Chapter 20
How Can I Run Sleep and Anesthesia Studies with Intracranial EEG?

Janna D. Lendner and Randolph F. Helfrich

Abstract The similarity of sleep and general anesthesia has fascinated scientists for a long time. At first glance, both states are characterized by similar behavioral correlates, namely decreased responsiveness, arousal and movement. Previously, non-invasive scalp electroencephalographic (EEG) recordings demonstrated highly comparable spectral signatures of both states, such as the ubiquitous presence of slow waves or delta oscillations. More recently, intracranial recordings in humans provided a more fine-grained perspective and revealed that sleep and anesthesia reflect highly distinct entities. Here, we outline how intracranial sleep and anesthesia recordings can be embedded into the clinical routine. We discuss caveats and shortcomings that need to be considered, especially in the context of epilepsy as the underlying neurological disorder. Subsequently, we provide a practical road map to obtain state-specific neural recordings and discuss technical prerequisites as well as important analytical considerations. Finally, we summarize how intracranial recordings extend our understanding about the mechanism-of-action of anesthetic drugs at the network level and to which extent these signatures overlap with physiologic sleep networks. Collectively, here we review how intracranial recordings in humans can be leveraged to gain important insights into sleep physiology and the neural correlates of (un-) consciousness.

Keywords Sleep · Anesthesia · Propofol · Unconsciousness · Intracranial EEG · Slow oscillations · Spindles · Ripples · Interictal discharges · Multitaper spectrogram

J. D. Lendner · R. F. Helfrich (✉)
Center for Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, Otfried-Mueller-Str. 27, 72076 Tübingen, Germany
e-mail: randolph.helfrich@gmail.com

J. D. Lendner
Dept. of Anesthesiology and Intensive Care Medicine, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2023

N. Axmacher (ed.), *Intracranial EEG*, Studies in Neuroscience, Psychology and Behavioral Economics, https://doi.org/10.1007/978-3-031-20910-9_20

20.1 Introduction

"You will fall asleep now" might be the most common phrase used by anesthesiologists before administering the hypnotic drug during everyday clinical care. At first glance, sleep and anesthesia share several behavioral signatures, including decreased arousal and movement [1]. However, upon closer inspection, both states reflect distinct entities. In contrast to someone asleep, patients undergoing anesthesia remain unresponsive to painful stimuli. In addition, anesthesia impairs memory formation and can be detrimental to cognitive functioning (especially in the elderly; [2, 3]), while sleep benefits memory formation and cognition [4]. The neural correlates of unconscious brain states have fascinated scientists for decades [1, 5]. Several scalp EEG studies identified electrophysiological signatures, such as high amplitude slow waves (<1.25 Hz) and delta activity (<4 Hz) that both occur in non-rapid eye movement (NREM) sleep and under deep anesthesia [6–8].

Intracranial EEG (iEEG) offers a unique window to study cognition, sleep physiology, sleep deprivation and anesthesia on the single subject level. Patients are typically monitored for multiple days; hence, several days and nights worth of data can be obtained. Furthermore, sleep deprivation is a common intervention to trigger seizures (see Sect. 20.3.2) and provides a valuable experimental condition to test causal links between sleep and cognition. In addition, iEEG often explores deeper brain structures, such as the hippocampus, the amygdala or thalamic nuclei, which are difficult to image using non-invasive methods, but are thought to reflect key nodes of the human memory network [4, 9, 10]. The high temporal resolution of iEEG enables extraction and analysis of e.g. high-frequency band activity (~70–150 Hz; HFA; [11, 12]) or of cardinal sleep oscillations, such as sharp-wave ripples (~80–120 Hz; [9, 13–15]), which cannot be observed at the scalp level. iEEG is typically used to sample multiple nodes of the suspected epileptic network (i.e. mesial or limbic structures, including the hippocampus, cingulate and orbitofrontal cortex). To target these deeper structures, electrodes have to transverse through intact cortex (i.e. lateral temporal and frontal); thus, enabling simultaneous multisite recordings with high spatiotemporal resolution, which allows dissecting network processes in great detail. With the advent of human single neuron recordings, it is now feasible to record single unit activity (SUA), field potential, HFA, intracranial and scalp EEG all simultaneously within the same patient [16, 17] (see also Chaps. 12 and 16).

20.2 The Clinical Context for Sleep and Anesthesia Studies

20.2.1 The Peri- and Post-operative Clinical Setting

Patients undergoing invasive intracranial monitoring have typically experienced a long-lasting ordeal of seizures, failed treatments and non-invasive diagnostic tests. Once the non-invasive work-up is completed and electrode implantation has been

planned to pinpoint the seizure onset zone, patients are admitted to neurosurgery for implantation of either subdural grid electrodes (ECoG), stereotactically placed depth electrodes (sEEG) or a combination of both. Once patients are out of the operating room and electrode placement has been radiologically confirmed, they are transferred to the epilepsy-monitoring unit (EMU). Depending on the duration of the procedure and the precise dosing of the anesthetics, patients might be drowsy or somnolent until all effects of the general anesthesia wear off over the course of the first few hours. Depending on the type of electrode (grid vs. depth) patients might experience different levels of discomfort. In general, depth electrodes are better tolerated with less post-operative pain, given that no craniotomy is necessary. However, depth electrodes targeting mesial temporal lobe areas typically transverse through the temporal muscles, hence, patients often report pain and discomfort while chewing or drinking. In addition, electrodes are covered in a head-wrap, often requiring a supine positioning with an elevated backrest; hence, habitual sleeping positions are not always feasible. Most patients are confined to bed rest during the entire monitoring. Therefore, patients often require one or two days (and nights) to adapt to the surroundings of the EMU during invasive monitoring, which in turn, impacts sleep quality and duration (see also Chaps. 4 and 5).

20.2.2 Factors Determining Sleep Quality in the Monitoring Unit

Peri-operative circumstances impact sleep in the first few hours, but once the immediate effects of the procedure wear off, most patients resume their habitual night-day cycle. In the context of sleep studies on the monitoring unit a few caveats apply. Depending on the medical center, some patients will be assessed clinically every few hours throughout the night to monitor their vital signs as well as their neurological state. Hence, the clinical routine might introduce sleep fragmentation and frequent arousals during the night (Fig. 20.1). Arousals during nighttime might also be triggered through alarms on the ward at night or warning sounds of intravenous infusion systems.

Another factor that influences sleep quality on the EMU is the current antiepileptic drug regime (see Sect. 20.2.3 for drug specific effects), which is typically tapered during monitoring to provoke seizures. While the patient or members of the family/staff can press a bedside button whenever the patient experiences epileptic prodromes or seizures, in some instances, especially during reduction of antiepileptic medication, patients may first present with subclinical seizure patterns. Subclinical events are noted by the EEG techs as suddenly occurring rhythmic spiking patterns in the EEG without obvious clinical correlate. In order to determine the precise clinical manifestation of a given pattern, the techs then wake up the patient and administer a series of tests to determine orientation and executive functions. Collectively, given the clinical circumstances and several contributing factors, an undisturbed night on

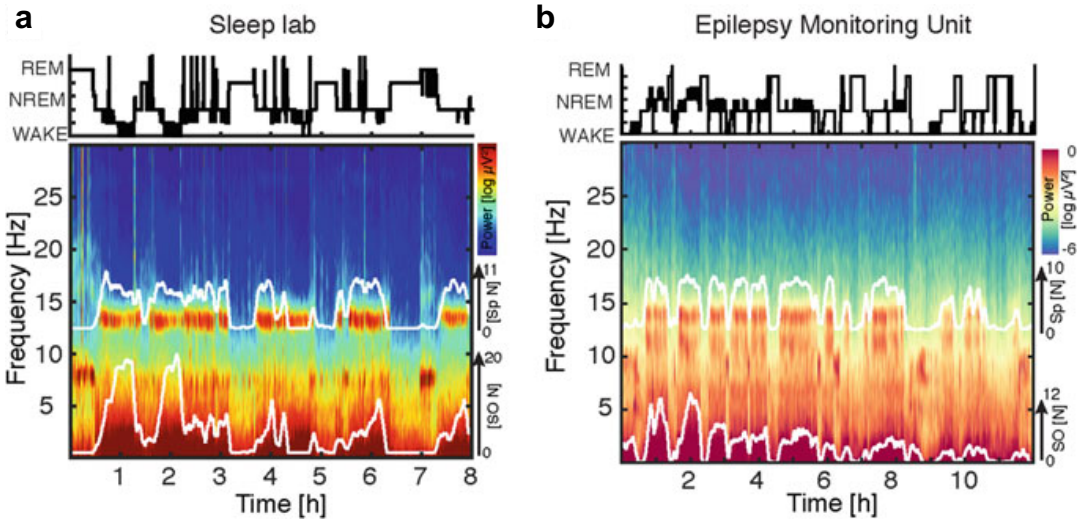

Fig. 20.1 Sleep architecture in the sleep lab and EMU. **a** Top: Hypnogram. Bottom: Multitaper spectral representation with number of detected slow oscillations and sleep spindles superimposed as recorded during a habitual night of sleep in a sleep lab. **b** Same conventions. Data recorded in the EMU. A comparable pattern is observed; thus, indicating the feasibility to conduct sleep studies in the EMU. Panel A is reproduced with permission from [60]. Panel B reproduced with permission from [14] under the Creative Commons Attribution (CC BY) license

the EMU is less common that in a dedicated sleep laboratory. This needs to be accounted for in studies that examine sleep physiology or sleep-dependent memory formation.

20.2.3 The Effects of Antiepileptic Drugs

Patients undergoing invasive monitoring failed multiple drug regimes and are typically being admitted while they are on a combination of different antiepileptic drugs (AEDs), which might include sodium channel blockers, GABAergic drugs or AMPA receptor antagonists. During monitoring, AEDs are typically tapered off to provoke habitual seizures. In the context of sleep studies, it is important to note that tapering off medications will increase both interictal spiking (see also Sect. 20.3.1) and the likelihood for seizures. On the other hand, AEDs themselves often impair sleep quality and its electrophysiological signatures. For instance, lamotrigine, a widely used sodium channel blocker, triggers sleep disturbances and fragmentation [18]. In contrast, GABAergic drugs, such as clobazam (a benzodiazepine), lead to daytime sleepiness and sedation [19]. AMPA receptor antagonists like perampanel are strong sedatives and are therefore taken only in the evening hours [20]. To date, the precise effects of many AEDs on sleep are not well known, but in the context of sleep studies detailed knowledge about the current medication status is helpful to interpret these findings [21–24]. This is of particular relevance, since certain anticonvulsants exhibit

distinct electrophysiological signatures, such as benzodiazepines, which introduce widespread EEG beta activity (~13–30 Hz).

20.2.4 Electrode Explantation as a Window into the Neural Correlates of Anesthesia

Once intracranial electrodes are in place and patients are awake and stable, they are typically transferred from the operating room (OR) to the monitoring ward, where electrodes are first connected to the clinical and research recording setup, a process that takes between 45 min to 1.5 h. In rare instances, the setup can already be completed in the OR; thus, enabling recording electrophysiological activity during the emergence of anesthesia [25]. However, as virtually all patients undergo post-operative imaging by means of CT- or MRI-based imaging to confirm electrode placement and to rule out perioperative complications such as brain hemorrhage, electrodes would have to be disconnected for scanning and then reconnected on the EMU, making this recording strategy highly impractical in the clinical context.

The more feasible route to obtain iEEG recordings during anesthesia is recording at the end of invasive monitoring, just before electrode explantation. Again, this is only viable if electrodes are explanted under general anesthesia, which is common for grid electrodes, in patients that cannot comply with lying still (e.g. young children or patients with anxiety disorders) or when the epileptogenic tissue is removed in the same session. Nowadays, many centers remove depth electrodes in the EMU under local anesthesia, while patients are awake. If patients undergo general anesthesia for explantation, then recording equipment may be transferred to the OR and recordings continue until the wires are physically removed; hence, capturing induction and maintenance of anesthesia. A few reports are available where patients underwent light anesthesia or sedation accompanied by research testing (e.g. tasks or auditory stimuli), then recovered as part of the research protocol and then were again anesthetized for final removal of the electrodes [26]. The exact clinical set up will vary between medical centers. However, often enough it will be possible to incorporate research studies into the individual clinical context, without jeopardizing patient safety and while respecting clinical time constrains and limited OR time. In most centers, protocols can be tailored to address specific questions; however, given the scarcity of reports, there is currently no consensus or gold standard available on how to conduct these studies.

20.3 Implications of Epilepsy as the Underlying Neurological Disorder

20.3.1 Sleep Stages and Epileptic Activity

An empirical observation in numerous overnight EEG recordings is that the frequency of epileptic spikes (interictal epileptic discharges; IEDs) sharply increases during NREM sleep and that they are less common during wakefulness and REM sleep (Fig. 20.2; [21]). In addition, most nighttime seizures occur during NREM sleep. In fact, epileptic activity that occurs during REM sleep is highly informative for clinical localization of the seizure onset zone (SOZ), while NREM spikes are less specific. The precise (patho-) physiologic underpinnings of these observations remain unknown, however, it has been argued that NREM sleep reflects a hyper-synchronized brain state that facilitates propagation of synchronized volleys of epileptic activity [24]. A related clinical observation is that hippocampal IEDs are common during NREM sleep, even if the SOZ is located outside of the medial temporal lobe. It has been argued that the anatomical structure and connectivity of the hippocampus abet its susceptibility to epileptic activity [21, 27]. Uncontrolled seizure activity outside of the medial temporal lobe might 'kindle' the hippocampus [28], i.e. induce a second independent source of seizure activity, thus, rendering a focal epilepsy multi-focal and therefore, not amendable to resective surgery. In the context of sleep studies, the spatial and temporal characteristics of IEDs need to be accounted for to circumvent a systematic bias when analyzing REM and NREM sleep separately. Likewise, special caution is necessary when analyzing hippocampal activity during sleep (see also Sect. 20.4.3).

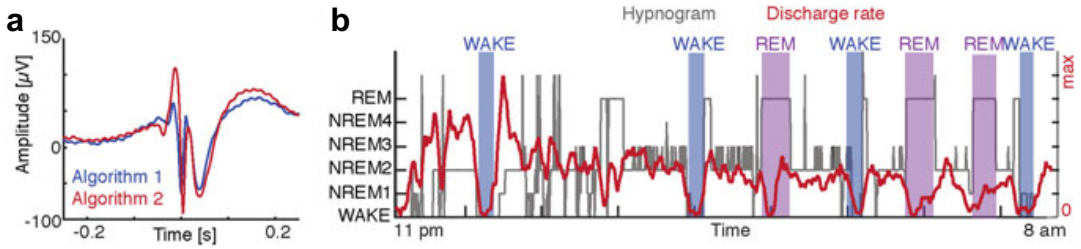

Fig. 20.2 The rate of interictal discharges increases during NREM sleep. **a** Inter-ictal discharges (IED) as detected by two automatic detectors [15, 27]. **b** Discharge rate (red) across the night (hypnogram in grey), highlighting more IEDs during NREM sleep as compared to wakefulness (blue) or REM sleep (purple). Panel A reproduced with permission from [14] under the Creative Commons Attribution (CC BY) license

20.3.2 Sleep Deprivation is a Powerful Trigger for Seizures

Invasive monitoring on the EMU provides a narrow time window (often between 4 and 7 days) to observe seizures and to determine the SOZ for subsequent surgical resection. In addition to tapering off the AEDs, (partial) sleep deprivation is another commonly employed tool to trigger seizures during monitoring [29, 30]. Patients are typically kept awake or are only allowed to sleep for approximately four hours, e.g. from 2 to 6 a.m. Seizures after sleep deprivation do not occur immediately, but manifest within the subsequent 24 h. The precise mechanisms are not fully understood yet, but it has been argued that sleep deprivation attenuates physiologic homeostasis for the excitatory-to-inhibitory balance; thereby, resulting in a net increase of excitation and subsequent epileptic activity [30–32]. In the context of iEEG sleep studies on e.g. overnight memory formation, sleep deprivation constitutes a valuable control condition that is already implemented in the clinical context. However, an important confound is that it also sharply increases epileptic activity, which might bias behavioral performance and electrophysiological signatures the next day.

20.3.3 The Relationship of Anesthesia and Epileptic Activity

General anesthesia induces a state of unconsciousness, often by increasing inhibition in the brain [5]. Common anesthetic agents like propofol bind to GABAergic receptors, similar to benzodiazepines, which are also used as anticonvulsants. Hence, anesthetic drugs are occasionally being used to treat a status epilepticus, i.e. a continuous epileptic seizure. This has also strong implications for intracranial EEG studies on general anesthesia. In contrast to sleep studies, where epileptic activity can be sharply increased, IEDs are typically strongly attenuated during general anesthesia; thus, potentially biasing and hampering a direct within subject comparison between both neuronal states. However, most studies focused on the neuronal correlates of the loss-of-consciousness (LOC) under anesthesia and in this scenario a strong attenuation of epileptic activity is desirable. From a clinical point-of-view, LOC from general anesthesia results from a maximum of inhibitory drive resulting in hypersynchronized medium to slow neural activity, while LOC during a seizure typically results from uncoordinated neuronal firing due to hyperexcitability.

20.4 Analysis Strategies

20.4.1 Technical Pre-requisites for Comparative Electrophysiology

In principle, data is continuously recorded during monitoring. However, in order to take full advantage of the acquired data, several prerequisites need to be met. First, it is desirable that iEEG during sleep and anesthesia are recorded using the same amplifier. Some centers run dedicated clinical and research systems that are either fully independent (parallel data streaming) or that run serially (data is streamed from the clinical to the research system). If a serial setup is employed, it might be difficult to transfer both the clinical and research system to the OR for recordings during anesthesia. In this scenario, it would be beneficial to use the clinical amplifier for both recordings. It is of critical importance to be aware of the operating room logistics where several disciplines (nurses, anesthesia techs, neurophysiologists, anesthesiologists and neurosurgeons) interact under both, time and space constrains. Continuous EEG recordings during this phase likely contain movement artifacts as well as artifacts from manipulation of wires and the head, which will require careful inspection during analysis. Wherever possible, noise should be attenuated during the recording, e.g. by shielding recording leads from surrounding noise sources or unplug unnecessary equipment in the vicinity.

To enable a direct comparison to non-invasive results and to facilitate gold-standard sleep staging, scalp EEG should be recorded simultaneously [33]. Implanted iEEG leads sometimes prohibit placement of scalp leads, but it is best practice to at least record from a few scalp locations (i.e. midline electrodes Fz, Cz and Pz along with C3/C4 to facilitate spindle detection) as well as electrooculogram (EOG) and electromyogram (EMG) electrodes to detect REM sleep.

In addition, data should be recorded at a sufficient high sampling rate (>500 Hz) to enable extraction of HFA and ripple oscillations. During recording data should be minimally processed with regard to low-pass, high-pass or band-stop filters.

20.4.2 How to Determine the Current Behavioral or Brain State?

Sleep staging from iEEG is theoretically possible, however, guidelines for sleep staging are only available for scalp EEG. Hence, it remains best practice to obtain simultaneous scalp EEG, EOG and EMG to facilitate sleep staging. The key challenge is the distinction of wakefulness and REM sleep, while NREM sleep can easily be detected given the presence of clear oscillatory key signatures, such as prominent slow waves and spindle oscillations.

With respect to anesthesia, the current gold standard to determine the loss of consciousness is based on clinical judgement by the physician. The Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale is a validated 6-point scale assessing responsiveness of patients, which has been defined by American Society of Anesthesiologists (ASA). For neuroscientific applications, sometimes a simplified categorization into awake/alert, sedated/drowsy (but arousable/responsive to predefined stimuli such as subject's name or mild prodding) and unconscious/unresponsive is employed. Lastly, anesthetic depth may be monitored with the help of special neuromonitoring devices such as the bispectral index (BIS) monitor, which was initially developed to prevent intraoperative awareness. Electrophysiological data (EEG, EMG) is measured from a few frontal sensors and then transformed into a numerical value between 0 and 100 that indicates the level of arousal (100 = wakefulness, 40–60 = sufficient anesthetic depth for surgery). However, the algorithm of this calculation is proprietary, thus, it remains unclear which EEG features are being evaluated. Furthermore, BIS has mainly been validated in propofol anesthesia and the efficacy and reliability of BIS monitoring remains controversial.

20.4.3 How to Address Epileptic Activity?

Epileptic activity is an inherent feature of iEEG data. Depending on the question, multiple approaches are conceivable. Typically, when addressing questions on sleep or cognitive physiology, it is considered best practice to exclude electrode contacts within the clinically identified SOZ and to reject any other channels that contain seizure or spiking activity [12]. However, in the context of sleep studies, these criteria might be overly conservative. As outlined above, even when the SOZ is outside of the MTL it is common to observe IEDs in hippocampal contacts. These IEDs should be rejected either based on visual inspection by a neurologist or by means of an automatic IED detector (Fig. 20.2). Several algorithms have been introduced in recent years [15, 27], but specificity and sensitivity have not fully been evaluated and detectors are not being used for clinical purposes, where the time-consuming visual inspection still constitutes the gold standard. It is common practice to only analyze nights where the patient did not experience any seizures or to discard recordings around the seizures with a large error margin of ± 2 h to avoid any pre- or postictal rhythmic slowing, which can easily be mistaken for physiologic slow waves.

20.5 Insights into Sleep and Anesthesia

20.5.1 The Human Memory Network During Sleep

Contemporary theories of memory consolidation emphasize the role of a two-step bidirectional hippocampal-neocortical dialogue, where novel information is initially encoded in hippocampal-dependent loops and overtime becomes mainly neocortex-dependent during consolidation [4, 10]. A hierarchy of sleep oscillations is thought to subserve the sleep-dependent reactivation, transfer and consolidation of mnemonic information. In this model, hippocampus-dependent information is spontaneously replayed during sleep, i.e. the very same pattern that was present during encoding is recapitulated during sleep in a time-compressed manner [34–37]. Replay is tightly linked to the expression of a hippocampal sharp-wave ripple (80–120 Hz; [37]), which in turn is nested in thalamo-cortical spindles (12–16 Hz) and neocortical slow waves (<4 Hz). Selective synchronization of these three cardinal sleep oscillations is thought to reflect an endogenous timing mechanism for the routing of information [4]. Before the advent of iEEG in humans, a major caveat of this theory was that most evidence stemmed from recordings in rodents, as non-invasive imaging of the human hippocampus did not offer a sufficiently high spatiotemporal resolution to detect ripple oscillations [9]. However, in recent years, the field of epileptology transitioned from using grid and strip electrodes on the outer surface of the MTL to employing depth electrodes that directly target the hippocampus, often in standardized bilateral implanting schemes; thus, providing the necessary resolution to examine the building blocks of systems memory consolidation in humans. Intracranial recordings from the sleeping brain have yielded important insights into sleep physiology in recent years. For instance, it has been shown that the hierarchical triple coupling is preserved in humans and that the precise SO-spindle coupling phase predicts hippocampal ripple expression [13–15, 38]. Hippocampal ripples then mediate the transfer of mnemonic information from the hippocampus to long-term neocortical storage (Fig. 20.3). Recently, intracranial recordings have been also used to also establish the presence of cortical ripples, however, their role in systems memory consolidation remains unclear [39, 40].

20.5.2 The Brain Under Anesthesia

In recent years, EEG studies under various anesthetics have revealed distinct spectral fingerprints of each drug [1, 5]. For example, the administration of GABAergic anesthetics such as propofol lead to an overall decrease of brain activity. Although this is true for most neural activity including IEDs, LOC under anesthesia is associated with a sudden increase of coherent slow and alpha oscillations (depicted in one frontal intracranial electrode Fig. 20.4a). We are currently lacking mechanistic insights into how the brain transitions from consciousness to anesthesia and how it recovers from

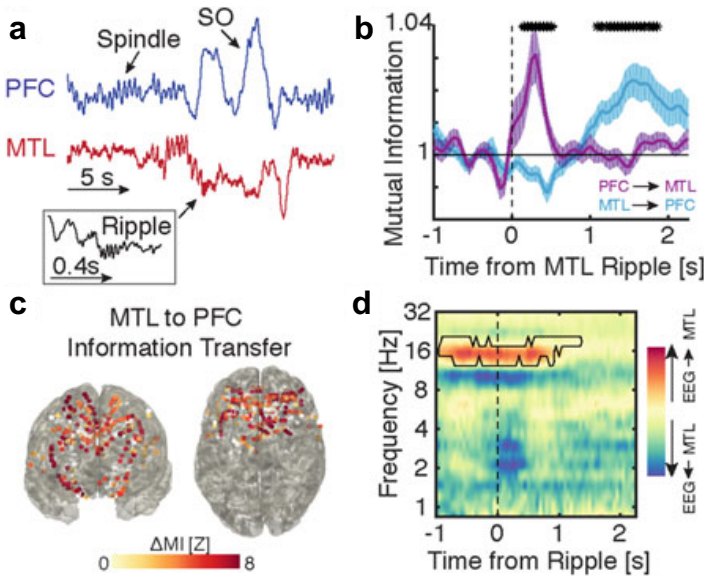

Fig. 20.3 Ripple-triggered information transfer between the hippocampus and neocortex. **a** Simultaneous recordings from frontal and hippocampal areas during NREM sleep highlight the presence of all cardinal sleep oscillations. **b** Bidirectional information exchange upon a hippocampal ripple. **c** Widespread increases in shared information between the hippocampus and neocortical intracranial contacts. **d** Spectrally-resolved information flow (transfer entropy) highlights a key role of spindle oscillations for mediating inter-areal information flow. Figure reproduced with permission from [14] under the Creative Commons Attribution (CC BY) license

the perturbation, with potential implications for coma and other states of altered arousal. Moreover, anesthesia can impact perioperative cognition beyond immediate recovery resulting in long-lasting cognitive deficits including memory impairments [3]. Although highly valuable, iEEG data during anesthesia remains scarce given the logistical challenges outlined above.

To date, iEEG has been used to illuminate the neural correlates of the loss-of-consciousness under general anesthesia. It has been demonstrated that network dynamics change dramatically upon anesthesia induction with prominent power increases in the delta- and alpha-bands [41–43]. Specifically, it has been shown that anesthesia alters spatiotemporal network configurations and alters coupling across temporal (i.e. delta-alpha or delta-gamma cross-frequency coupling; [43]) and across spatial scales (delta-, alpha- or gamma-band phase synchronization; [44–46]). It has been argued that impaired network synchronization is detrimental for information integration in large-scale cortical networks [41, 43, 46]. This consideration is in line with the observation that sensory processing in primary sensory areas remained intact under general anesthesia, while subsequent processing in secondary sensory and higher-order association areas was attenuated [47–49].

It has been proposed that neural networks operate close to criticality, i.e. at a transition point between ordered and chaotic network states, which may be optimal for information processing and transmission capacities [50–52]. Several findings indicated that anesthesia renders neural activity less critical, i.e. more predictable [53]. It has been argued that high variability close to possible network transition

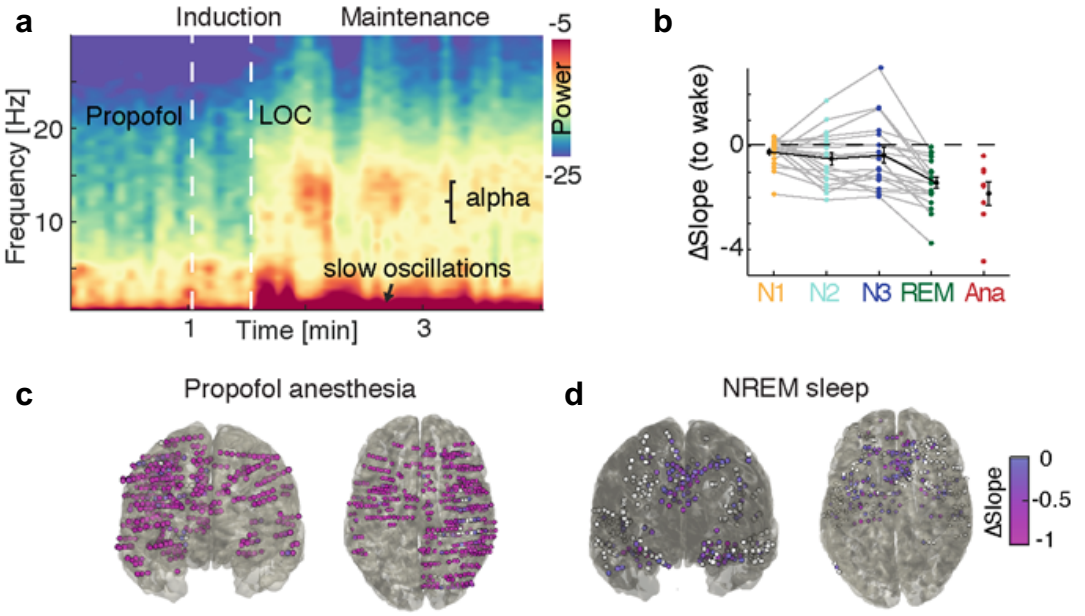

Fig. 20.4 Aperiodic activity dissociates arousal levels in sleep and anesthesia. **a** Multitaper spectrogram during induction of propofol anesthesia highlights the emergence of both slow waves and alpha oscillations during loss-of-consciousness. **b** Decreased arousal is associated with a reduction of the spectral exponent. States that are characterized by increased inhibition lead to a stronger reduction of the spectral slope. The steepest slope is observed during anesthesia. **c** Reduction of the slope in iEEG recordings highlights that anesthesia induces a brain wide reduction. **d** On the contrary, during sleep this reduction is confined to key nodes of the memory network, namely medial temporal and medial frontal areas. Figure reproduced with permission from [56] under the Creative Commons Attribution (CC BY) license

states is necessary to remain conscious, while anesthesia induces a shift away from the network bifurcation and thereby, promotes unconsciousness [54–57].

Collectively, this set of findings indicates that anesthesia promotes altered states of consciousness by impairing information flow and integration in cortical networks. Furthermore, the available evidence suggests that hyper-synchrony (as indicated by increased power and connectivity) heavily constrains the neural repertoire, which is necessary for consciousness. Collectively, iEEG under anesthesia provides a unique opportunity to assess the neural correlates of consciousness through the lens of pharmacologically induced unconsciousness.

20.5.3 Comparative Electrophysiology of Sleep and Anesthesia

In the last decade, several seminal findings were published using iEEG to understand sleep or anesthesia. However, to date only very few comparative approaches have been reported [25, 47, 56]. Hence, it remains unclear if anesthesia actually hijacks sleep pathways during induction, emergence or maintenance.

Until recently, slow oscillations have been considered a hallmark of the unconscious brain and a marker of cortical inhibition as they occur both in deep sleep and under anesthesia [1, 24]. However, this notion was in stark contrast to the presumed active role of NREM sleep in information processing [4]. Recent comparative evidence provided functional insights beyond these prominent oscillatory signatures. Computational modeling indicated increased inhibition is associated with a steepening on the electrophysiological power spectrum (reduction of the spectral exponent; [58]). Indeed, this shift towards inhibition was also observed during propofol anesthesia in rodents, monkeys and humans (Fig. 20.4; [56]). Importantly, anesthesia induced a brain-wide reduction of the spectral exponent (Fig. 20.4c). A similar exponent reduction was also observed during sleep, which had several implications [59]. First, contrary to popular belief, inhibition was maximal during REM and not NREM sleep, possibly sub-serving sleep-dependent neural homeostasis. Second, this reduction was mainly confined to the human memory network, i.e. encompassing medial temporal and medial frontal areas (Fig. 20.4d). However, it is critical to note that this line of inquiry is in early stages and we foresee that a direct, within subject comparison of sleep and anesthesia with iEEG will provide important insights into physiological as well as pathophysiological mechanism underlying e.g. post-operative cognitive decline.

20.6 Conclusions

In summary, intracranial recordings in humans can be leveraged to gain important insights into sleep physiology and the neural correlates of (un-) consciousness. We reviewed the most important technical considerations and prerequisites to successfully implement these recordings in a clinical environment. Recording sleep and anesthesia data during invasive monitoring constitutes an interdisciplinary team effort that involves multiple disciplines (neurology, neurosurgery, anesthesiology) and requires support from nurses and EEG techs. The obtained data provides a unique window in the correlates of (un-) consciousness in the human brain and therefore, constitutes an important link to recordings in non-human primates and rodents.

Acknowledgements This work was supported by the German Research Foundation (DFG Emmy Noether Program, HE 8329/2-1; R.F.H.), the Hertie Foundation (Hertie Network of Excellence in Clinical Neuroscience; R.F.H.), the Jung Foundation for Science and Research (Ernst Jung Career Advancement Award; R.F.H.) and the Medical Faculty of the University Medical Center Tübingen (JRG Plus Program; R.F.H.).

References

1. Brown EN, Lydic R, Schiff ND (2010) General anesthesia, sleep, and coma. N Engl J Med 363:2638–2650. https://doi.org/10.1056/NEJMra0808281
2. Brown EN, Purdon PL (2013) The aging brain and anesthesia. Curr Opin Anaesthesiol 26:414–419. https://doi.org/10.1097/ACO.0b013e328362d183
3. Radtke FM, Franck M, Lendner J et al (2013) Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 110(Suppl 1):i98-105. https://doi.org/10.1093/bja/aet055
4. Klinzing JG, Niethard N, Born J (2019) Mechanisms of systems memory consolidation during sleep. Nat Neurosci 22:1598–1610
5. Brown EN, Purdon PL, Van Dort CJ (2011) General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci 34:601–628. https://doi.org/10.1146/annurev-neuro-060909-153200
6. Alkire MT, Hudetz AG, Tononi G (2008) Consciousness and anesthesia. Science 322:876–880. https://doi.org/10.1126/science.1149213
7. Murphy M, Bruno M-A, Riedner BA et al (2011) Propofol anesthesia and sleep: a high-density EEG study. Sleep 34:283-291A
8. Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262:679–685
9. Buzsáki G (2015) Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 25:1073–1188. https://doi.org/10.1002/hipo.22488
10. Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119–130. https://doi.org/10.1038/nrn1607
11. Leszczyński M, Barczak A, Kajikawa Y et al (2020) Dissociation of broadband high-frequency activity and neuronal firing in the neocortex. Sci Adv 6:eabb0977. https://doi.org/10.1126/sciadv.abb0977
12. Parvizi J, Kastner S (2018) Promises and limitations of human intracranial electroencephalography. Nat Neurosci 21:474–483. https://doi.org/10.1038/s41593-018-0108-2
13. Axmacher N, Elger CE, Fell J (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain 131:1806–1817. https://doi.org/10.1093/brain/awn103
14. Helfrich RF, Lendner JD, Mander BA et al (2019) Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans. Nat Commun 10:3572. https://doi.org/10.1038/s41467-019-11444-x
15. Staresina BP, Bergmann TO, Bonnefond M et al (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 18:1679–1686. https://doi.org/10.1038/nn.4119
16. Fried I, Rutishauser U, Cerf M, Kreiman G (2014) Single neuron studies of the human brain: probing cognition. MIT Press
17. Rutishauser U (2019) Testing models of human declarative memory at the single-neuron level. Trends in cognitive sciences
18. Foldvary N, Perry M, Lee J et al (2001) The effects of lamotrigine on sleep in patients with epilepsy. Epilepsia 42:1569–1573
19. Gauthier AC, Mattson RH (2015) Clobazam: a safe, efficacious, and newly rediscovered therapeutic for epilepsy. CNS Neurosci Ther 21:543–548
20. Rocamora R, Álvarez I, Chavarría B, Principe A (2020) Perampanel effect on sleep architecture in patients with epilepsy. Seizure 76:137–142
21. Beenhakker MP, Huguenard JR (2009) Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? Neuron 62:612–632. https://doi.org/10.1016/j.neuron.2009.05.015
22. Derry CP, Duncan S (2013) Sleep and epilepsy. Epilepsy Behav 26:394–404
23. Méndez M, Radtke RA (2001) Interactions between sleep and epilepsy. J Clin Neurophysiol 18:106–127

24. Steriade M (2005) Sleep, epilepsy and thalamic reticular inhibitory neurons. Trends Neurosci 28:317–324
25. Lewis LD, Piantoni G, Peterfreund RA et al (2018) A transient cortical state with sleep-like sensory responses precedes emergence from general anesthesia in humans. elife 7:e33250
26. Krom AJ, Marmelshtein A, Gelbard-Sagiv H et al (2020) Anesthesia-induced loss of consciousness disrupts auditory responses beyond primary cortex. Proc Natl Acad Sci 117:11770–11780
27. Gelinas JN, Khodagholy D, Thesen T et al (2016) Interictal epileptiform discharges induce hippocampal-cortical coupling in temporal lobe epilepsy. Nat Med 22:641–648. https://doi.org/10.1038/nm.4084
28. Sato M, Racine RJ, McIntyre DC (1990) Kindling: basic mechanisms and clinical validity. Electroencephalogr Clin Neurophysiol 76:459–472
29. Badawy RA, Curatolo JM, Newton M et al (2006) Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 67:1018–1022
30. Malow BA (2004) Sleep deprivation and epilepsy. Epilepsy Curr 4:193–195
31. Tononi G, Cirelli C (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81:12–34. https://doi.org/10.1016/j.neuron.2013.12.025
32. Huber R, Mäki H, Rosanova M et al (2013) Human cortical excitability increases with time awake. Cereb Cortex 23:332–338. https://doi.org/10.1093/cercor/bhs014
33. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques, and scoring systems for sleep stages of human subjects
34. Antony JW, Schapiro AC (2019) Active and effective replay: systems consolidation reconsidered again. Nat Rev Neurosci. https://doi.org/10.1038/s41583-019-0191-8
35. Higgins C, Liu Y, Vidaurre D et al (2021) Replay bursts in humans coincide with activation of the default mode and parietal alpha networks. Neuron 109:882-893.e7. https://doi.org/10.1016/j.neuron.2020.12.007
36. Ólafsdóttir HF, Bush D, Barry C (2018) The role of hippocampal replay in memory and planning. Curr Biol 28:R37–R50. https://doi.org/10.1016/j.cub.2017.10.073
37. Zhang H, Fell J, Axmacher N (2018) Electrophysiological mechanisms of human memory consolidation. Nat Commun 9:4103. https://doi.org/10.1038/s41467-018-06553-y
38. Skelin I, Zhang H, Zheng J et al (2021) Coupling between slow waves and sharp-wave ripples engages distributed neural activity during sleep in humans. Proc Natl Acad Sci 118
39. Khodagholy D, Gelinas JN, Buzsáki G (2017) Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. Science 358:369–372. https://doi.org/10.1126/science.aan6203
40. Vaz AP, Inati SK, Brunel N, Zaghloul KA (2019) Coupled ripple oscillations between the medial temporal lobe and neocortex retrieve human memory. Science 363:975–978. https://doi.org/10.1126/science.aau8956
41. Breshears JD, Roland JL, Sharma M et al (2010) Stable and dynamic cortical electrophysiology of induction and emergence with propofol anesthesia. Proc Natl Acad Sci USA 107:21170–21175. https://doi.org/10.1073/pnas.1011949107
42. Lewis LD, Ching S, Weiner VS et al (2013) Local cortical dynamics of burst suppression in the anaesthetized brain. Brain 136:2727–2737. https://doi.org/10.1093/brain/awt174
43. Mukamel EA, Pirondini E, Babadi B et al (2014) A transition in brain state during propofol-induced unconsciousness. J Neurosci 34:839–845. https://doi.org/10.1523/JNEUROSCI.5813-12.2014
44. Huang Y, Wu D, Bahuri NFA et al (2018) Spectral and phase-amplitude coupling signatures in human deep brain oscillations during propofol-induced anaesthesia. Br J Anaesth 121:303–313
45. Lewis LD, Weiner VS, Mukamel EA et al (2012) Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci USA 109:E3377-3386. https://doi.org/10.1073/pnas.1210907109
46. Malekmohammadi M, Price CM, Hudson AE et al (2019) Propofol-induced loss of consciousness is associated with a decrease in thalamocortical connectivity in humans. Brain 142:2288–2302

47. Banks MI, Krause BM, Endemann CM et al (2020) Cortical functional connectivity indexes arousal state during sleep and anesthesia. Neuroimage 211:116627
48. Nourski KV, Banks MI, Steinschneider M et al (2017) Electrocorticographic delineation of human auditory cortical fields based on effects of propofol anesthesia. Neuroimage 152:78–93. https://doi.org/10.1016/j.neuroimage.2017.02.061
49. Nourski KV, Steinschneider M, Rhone AE et al (2018) Auditory predictive coding across awareness states under anesthesia: an intracranial electrophysiology study. J Neurosci 0967–18. https://doi.org/10.1523/JNEUROSCI.0967-18.2018
50. Beggs JM (2008) The criticality hypothesis: how local cortical networks might optimize information processing. Philos Trans A Math Phys Eng Sci 366:329–343. https://doi.org/10.1098/rsta.2007.2092
51. Shew WL, Plenz D (2013) The functional benefits of criticality in the cortex. Neuroscientist 19:88–100. https://doi.org/10.1177/1073858412445487
52. Zimmern V (2020) Why brain criticality is clinically relevant: a scoping review. Front Neural Circuits 14
53. Toker D, Pappas I, Lendner JD et al (2022) Consciousness is supported by near-critical slow cortical electrodynamics. Proc Natl Acad Sci 119:e2024455119
54. Cocchi L, Gollo LL, Zalesky A, Breakspear M (2017) Criticality in the brain: a synthesis of neurobiology, models and cognition. Prog Neurobiol 158:132–152. https://doi.org/10.1016/j.pneurobio.2017.07.002
55. Colombo MA, Napolitani M, Boly M et al (2019) The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. Neuroimage 189:631–644. https://doi.org/10.1016/j.neuroimage.2019.01.024
56. Lendner JD, Helfrich RF, Mander BA et al (2020) An electrophysiological marker of arousal level in humans. Elife 9:e55092
57. Sarasso S, Boly M, Napolitani M et al (2015) Consciousness and complexity during unresponsiveness induced by Propofol, Xenon, and Ketamine. Curr Biol 25:3099–3105. https://doi.org/10.1016/j.cub.2015.10.014
58. Gao R, Peterson EJ, Voytek B (2017) Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage 158:70–78. https://doi.org/10.1016/j.neuroimage.2017.06.078
59. Helfrich RF, Lendner JD, Knight RT (2021) Aperiodic sleep networks promote memory consolidation. Trends Cogn Sci 25:648–659. https://doi.org/10.1016/j.tics.2021.04.009
60. Helfrich RF, Mander BA, Jagust WJ et al (2018) Old brains come uncoupled in sleep: slow wave-spindle synchrony, brain atrophy, and forgetting. Neuron 97:221-230.e4. https://doi.org/10.1016/j.neuron.2017.11.020