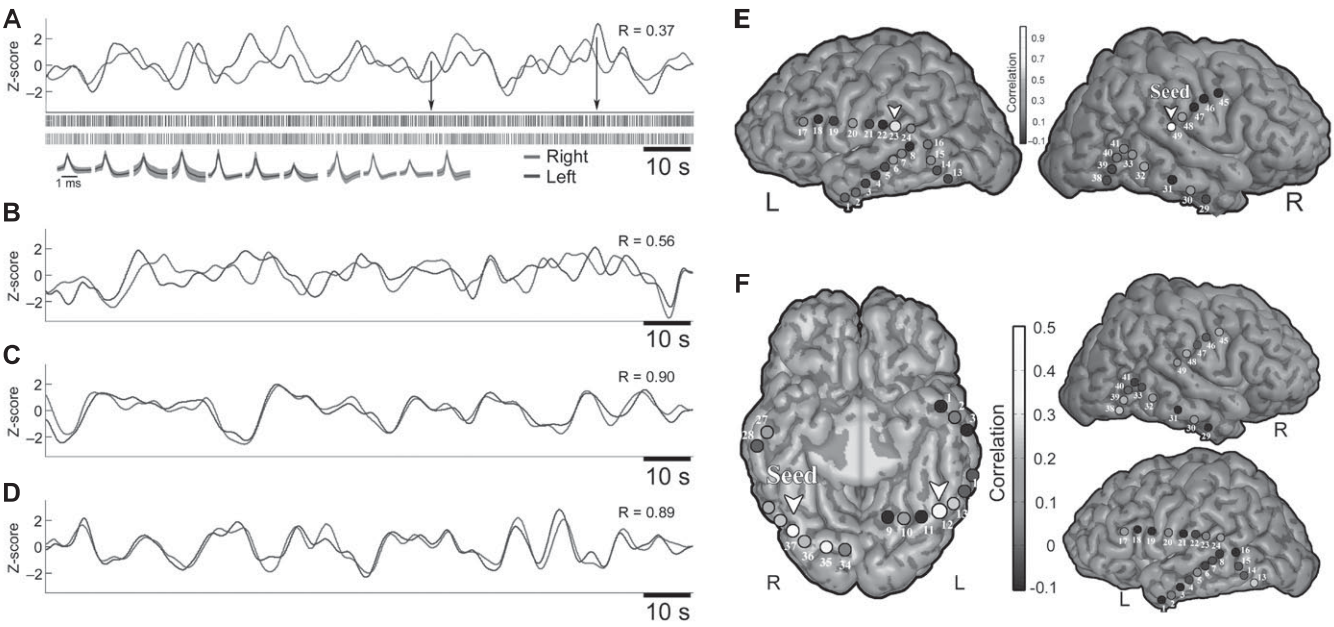


Figure 10.6
Ultraslow (<0.1 Hz) fluctuations of neuronal activity in rest and sleep. (A–D) Examples of correlated ultraslow (<0.1 Hz) fluctuations in neuronal activity between left and right auditory cortices across hemispheres. (A) Firing-rate modulations during rest in wakefulness. Vertical lines show actual spike times. Black arrows indicate the relation between time courses of slow firing-rate modulations and neuronal discharges. Waveforms of neuronal action potentials are shown below. (B) Local field potential (LFP) gamma-power modulations during rest in wakefulness. (C) LFP gamma-power modulations during rapid eye movement (REM) sleep. (D) LFP gamma-power modulations during non-REM stage N2 sleep. Note that ultraslow fluctuations are robustly correlated across hemispheres, and correlations are markedly enhanced during sleep. (E) Correlations between ultraslow fluctuations in electrocorticography (ECoG) gamma power of an auditory-related electrode ("seed," arrow) and all other electrodes reveal a highly selective spatial topography of ultraslow fluctuations. Results are shown on a cortical reconstruction seen from a lateral view. Note that a strong correlation in the contralateral hemisphere is found over the homotopic auditory cortex. L, left; R, right. (F) Correlations between ultraslow fluctuations in ECoG gamma power of a visual, face-selective electrode ("seed," arrow) and all other electrodes. Results shown using a ventral view (left) and lateral view (right). The strongest correlation is found in a contralateral face-selective region while minimal correlations are observed between visual and auditory electrodes, indicating the functional selectivity of spontaneous correlations. Modified from Nir et al. (2008).

selectively involved in the representation and learning of specific contents to reactivation in subsequent sleep and to verbal memory recall in the morning while avoiding measurements within the seizure onset zone (where ripples and associated neuronal bursts in sleep are often pathological).

Emerging New Theme: Regional Diversity of Sleep Oscillations

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, thereby showing that initial indications of local sleep oscillations in animals (Sirota & Buzsáki, 2005; Mohajerani et al., 2010; Vyazovskiy et al., 2011) or in patients with sleep disorders (Terzaghi et al., 2009) constitute the rule rather than the exception. Thus, an important new theme that 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 was 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.

Future Directions

Microelectrode studies of human sleep have provided important novel insights into human sleep neurophysiology, but so far such studies have been conducted by a limited number of research centers, and further research is bound to provide new insights on sleep function and its role in health and disease.

An intriguing future direction is the relation between dreaming and underlying brain activity. Although dreams have fascinated us since the dawn of time, their rigorous, scientific study is only a recent development (Nir & Tononi, 2010). As with other investigations of conscious processes, this research ultimately relies on reports from human subjects, and patient studies offer the unique opportunity to relate such reports to detailed measurements of brain activity. Understanding the relation between brain activity in REM sleep and wakefulness to eye movements also remains unexplored. For example, does such activity in REM sleep follow a feedforward propagation as it does upon visual stimulation in wakefulness (Mormann et al., 2008)? Or perhaps dreaming is more related to top-down processes as may be the case in mental imagery where mnemonic activity precedes that of visual representations (Takeuchi et al., 2011)?

Intracranial depth electrodes can also be adapted with microdialysis probes (Fried et al., 1999) to investigate the neurochemical modulation of sleep–wake states (Jones, 2005). Given that rodents and other mammals switch between vigilance states much more rapidly, microdialysis samples typically collected 10 minutes apart in animal studies inevitably integrate over different sleep states. By contrast, in humans it is possible to collect samples that occur exclusively in specific sleep stages, including REM sleep. Indeed, human microdialysis studies have begun to

examine such changes—for example, by measuring levels of ventricular serotonin (Zeitzer et al., 2002) and extracellular adenosine (Zeitzer et al., 2006) as well as hypocretin and melanin-concentrating hormone levels across the sleep–wake cycle (Blouin et al., 2013). In this latter study, neurochemical changes in the amygdala were correlated not only with vigilance and arousal but also with emotional and social behaviors. Indeed, elucidating the relation between neuromodulation and cognitive aspects of daytime behaviors is a fascinating avenue for future research. From a technical standpoint, future advances including zero-flow microdialysis (Cavus et al., 2005) and methods with superior temporal resolution (e.g., microdialysis with faster recovery time or electrochemical sensing probes) could help bridge the gap between neuromodulatory changes (currently studied with a temporal resolution of minutes) and millisecond-precision electrophysiology. Bridging this gap could help in understanding, for example, whether the local occurrence of sleep oscillations may be accompanied by local neuromodulatory changes (for instance, via local modulation of presynaptic release; Laplante et al., 2005).

Another line of future research is to better understand responses to external sensory stimuli during sleep, and in what ways signal propagation along ascending sensory pathways differs between states of vigilance. Increasing evidence suggests that cortical responses are largely preserved across sleep in primary sensory regions (Issa & Wang, 2008; Nir et al., 2012), calling into question the traditional proposal that the thalamus does not relay peripheral signals effectively to the cortex in sleep (McCormick & Bal, 1994; Steriade, 2003). However, it remains unclear to what extent such stimuli effectively drive the activity of high-order regions and what may be the fate in sleep of late sustained components (e.g., P300 in response to deviant stimuli) that are better linked to conscious perception (Dehaene & Changeux, 2011).

Finally, other intriguing directions include further explorations of the relation between sleep and memory consolidation (see above), investigations of sleep deprivation and the cognitive effects of sleepiness (Banks & Dinges, 2007), understanding dynamics of brain activity during state transitions such as those accompanying the descent to sleep (Bodizs et al., 2005; Magnin et al., 2010), and the phenomenon of sleep inertia (Marzano et al., 2011).

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