Chapter 10

Human Intracranial Cognitive Neurophysiology

Randolph F. Helfrich

Abstract

The neurophysiological mechanisms that enable cognitive functions are typically studied noninvasively in humans using scalp magnetic resonance imaging (MRI) and magneto- or electroencephalography (M/EEG) or invasively in rodents or nonhuman primates. Intracranial EEG as recorded in pharmacoresistant epilepsy patients who undergo evaluation for resective epilepsy surgery provides a unique approach to bridge the gap between noninvasive in humans and invasive studies in rodents and nonhuman primates. In recent years, iEEG has provided important insights into the functional architecture of human cognitive systems. Here, the principles of successfully conducting intracranial experiments in humans are discussed, with a particular focus on implementing recording setups and analyzing the data. The high spatiotemporal resolution of iEEG provides a number of opportunities and challenges, which are outlined alongside potential solutions. Collectively, intracranial cognitive neurophysiology is a rapidly progressing field providing key insights into the organization of human cognitive systems.

Key words Stereoelectroencephalography (sEEG), Electrocorticography (ECoG), High-gamma activity, Broadband population activity, Prefrontal cortex, Attention, Memory, Cognition, Epilepsy, Invasive neurophysiology

1 Introduction

Cognitive neuroscience has employed a variety of methods to understand the neuronal basis of higher cognitive functions, such as attention, memory, or decision-making [1]. Several lines of research were triggered by the clinical neurosciences, which provide a unique perspective onto the organizing principles of human behavior [2, 3]. For instance, several key principles on the organization of human memory were obtained from carefully studying patient H.M., after neurosurgeon William Scoville removed both hippocampi to cure his temporal lobe epilepsy [4, 5]. While the procedure greatly reduced the number of seizures, it also heavily impaired H.M.'s ability to form new memories. Likewise, key elements of prefrontal cortex organization were only understood when carefully studying patients, such as Phineas Gage, who suffered from damage to the prefrontal lobes [2, 6]. In the following

Robert P. Vertes and Timothy A. Allen (eds.), *Electrophysiological Recording Techniques*, Neuromethods, vol. 192,
https://doi.org/10.1007/978-1-0716-2631-3_10,

decades, invasive studies in rodents and nonhuman primates further elucidated the single neuron and microcircuit mechanisms that enable cognitive processing, while noninvasive studies in humans enabled a better understanding of the large-scale network mechanisms behind cognitive operations [7–12]. However, all employed methods have their shortcomings: while EEG and fMRI provide whole-head coverage, both methods are severely limited with regard to either spatial (EEG) or temporal (MRI) resolution. Furthermore, there is no established transfer function to translate EEG to fMRI findings and vice versa. Likewise, there is no established method to infer local population activity at the level of single- or multiunit activity from electric field potentials or neurovascular coupling [13, 14]. To date, it remains challenging to bridge the gap between invasive experiments in animals and noninvasive imaging in humans. Intracranial electrophysiology in humans offers one possibility to bridge the gap between different species and imaging modalities (Fig. 1) and to gain a better understanding into the organizing principles of human cognitive networks [3].

1.1 Human Intracranial Clinical Neurophysiology

Multiple clinical procedures require the implantation of electrodes into the human brain, either for diagnostic or therapeutic purposes [15]. For instance, deep brain stimulation has become a widely utilized treatment option for Parkinson's disease [16]. Here, multi-contact electrodes are placed stereotactically into the subthalamic nuclei to deliver electric currents to alleviate the symptoms of the "shaking palsy." Electrophysiological recordings during placement of these electrodes during implantation ensure the correct placement within the subthalamic nucleus based on either characteristic firing patterns or based on characteristic spectral features [17]. However, the usability for cognitive experiments is usually limited: First, only a single subcortical region is being explored. Second, recordings are usually confined to the operating room, since most medical centers directly attach the battery once correct electrode placement has been confirmed. Only very few centers will externalize the electrode leads to enable recordings over multiple days on the monitoring unit. Third, the electrodes are inserted into a cortical region, which is part of a pathologic network, thus hampering the interpretation and physiological plausibility of the signals that can be recorded. Fourth, the subthalamic nucleus is part of the motor network, and it is unclear to which extent it is involved in cognitive operations [18].

A different clinical procedure that enables access to widespread regions, which have been implicated in cognitive control, is invasive EEG monitoring for localization of the seizure onset zone prior to resective epilepsy surgery (Fig. 2). Here, patients with focal seizures, who failed at least 2–3 anticonvulsant drug regimens and where noninvasive monitoring by means of scalp electroencephalography (EEG), high-density EEG, magnetoencephalography

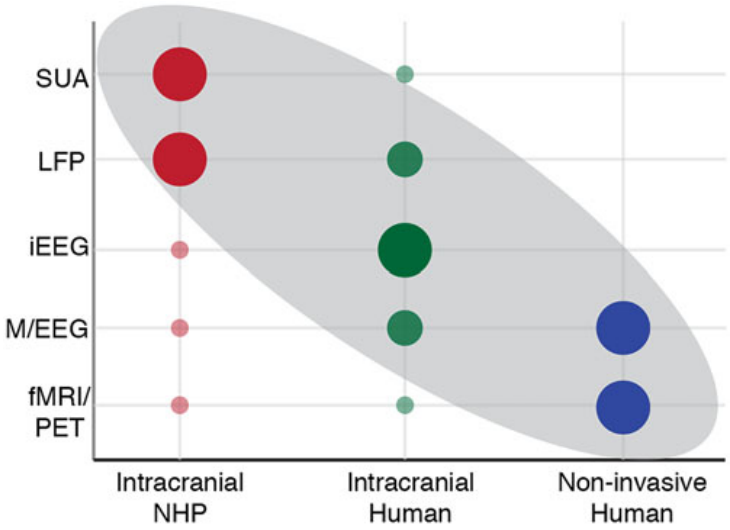

Fig. 1 Methods of cognitive neuroscience in different species. Different methods (*y*-axis) are being used in primate electrophysiology. While recordings in nonhuman primates (NHP) mostly focus on invasive recording of single- or multiunit activity (SUA/MUA) along with local field potentials (LFP), imaging in humans is typically confined to noninvasive methods, such as M/EEG, fMRI, or PET. Intracranial electrophysiology in humans using invasive recordings bridges this gap

(MEG) as well as magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging remained equivocal, are being implanted with intracranial electrodes into regions where the seizure origin is suspected (Fig. 2). Approximately, two thirds of the cases suffer from temporal lobe epilepsy, which requires coverage of several nodes of the limbic system as well interconnected frontal regions. A typical implantation features bilateral implantations into the hippocampus, amygdala, orbitofrontal cortex and anterior cingulate cortex, and insula. Note that electrodes transverse either through lateral temporal or lateral frontal cortex; thus, activity from these regions can be recorded using electrodes with evenly spaced contacts throughout the electrode shaft. While these patients suffer from epilepsy, only few electrode contacts will cover the seizure onset zone, with the majority of electrodes recording activity from healthy brain tissue [3]. Since patients are monitored from multiple days following implantation, during which the anticonvulsant drugs are typically weaned off, this constitutes a short and narrow time window where one can record intracranial EEG from intact cortex while patients engage in cognitive tasks. Given that electrodes are placed in their brain, patients are confined to their beds for multiple days and often volunteer their time to participate in experiments.

Note that additional clinical indications for electrode implantation exist, such as deep brain stimulation for obsessive-compulsive disorder or depression [21, 22]; here I will focus on the

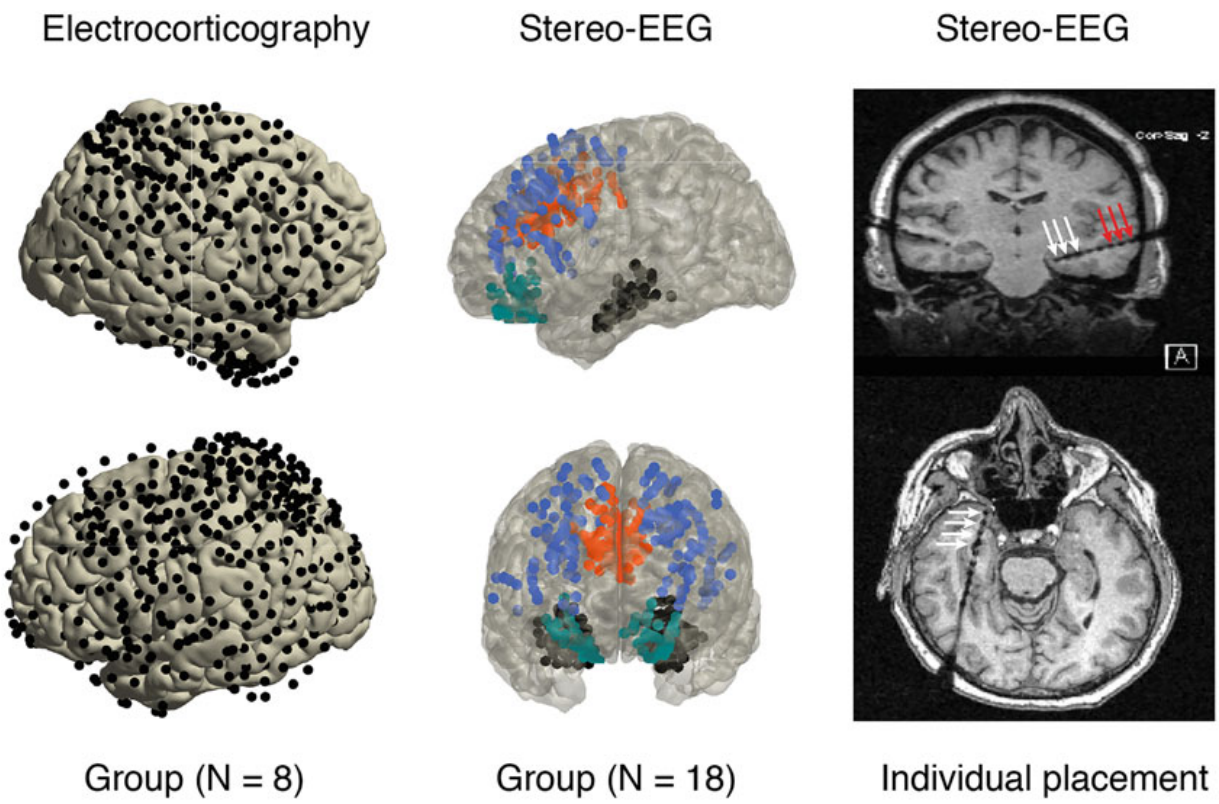

Fig. 2 Intracranial electrode coverage. Typical implantation schemes at group level (first column) either for subdural grid electrodes (each black dot depicts one electrode on a standardized brain) or (center column) stereotactically placed depth electrode (stereo-EEG) in the medial temporal lobe (black dots) or in subregions of the prefrontal cortex (dorsolateral: blue; medial: red; orbitofrontal: green). (Right column) Individual electrode trajectories superimposed on subject-specific MRIs. Black dots depict individual electrode trajectories targeting the hippocampus (white arrows). Note that electrodes are multi-contact probes that transverse through lateral temporal areas (red arrows) or posterior cortex, thus providing extensive coverage. (Panel A adapted from [19]; panel B adapted from [20] under the CC-BY license)

experiments in the context of epilepsy monitoring over the course of 1–2 weeks.

1.2 Advantages of Human Intracranial Electrophysiology

Recording brain activity directly from the cortex offers an exceptional spatial as well as temporal resolution. Typically, when using noninvasive imaging, the skull acts as a low-pass filter, thus attenuating signals greater than ~40 Hz [13]. Intracranial recordings enable the reliable assessment of activity in the range of 70–200 Hz, the so-called high-frequency bands (HFB) or high-gamma (HG) bands [23–25]. Previous studies demonstrated that HFB index local cortical processing [26, 27], which correlates with behavior on a single-trial basis, thus constituting an ideal surrogate marker of local population activity [3]. Note that the physiologic basis of the HFB is not fully understood [28]. In addition, analysis of HFB activity enables pinpointing neural processing within the millisecond range, thus constituting a major advantage over spectral analysis on low-frequency (delta, theta, alpha) activity, where a

single cycle might span over 100 ms [7, 14]. In addition to providing an excellent temporal resolution, spatial resolution is also superior with task- or behavior-relevant activity often being confined to a single electrode contact, which captures activity from only few millimeters of the cortex [29]. Multiple advantages of conducting experiments in humans and not in nonhuman primates (NHP) apply. For instance, NHP need to be trained on a task for a month, while most human participants can readily perform a cognitive experiment and only require a few trials to learn an entirely new task. This does not only speed up experiments but also enables a unique view into the architecture of human flexible behavior. Furthermore, experiments in humans allow exploring uniquely human cognitive functions, such as context-dependent language processing and production.

1.3 The Physiologic Basis of the Intracranial EEG Signal

While intracranial EEG captures "local" signals within a few millimeters of the cortex, most researchers refrain from referring to these signals as "local field potentials," which is reserved for signals as obtained from micro- (~μm) and not macro- (~mm) electrodes [13]. Like scalp EEG, intracranial EEG records a voltage gradient across a predefined reference. Using bipolar referencing between adjacent electrode pairs enables isolating a fairly local signal [30], but to date, it remains speculative what this signal exactly captures [28]. It has been estimated that an intracranial EEG electrode captures ~500,000 neurons [3]. Critically, the signal can be decomposed into low-frequency (e.g., delta, theta, alpha, or beta components, spanning ~1–30 Hz), low-gamma (~30–70 Hz) as well as the high-gamma or high-frequency band signal (HFB, ~70–150 Hz), which provide complementary information. Notably, lower frequencies typically travel further in the cortical tissue, thus constituting summation across a larger population. On the contrary, high-gamma signatures are often local and confined to a single electrode contact (contact length ~2 mm, diameter ~1 mm). However, given that the original signal contains diverse components, it is difficult to disentangle different contributions to the overall signal. In recent years, it has been noticed repeatedly that the ECoG signal contains more (or at least) equivalent information about the behavioral state [31], which implies that it integrates relevant information across the population, potentially also reflecting additional afferent inputs [28].

1.4 Electrode Coverage Determines the Questions That Can Be Asked

Electrode placement is tailored individually according to the clinical hypothesis about the seizure onset zone. While medial temporal epilepsy often requires a bi-hemispheric implantation using a fairly standardized electrode placement scheme, other cases, such as focal dysplasias or cryptogenic epilepsies, require an individually tailored approach. In group studies, this leads to a homogenous electrode placement, which hampers group comparisons and generalizability.

Furthermore, not every patient is well suited to participate in a specific study. For instance, a multitude of studies investigated different aspects of human memory formation [32]. Contemporary theories highlight a key role of the hippocampus [33]. Hence, patients who suffer from medial temporal lobe epilepsy constitute the typical cohort who participates in these experiments. Implantation will sometimes involve interconnected nodes of the limbic system, such as the anterior cingulate cortex or orbitofrontal cortex (cf. Fig. 2), enabling, for instance, studying network interactions between the MTL and the PFC [20, 34, 35]. However, if no additional implantation is required, then the study of subcortical-cortical interactions is often confined to studying medial vs. lateral temporal interactions [36].

Hence, if large-scale neocortical coverage is necessary, e.g., in order to study prefrontal-parietal interactions [19], then a different cohort of patients has to be approached. In this case, most commonly, patients suffer from seizures, which are caused by a cortical dysplasia. Implantation extent here depends on whether MR or PET imaging identified a structural correlate or not. An identifiable lesion typically involves a more tailored sEEG implantation, while no lesion requires implantation of larger subdural grids.

Taken together, the questions that can be asked depend on the underlying pathology, and some network nodes (e.g., occipital lobe) are rarely explored invasively with the main reason being that resection does not constitute an option. For example, in the case of occipital lobe epilepsy, resection would imply a visual field defect spanning an entire hemi field, which oftentimes is less desirable.

1.5 Novel Techniques: Unit Recordings and Related Approaches

Intracranial cognitive neurophysiology is not constrained to only recording macro-signals, but researchers and clinicians developed means to also record local field potentials, multi- as well as single unit recordings. Two approaches have been introduced [37, 38]. Both require implantation of additional hardware and additional recording equipment. The first technique is based on implantation an additional electrode array ("Utah array") in the cortex [39]. Here typically a cortical site is chosen that is part of the expected resection zone. This approach has the advantage that many neurons can be recorded simultaneously, signal quality is generally very good, and a clear anatomical mapping is possible. Disadvantages include that Utah arrays sometimes cause gliosis and cortical scarring; thus, it is only acceptable if the cortex is part of the resection zone and will be removed during the subsequent surgery. Recordings are generally limited to the neocortex. An alternative access that is less invasive is based on the Behnke-Fried microwire electrodes, where an additional wire bundle is inserted through the lumen of the macro-electrodes, only protruding a few millimeters past its exit point at the electrode tip [15, 38]. This approach has

been shown to be safe and reliable, constituting no additional risk for the patient. Sometimes the patients experience some additional discomfort, since connection equipment adds additional weight to the head wrap. Critically, once electrodes are being inserted, the position cannot be changed retrospectively. In the last decade, this approach has yielded a wealth of information about memory systems, mainly recorded from the medial temporal lobe and further illuminating the single unit correlates of human memory.

1.6 The Bigger (Clinical) Picture

It is important to keep in mind that invasive monitoring for seizure onset localization is not a clinical procedure being carried out in isolation but is embedded in a much larger clinical workup and, more importantly, constitutes an important diagnostic test for the patient in his or her often decade-long struggle with epilepsy. At the point when clinicians decide that an invasive monitoring is necessary, most patients suffered from seizures for years and underwent multiple ambulatory EEG recordings as well as noninvasive video-EEG monitoring and several MRI scans. Most likely, they received additional diagnostic tests, such as PET or MEG as well. Critically, these patients already tried and failed more than three anticonvulsant medications (more realistically $\gg 5$) but, despite the medications, which commonly cause side effects, still suffered from seizures.

Furthermore, it is important to keep in mind that after invasive monitoring, their journey is not yet over, but that depending on the outcome of the monitoring, they will either receive brain surgery, where the seizure onset zone can be removed, or they might learn that they suffer from multifocal epilepsy, where resection is not an option, but instead they might elect to receive an implantable neurostimulator, such as vagal nerve stimulation (VNS) [40], thalamic deep brain stimulation (DBS) [41, 42], or a responsive neurostimulator (RNS) [43]. If the patient is a candidate for resective surgery, then chances for seizure freedom are generally good (~80%), while some patients still require additional medications [44, 45]. Hence, when conducting these experiments, it is critical to be aware of the circumstances of the participants, who are in an exceptional situation, which might be stressful, but also provides the perspective of being cured after a sometimes decade-long struggle with disabling seizures.

2 Materials

2.1 Subjects: Patient Recruitment and Exclusion

Intracranial human electrophysiology relies on clinical procedures. Therefore, per definition study participants suffer from a neurological disease. In the context of intracranial EEG monitoring, all patients suffer from seizures. Specifically, these patients suffer from pharmacoresistant epilepsy as outlined above. Importantly,

they are only candidates for electrode implantation if clinicians have the hypothesis that the patients suffer from a focal epilepsy, i.e., that they can identify single regions where the seizures emerge from, which then constitutes the target for curative resective surgery.

Critically, the while aberrant electric activity can spread throughout the whole brain during generalization of a seizure, the seizure onset zone is often mostly confined to very few electrode contacts. Thus, the majority of electrodes capture activity from intact cortical and subcortical areas. During the 1- or 2-week-long monitoring, anticonvulsive drugs are often tapered off to actually provoke seizures, so in some instances the patient is medication-free during the behavioral testing.

2.2 The Hospital Room and Potential Noise Sources

Recording at the bedside is obviously not the optimal environment for cognitive experiments and differs from a typical cognitive neuroscience lab environment in several important ways.

First of all, recordings need to be adjusted to the clinical schedule; hence, interruptions by the medical team are common, but more critically, one deals with an environment where multiple electric devices are running and one might encounter devices that are not commonplace in a research environment, such as intravenous drip lines. This can lead to unexpected artifacts, signal distortions, and shortcomings that need to be accounted for.

In addition, all patients suffer from the same underlying neurological disease, namely, epilepsy, which gives to an entirely different set of artifacts, including focal or generalized seizure activity, interictal spiking activity, or interictal focal slowing [45, 46]. Especially, epileptic discharges (Fig. 3) and slowing can appear outside of the seizure onset zone and to some extent reflect responses to the pathological insults in interconnected network nodes [47]. Likewise, patients may have received anticonvulsant medications, such as benzodiazepines, which introduce their very own EEG signatures, such as enhanced beta activity, in the EEG. Other drugs block sodium channels or glutamatergic signal transmission, thus systematically shifting the balance of excitation and inhibition [48]. Therefore, it is considered best practice when a physician with training in neurophysiology, epileptology, and sleep physiology reviews the raw EEG traces to flag artifactual or pathological activity prior to data processing.

2.3 Recordings Equipment

When conducting research experiments in the clinical environment, researchers typically rely on hardware that is already present. However, in several instances multiple equivalent alternatives are available, each providing distinct advantages and disadvantages.

2.3.1 Electrodes

Electrode placement is solely dictated by clinical needs but is characterized by distinct practices. For instances, stereotactically placed depth electrodes have traditionally been used more often in, e.g.,

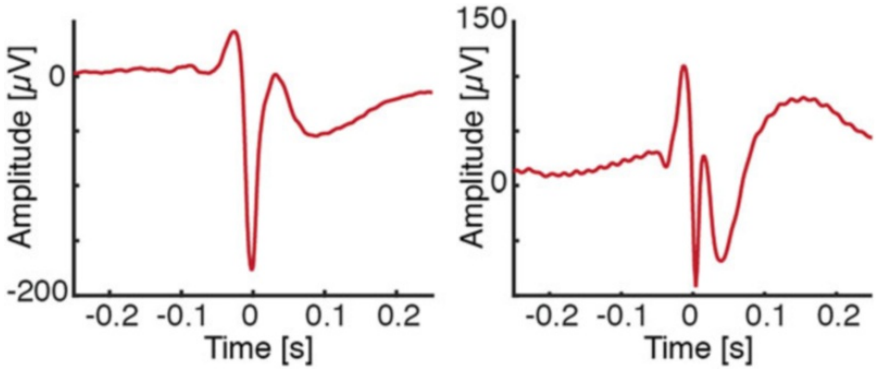

Fig. 3 Waveform shapes of interictal epileptic discharges. Two examples of typical interictal discharges as recorded by intracranial EEG from the medial temporal lobe of two patients. (Adapted from [20] under the CC-BY license)

France, where the seminal work by, e.g., Talairach and Tournoux led to highly individualized implantation schemes [49], based on detailed clinical hypothesis. In contrast, in the USA subdural grid and strip have been favored for decades over depth electrodes [3]. Recently, depth electrodes have been favored on both the USA and Europe mainly given the lower incidence of complications, such as hygromas or bleedings associated with depth electrodes [50].

As a researcher one does have no influence on the electrode type and implantation schemes. However, to increase yield of electrode contacts, one might favor, e.g., depth electrodes with more contacts along the shaft with tighter spacing between individual contacts. Likewise, a typical 8 × 8 grid with 1 cm spacing can be replaced by a high-density 16 × 16 electrodes grid with the same dimensions, thus not increasing the risk of the clinical procedure but leading to a higher yield of available information.

2.3.2 *Amplifiers*

Clinical recordings need to continue during cognitive testing; therefore, researchers face two options. One can either extract the (anonymized) EEG recording from the clinical system after testing or one might elect to split the signal prior to recording. The advantage of using the clinical system is obviously that no additional hardware is necessary. Disadvantages include the typically lower sampling rate of clinical systems. In an attempt to reduce noise, some clinical systems impose additional filters, which are not desirable for research purposes and, for instance, might even restrict analysis of high-frequency band activity. In addition, clinical systems often do not contain multiple trigger channels for time stamping events of interest. If signals are split, then one might circumvent the low sampling rate but might introduce additional noise into the circuit. Here, it is critical to ensure that both amplifiers (clinical and research) rely on the same ground electrode and are synchronized. Ideally, the data can be streamed out of the clinical system at a high

sampling rate in an anonymized format and stored separately from the clinical recording.

2.3.3 Stimulus Presentation and Synchronization with the Recording System

In a hospital room, there is no dedicated equipment for stimulus presentation; hence, typically researchers will place a laptop in front of the subjects for stimulus presentation [51]. While typical research systems exhibit trigger-in and –out options, typically by means of USB or LPT connections, most clinical systems do not exhibit similar dedicated channels for sending digital trigger information. One possible solution to circumvent these issues is the use of analog triggers, which can typically be connected to auxiliary bipolar channels that would typically capture peripheral activity, such as the electrocardiogram (ECG), electromyogram (EMG), or electrooculogram (EOG). For instance, triggering by means of a photodiode that is attached to the corner of the presentation screen or by sending trigger information through the line-out port of the soundcard constitutes two common options to obtain an analog signal that can be recorded on additional channels using appropriate adapters. The main advantage is that an analog trigger signal is recorded that is sampled at the very same sampling frequency as the EEG data, thus enabling temporally precise alignment of behavior and EEG activity. On the contrary, digital triggers as sent through USB might experience a variable delay given system background processes. Furthermore, USB signals constitute a discretely sampled signal, which implicitly groups the triggers into discrete bins.

2.4 Beyond Field Potentials: Recording Single Unit Activity

Clinical recordings are typically sampled at 500–2000 Hz, and electrode montages are tailored to optimally detecting the seizure onset zone. While outside of the scope of this chapter, it is worthwhile to mention that several approaches have been introduced in the past to also record single- and multiunit activity alongside with local field potentials [38]. Here, the clinical macroelectrodes are also equipped with additional microelectrodes. A custom macroelectrode with a hollow lumen is used to insert the microwires. Through this lumen additional high impedance 8 contact wire bundles are inserted, which exit the electrode shaft at the electrode tips and are protruding by approx. 2–5 mm. When recording these signals at 30–40 kHz, it becomes feasible to detect spiking activity and actually sort neuronal activity into putative excitatory and inhibitory cells as well as multiunits. Recording single unit activity is technically challenging and, to date, only carried out at few medical centers in the world. Thus, the interested reader is referred to more specialized literature on this topic as reviewed recently [37].

3 Methods

3.1 Data Extraction and Preprocessing

Depending on whether the data was recorded using a clinical or research amplifier, the EEG signals have to be extracted from a continuous clinical recording and epoch it relative to the experimental triggers. Visual inspection of the data might already feature prominent artifacts, noise, or a relatively clean signal, depending on the reference that was used during recording. Most clinical recordings utilize a monopolar (e.g., scalp EEG electrode or bone screw electrode) as the reference during recording but visualize the data using a common average or bipolar referencing scheme during the monitoring. Hence, in the first step of preprocessing, it is important to determine which referencing was utilized. Oftentimes, switching to an appropriate referencing scheme already attenuates noise or artifacts. Typical amplifiers feature multiple pre-amps (e.g., 8 preamps with 32 channels each); hence, one might even recognize different noise levels between the different preamps, solely based on the covariance (or shared noise) between adjacent recordings channels or channels that were connected to the same preamp. Thus, in order to determine an optimal referencing scheme, it helps to assess the covariance in the signal. When using depth electrodes, it became common practice to utilize bipolar referencing or local Laplacian referencing, where a contact is either referenced across one or two adjacent electrode contacts. Other common referencing practices for depth electrodes include referencing against the closest white matter contact or a distant gray matter contact. A recent comparison favored the Laplacian approach to study local population activity [30]. For subdural grid electrodes, no standard emerged, yet common average referencing (given common noise levels across all preamps), Laplacian, or bipolar is common.

Additional preprocessing steps might include detrending and demeaning the signal, as well as filtering out line noise. It is best practice to also visualize all channels in the frequency domain (semilog or log-log plots) to identify additional peaks in the power spectrum that might point toward additional noise sources of hospital equipment in the signal. High- or low-pass filtering is not a prerequisite and may even constrain subsequent analyses. Downsampling may be used to reduce the computational load; however, one should pay attention to, e.g., the Nyqvist (maximal resolution that can be resolved is half the sampling rate) and Rayleigh frequencies (frequency resolution scales as 1 over the length of the data segment, e.g., a resolution of 0.2 Hz is possible for a 5 s trial, but not for a 3 s trial) when determining sampling rate and epoch length.

3.2 Low-Frequency Activity and the Broadband Signal

Ideally the data is not filtered using a high- or low-pass filter prior to further processing, thus enabling analysis of both broadband as well as band-limited signals. Simply averaging in the time domain yields typical event-related potentials (ERPs), which, however, only vaguely resemble ERPs as observed in scalp EEG. Recently, Kam et al. demonstrated the average across multiple intracranial ERPs from different electrode contacts is necessary to obtain an ERP that resembles an ERP as observed at scalp level [52]. The authors concluded that scalp ERPs reflect the summation of multiple underlying responses.

In the late 1990s, Nathan Crone and colleagues first discovered the high-gamma signal (cf. Fig. 4), which later became essential for cognitive intracranial neurophysiology [23]. Gamma oscillations (~40 Hz) were first described in animals, mostly in response to distinct sensory stimuli [53]. In the early 1990s, they were linked to the "binding-by-synchrony hypothesis" [10], and theoretical work implicated them in several cognitive processes [9, 12]. When recording intracranial EEG data with a sufficient high sampling rate, Crone et al. observed a signal in the 70–150 Hz range that they termed high gamma but, which in contrast to gamma oscillations, was not strictly oscillatory in nature but was broadband with no clear peak in the power spectrum [54, 55]. In 2005, Edwards et al. replicated the seminal finding and showed that the signal in the high-gamma range can directly be linked to behavior on the single-trial and single-electrode level [24]. In the following decade, high gamma (HG, in the meantime also termed high-frequency band activity, HFB) was often conceptualized as reflecting multi-unit spiking activity of the underlying neuronal population [56–59]. More recently, it had been shown that this link is oversimplified and that high gamma does not only reflect strictly local activity [28]. Notably, the high gamma is well suited to describe behavior.

From an analytical point of view, multiple approach to extract high gamma have been described: Band-pass filtering in the, e.g., 70–150 Hz range followed by applying a Hilbert transform has been utilized as well as wavelet or Fourier-based approaches [60, 61]. In order to obtain a cleaner estimate, smoothing or averaging across distinct sub-bands is common. For instance, filtering in 10 Hz wide bins (70–80 Hz, 80–90 Hz, etc.) and averaging the resulting traces are conceptually similar to applying a 10 Hz low-pass filter of the resulting trace [62]. Critically, when baseline correction is performed for every frequency bin separately, then one can also correct for the prominent 1/f drop-off in electrophysiological signals and thus obtain a more balanced high-gamma estimate [19, 26]. A critical aspect inherent to all approaches is that one should define the upper frequency cutoff as a function of the Nyquist frequency. Theoretically, in order to estimate, e.g., a 150 Hz component, one needs at least a sampling rate of

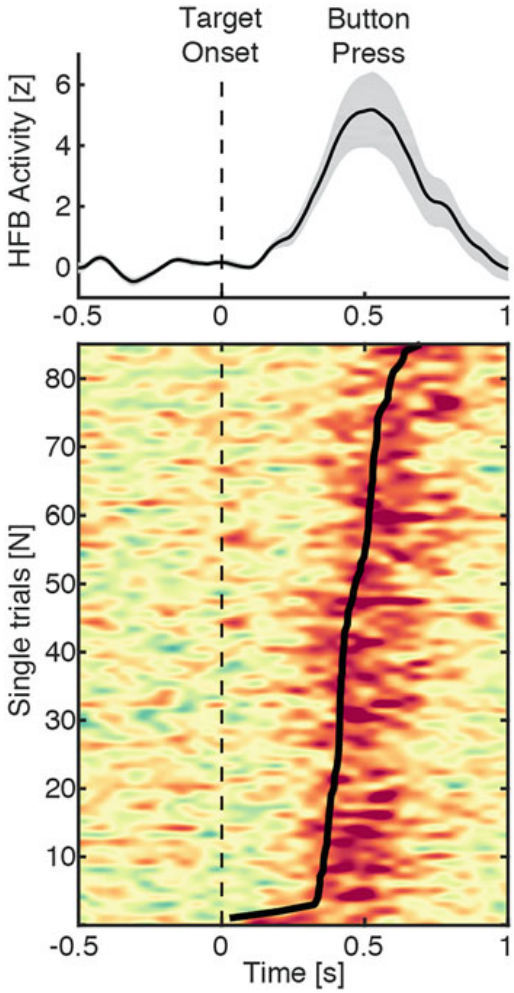

Fig. 4 Single-trial reliability in human intracranial electrophysiology. Recording from the motor cortex of a single subject during a button press. (Upper panel) Grand average across all trial highlights a time-locked increase in high-frequency band (HFB, 70–150 Hz) activity. (Lower) Reaction time sorted, stacked single trials underlying the average with reaction times superimposed (black line). Warmer colors indicate higher HFB activity, which accurately tracks behavior on a single trial basis

300 Hz; practically one should oversample the upper cutoff by at least a factor of three to obtain a clean estimate.

3.3 Localizing Effects in Time and Space

One idiosyncrasy of human intracranial electrophysiology is the heterogeneous electrode placement across subjects. Thus, for researchers with experience in scalp EEG or MEG, who are accustomed to grand averages and group statistics, intracranial EEG might at first appear very different. But even within single subjects, there is substantial heterogeneity among neighboring electrodes, since effects are often highly circumscribed in space and time. Therefore, simply averaging across all contacts in a given region of interest typically abolishes or greatly attenuates the effects.

Therefore, different analytical approaches are necessary. A common technique is defining "active" electrodes first, which has been directly motivated by invasive recordings in rodents or nonhuman primates [19, 23, 63]. Here, activity is assessed relative to baseline when averaged across all conditions [62]. Thus, this approach is agnostic to the experimental manipulation, which then can be assessed based on the subset of selected electrodes, thus further reducing the search space.

3.4 Univariate and Multivariate Analytical Approaches: Correlation in Space and Time

The precise analysis of electrophysiological data typically depends on the question at hand, but here I briefly outline a possible analysis strategy and detail how one can advance from uni- to multivariate analyses while taking into account possible pitfalls for future analysis.

3.4.1 Univariate Analyses

Activity as defined in the time domain can enable researchers to detect electrodes that are modulated during the task as well as enable detecting differences between experimental conditions. Inspecting evoked responses in both the broadband (ERP, biased toward low frequencies) and high-frequency band activity should be best practice to assess the presence of task-related activity as well as identifying sharp transients that could reflect residual artifacts.

Intracranial EEG data can be analyzed in a similar way as local field potentials. Therefore, researchers utilize both time-domain averaging. When applied without filtering, then one can extract event-related potentials. Additional filtering (e.g., in the 70–150 Hz range) and extracting the analytical amplitude can isolate the high-gamma signal, which again can be averaged in the time domain. Different tools are available for spectral analysis, including Fourier-, the wavelet, or the Hilbert transform, which yield comparable results [60]. Spectral analysis can be averaged over time or carried out using a sliding window to obtain a time-frequency representation of activity. The exact analysis depends on the research question at hand, but recently, it became best practices to not separate activity in predefined frequency bands but to employ data-driven approaches to extract oscillatory and broadband signatures [64]. For example, spectral parameterization enables extracting oscillatory features from power spectral densities. The derived parameters (peak frequency and bandwidth) can then be used to extract time-domain activity. Importantly, spectral transformations enable access to both amplitude- and phase-time series. Since high gamma is not an oscillation [25], one typically extracts the range from 70 to 150 Hz, but especially the upper cutoff is sometimes extended up to 200 Hz depending on the sampling rate, resulting in a highly comparable signal given the $1/f$ exponential decay function of the power spectrum.

3.4.2 Multivariate Analyses

Multiple multivariate methods have been applied to electrophysiological data. Most commonly, they can be grouped into connectivity metrics and information-theoretical metrics.

Metrics of Network Connectivity Are Mostly Bivariate Metrics of Interactions

These can be undirected (A and B interact) or directed (A drives B) in nature and can be applied to studying interactions across spatial sites as well as interactions across different temporal scales, also termed cross-frequency coupling. Interaction metrics are typically based on the correlation coefficient (bounded between −1 and 1) or coherence (bounded between 0 and 1), which takes the circular nature of phase-time series into account. Many variants of these two approaches have been introduced (for a review, see [65]) to reduce effects of volume spread in the cortical tissue (attenuate zero phase lag) or account for uneven numbers in trials, which might bias the estimates. While these methods have been used to study interactions across multiple spatial locations, they can also be employed to study cross-frequency interactions, most commonly in the form of cross-frequency coupling where the phase of a slower spectral component modulates the amplitude of the faster component [7, 66–69].

Extracting Task- or Behaviorally Relevant Information from Neuronal Populations Is of Great Interest in Linking Physiology to Behavior [70]

Typical approaches include decoding or classification techniques (e.g., linear discriminant analysis or support vector machines), which are geared toward distinguishing patterns of activity, from either one or multiple electrodes, into predefined groups or classes [70]. In these types of analysis, the algorithm of classifier learns the neural pattern associated with one condition and can predict condition the labels based on previously held-out samples (Fig. 5). Critically, this approach is ideally suited for multivariate representations, which can also be visualized using dynamical systems state-space models [71–73]. This analytical approach quantifies data at different time points as point processes in a highly dimensional space, whose dimensions are constrained by the number of recording locations. Hence, several methods for dimensionality reduction, such as principal component analysis, have been utilized in the past to isolate the most behaviorally relevant dimensions [74, 75]. Representational similarity analysis constitutes a related approach where the correlation and stability of a predefined pattern are assessed across different repetitions [35, 76]. Likewise, Shannon information theoretical metrics (cf. Fig. 5c) have been calculated based on neural data (Fig. 6) to, e.g., infer the shared information between different network nodes [20, 70, 77]. Information theory is becoming a popular tool, since it offers the advantages of being model-free and nonlinear in nature. In summary, electrophysiological data exhibits rich spatiotemporal patterns, and the field is currently employing a variety of methods to extract different aspects of the data. Depending on the research

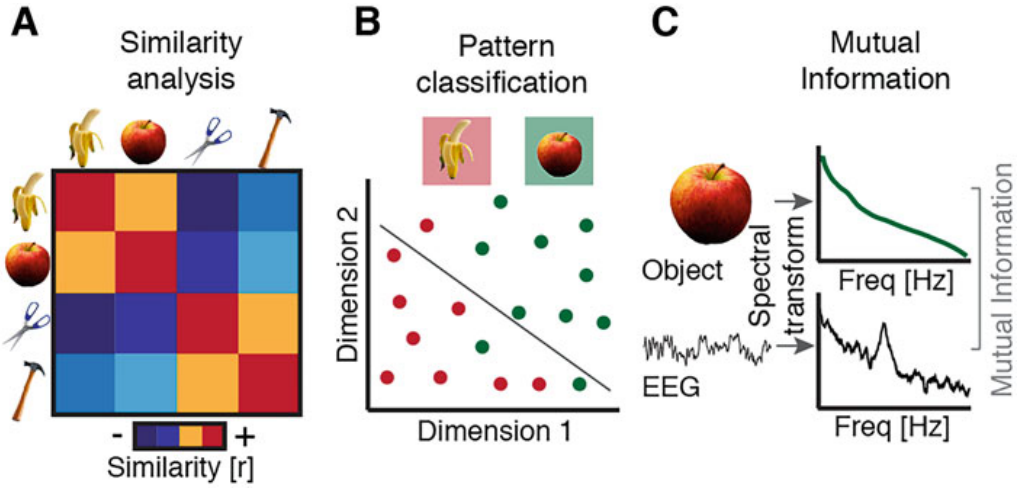

Fig. 5 Multivariate analysis approaches. (**a**) Representational similarity analysis: average correlation coefficients between similar categories across multiple repetitions across multiple channels can indicate how similar different responses are. (**b**) Multivariate discrimination or classification, sometimes also termed decoding. A classifier is trained to distinguish multiple categories based on activity across multiple contacts and time points. Previously held-out samples can then be grouped into the respective categories and metrics of successful classification can be obtained. (**c**) Mutual information framework based on the Shannon entropy enables nonlinear correlations between multiple variables recorded in different modalities, such as behavior and electrophysiology

question, different methods are most applicable with currently only little consensus on best practices.

3.5 From Correlation to Causality: Using Clinical Mapping to Inform Cognitive Experiments

The clinical setting offers several opportunities to further inform cognitive experiments. One of these opportunities is cortical mapping by means of electrical stimulation [78]. Here, clinicians stimulate distinct electrode contacts to infer whether a given electrode is implicated in a distinct cortical function. Typically, only "eloquent" cortex is being mapped, i.e., it is being determined which electrodes cover language- or motor-related regions to circumvent postsurgical functional impairments. However, while these mappings are being carried out routinely, one can already infer cognitive function from the stimulation protocols [79, 80] and, subsequently, adapt experimental protocols accordingly. In addition, several experiments also stimulated cortical areas during cognitive performance [81, 82].

3.6 Available Resources

Several open access tools are available for the analysis of intracranial human electrophysiology data, which either facilitate electrode localization [83–86] and reconstruction of individual implantation schemes or provide a more integrated analysis pipeline [87], based on the popular fieldtrip toolbox [88]. Recently, a standard for data sharing has been introduced [89] with several open access datasets now being available [90, 91].

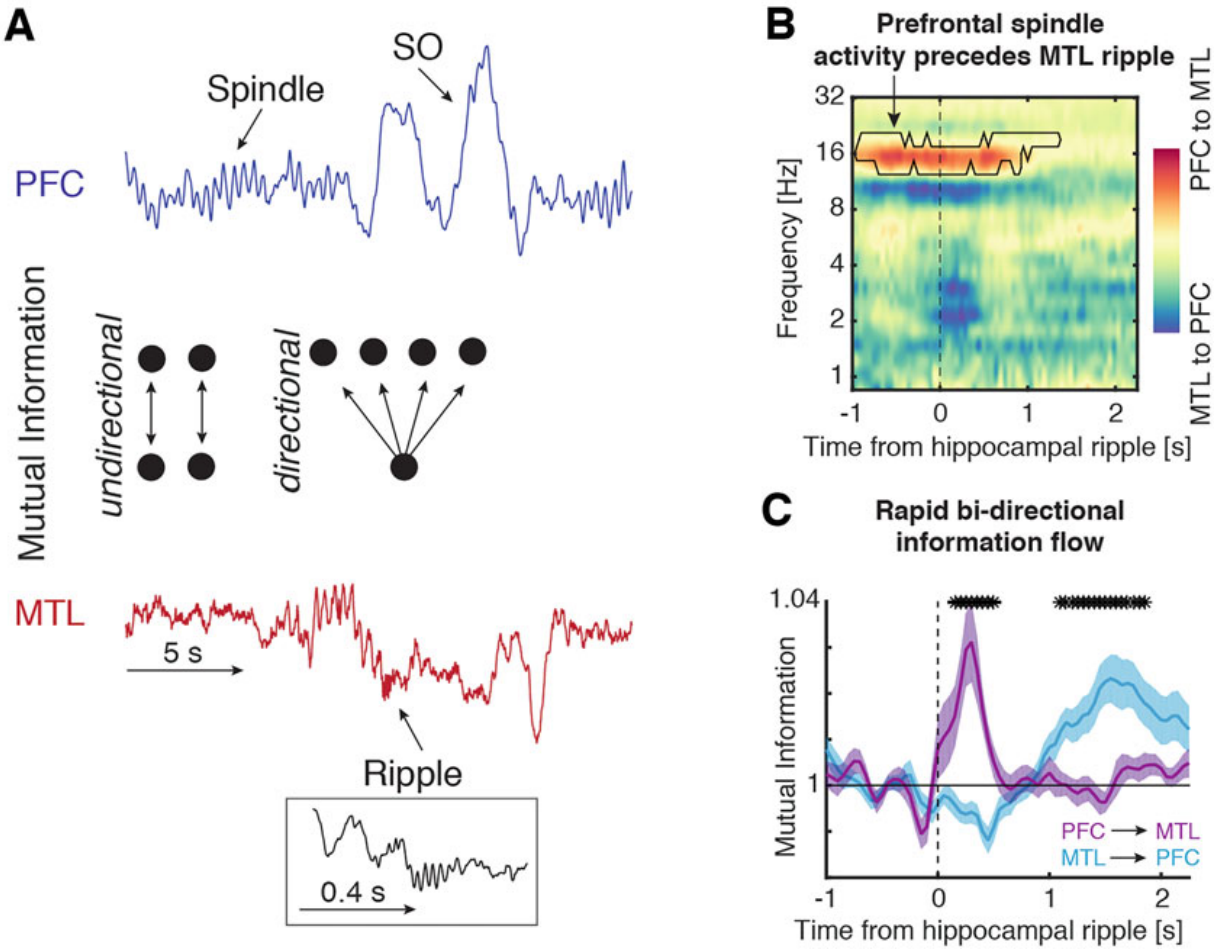

Fig. 6 Information-theoretical analyses on intracranial EEG data. (**a**) Simultaneous recordings from the prefrontal cortex (PFC) and medial temporal lobe (MTL) indicate the presence of multiple different oscillations: slow oscillations (SO, ~1 Hz), spindle oscillations (12–16 Hz), and ripple oscillations (~100 Hz). (**b**) Frequency-specific directed information flow analyses reveal a unidirectional influence of cortical spindles on hippocampal activity. (**c**) Bidirectional interactions become evident in the broadband signals when considering time lags. (Adapted with permission from [20] under the CC-BY license)

4 Notes

4.1 Being a Cognitive Neuroscientist on the Epilepsy Monitoring Unit

The first rule when working with patients is that patient well-being and will must come first. Therefore, it is of utmost importance to highlight that participation in research is voluntary but does not benefit their treatment. Likewise, refusal to participate in research does not abridge their clinical care. The second most important rule is to let the techs and doctors do their job and stay out of their way. In the case of epilepsy monitoring, this can be taken figuratively: Try not to occlude the wall-mounted camera when setting up experiments, since obtaining simultaneous EEG and video monitoring is critical to determine the semiology and origin of the epilepsy. In addition, avoiding the early morning or afternoon ward rounds typically leaves plenty of time to approach the patients.

Notably, by the end of a monitoring week, it is not uncommon that researchers spent more time with the patient than their doctors, and patients often appreciate a familiar face that is not pressed for time. Obviously, researchers are in no position to discuss clinical treatment or long-term outcome but obviously can provide perspective on the link of cognitive and clinical neurophysiology. Oftentimes it is being appreciated that someone can provide additional perspective into, e.g., memory systems if the patient just engaged in a memory task. From my experience, I found it valuable to provide one or two articles that are written for a general audience when patients express their interest [92, 93].

4.2 What Happens if the Patient Has a Seizure?

Clinicians want their patients to seize in the monitoring unit in order to localize the seizure onset zone. However, they do not want to provoke generalized tonic-clonic seizures, and they want to avoid that the patients enter a not self-limiting seizure (also termed a status epilepticus, i.e., an ongoing seizure which can last for days). To localize the seizure onset zone, clinicians need to observe where the seizure starts and how it spreads in the EEG, but once it generalizes to all sensors, it provides only very little additional clinical information. On the contrary, too many generalized seizures exhaust the patient and are detrimental in the long run. In addition, clinicians require a video of the seizures to help them localize based on the patients' behavior (semiology) but also determine if the observed seizure corresponds to their habitual presentation. To maximize the likelihood to observe a seizure, patients are typically tapered off their medications, and so it is not unlikely that the patient will experience a seizure when the researchers are in the room. In this case, the researcher should immediately inform the EEG techs (there is an emergency button), abort their experiment and remove their equipment (laptops, cables, etc.), and leave the room. One should again pay attention to not block the way of nurses, techs, and doctors (who will likely rush into the room) and not occlude the camera. Depending on the severity, the patient can be approached for another experiment after 2 or 3 h, but some prefer to get a good night of sleep prior to the next experiment.

4.3 Ethics of Human Intracranial Neurophysiology

When interacting with patients, special ethical considerations apply in comparison to patients involving healthy participants [94]. It is important to keep in mind that these patients undergo a medical procedure, and participation in research is voluntary and does not benefit their treatment. Especially, when the clinician is also the principal investigator, patients might feel inclined to participate; hence, it is of utmost importance to highlight that their decision is voluntary and can always be revoked without compromising their medical care. On the contrary, if collaborators, who are not part of the medical team, carry out research, it is important to not elicit any unwarranted hopes about what the research can contribute to their

medical care. It is typically best practice to highlight that the research does not benefit their clinical care but that one is hoping to gain novel insights into the underlying processes without advantages for the research subject who volunteer their time. There is no consensus whether participants should be reimbursed for their participation. While this potentially could generate the wrong incentives, some groups provide gift certificates to express their gratitude.

A challenge for ethical protocols is the implantation of additional hardware, such as single unit probes, which are not necessary for the clinical assessment and might potentially bear an additional risk for the patients [38]. In this case, it is critical to minimize patient risk and define a research question where the potential outcome clearly outweighs its risks.

4.4 Artifacts in Electrophysiological and Behavioral Data

A hospital room is less than ideal to conduct experiments, both from a technical and from procedural viewpoints. Several staff members, i.e., nurses, nursing assistance, service workers who deliver food, healthcare chaplaincy, EEG techs, resident, and attending epileptologist or the neurosurgeon who implanted the electrodes, might enter the room at any point during the day to check "on their patient." Therefore, it is critical to be considerate and tailor experiments to clinical circumstances, i.e., limit the duration of a given experiment to approx. 30 min and communicate clearly and regularly with the staff. This however still means that the majority of experiments might get disturbed; hence, it is crucial to take notes to later account for inconsistencies or oddities in behavioral log files or electrophysiological recordings. Other sources of behavioral variability are obviously time of day (remember sleep is often suboptimal in hospitals), time from last seizure, presence or absence of relatives, etc.

However, more severe problems are artifacts in the electrophysiological recordings. A hospital room is not an electrically shielded chamber, but at any point in time if multiple electric devices are active, line noise is common, and some artifacts are difficult to trace. For instance, intravenous drip artifacts or bed pumps that are turned on periodically are occasionally observed in the signal. If one can identify a distinct source, it may be briefly turned off after consultation with staff members. Research equipment should be battery powered. Most artifacts are readily observable in time-domain data, but some more subtle artifacts (i.e., low-amplitude electric artifact every time the subject presses a key when the computer is attached to the socket) might only show up in trial-averaged or spectrally decomposed data, thus requiring preprocessing.

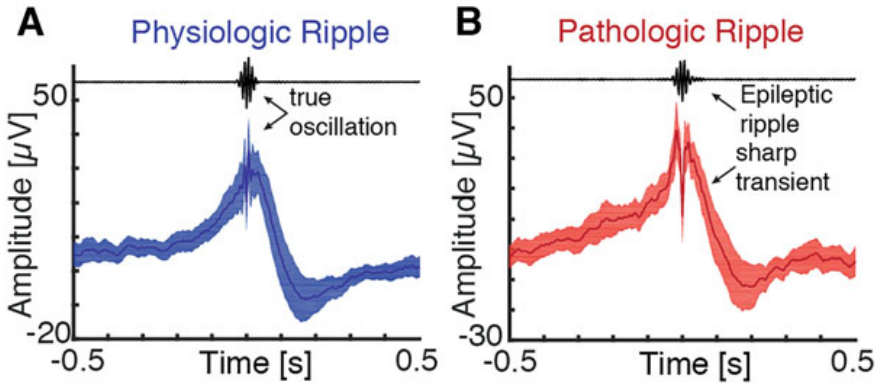

Fig. 7 Physiologic and pathological activity share common spectral features. (**a**) Ripple activity in the hippocampus can be physiologic in nature and is nested in a ~3 Hz sharp wave (blue). After band-pass filtering (black), the signal is rendered perfectly sinusoidal. Ripples have been implicated in systems level memory consolidation [96]. (**b**) In the epileptic brain, similar signatures may emerge at similar time points (esp. after band-pass filtering). In the time-domain (red) signal of the raw data, it is evident that an epileptic sharp transient was present. (Adapted with permission from [20] under the CC-BY license)

4.5 Distinguishing Physiologic and Pathologic Activity

All patients suffer from epileptic activity, which is not necessarily constrained to the seizure onset zone and might potentially also affect interconnected network nodes. Hence, epileptic or pathologic activity could potentially also be observed outside of the seizure onset zone. Unfortunately, epileptic activity does not exhibit a stereotypical waveform shape, and ictal activity might be interleaved with interictal activity, which itself can present as pathological slowing or intermittent sharp discharges (Fig. 7). To date, automatic algorithms failed to capture the full extent of pathologic activity, thus making it best practice in clinical care that an epileptologist visually inspects all traces for epileptic activity [95]. In the research context, this is not always possible but should be gold standard wherever possible. In instances where this is not possible, algorithms that detect sharp transients could be employed, and high-amplitude transients should be excluded, which most commonly do not constitute true physiologic activity.

4.6 Exceptional Spatiotemporal Resolution: Finding Consistent Effects on the Group Level Despite Heterogenous Intracranial Electrode Placements

The major advantage of intracranial recordings is also a limitation in certain circumstances. Specifically, the anatomy and pathology are unique for every subject, thus requiring an individualized electrode implantation scheme. In addition, higher-order association cortex, such as the prefrontal cortex, is not as hierarchically organized as, for instance, primary sensory areas, which feature a clear and reproducible functional organization (e.g., retinotopy in V1). Now, intracranial EEG electrodes record a very local signal that can look vastly different at the next electrode a few millimeters away. Therefore, even averaging within large region of interests of a single participant can greatly diminish and even abolish effects that are

present at a single electrode. Several approaches have been employed to reduce the impact of this heterogeneity: preselecting electrodes based on condition averages as outline above is one option [62, 63, 97]; alternatively one could employ functional localizers [98]. Analytically, dimensionality reduction methods [74] and state-space models [71] enable extraction of the most salient trajectories in the neural data. Likewise, decoding algorithms extract relevant patterns from the data and thereby minimize the impact of non-informative electrodes [70].

4.7 Defining a Good Question for Intracranial Neurophysiology

The very circumscribed effects and the exploration of only few selected regions in every given patient require a specific tailoring of the research question to the implantation scheme, thus requiring a specific hypothesis that should be answered. For instance, fMRI and M/EEG provide whole-head coverage and signal characteristics (i.e., spatial blurring) that are more amendable for exploratory group analyses. The heterogeneous nature of intracranial EEG is less well suited for this kind of data-driven approach. On the contrary, iEEG is an ideal tool to address a specific hypothesis, which emerged from noninvasive imaging. Also in light of limited time per experiment in comparison to noninvasive imaging, the experimental contrasts should maximize the behavioral effects in order to detect neurophysiological correlates.

Intracranial neurophysiology is also well suited for questions that cannot be addressed in nonhuman primates, such as the neurophysiological implementation of speech [99–101], emotions [34], or human communication and interactions. In the same vein, several recent approaches employed a comparative electrophysiology approach [19, 102], where invasive data, which is recorded at the same resolution, was used to reveal that organizing principles in humans and nonhuman primates in the attention network were well preserved.

5 Conclusions

In summary, here I reviewed recent trends in using intracranial recordings in epilepsy patients to illuminate the neurophysiological basis of higher cognitive functions in humans [3]. Critically, this line of research does not constitute a one-way street but provides the unique opportunity for true two-way translational research. Recent applications include speech prosthesis or brain-computer interfaces. Likewise, this line of research contributes to refinement of closed-loop brain stimulation technologies that collectively have the goal to electrically disrupt seizure activity. At the intersection of the clinical and cognitive neurosciences, intracranial human electrophysiology provides the ideal bridge to translate findings as obtained invasively in nonhuman primates or rodents to

noninvasive imaging findings. In the next decade, this approach will constitute an important tool to understand the organizing principles of human cognition.

Acknowledgments

This work was supported by the German Research Foundation (DFG, HE 8329/2-1), the Hertie Foundation (Hertie Network of Excellence in Clinical Neuroscience), and the Baden-Württemberg Foundation.

References

1. D'Esposito M (2010) Why methods matter in the study of the biological basis of the mind: a behavioral neurologist's perspective. In: Reuter-Lorenz P, Baynes K, Mangun GR, Phelps EA (eds) The Cognitive neuroscience of mind: a tribute to Michael Gazzaniga. MIT Press, Cambridge, London, pp 203–221
2. Szczepanski SM, Knight RT (2014) Insights into human behavior from lesions to the prefrontal cortex. Neuron 83:1002–1018
3. Parvizi J, Kastner S (2018) Promises and limitations of human intracranial electroencephalography. Nat Neurosci 21:474–483
4. Corkin S (2002) What's new with the amnesic patient H.M.? Nat Rev Neurosci 3:153
5. Squire LR (2009) The legacy of patient H.M. for neuroscience. Neuron 61:6–9
6. Vaidya AR, Pujara MS, Petrides M et al (2019) Lesion studies in contemporary neuroscience. Trends Cogn Sci (Regul Ed) 23: 653–671
7. Helfrich RF, Knight RT (2016) Oscillatory dynamics of prefrontal cognitive control. Trends Cogn Sci (Regul Ed) 20:916–930
8. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202
9. Engel AK, Fries P, Singer W (2001) Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2: 704–716
10. Singer W, Gray CM (1995) Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 18:555–586
11. Buzsaki G (2006) Rhythms of the brain. Oxford University Press
12. Varela F, Lachaux JP, Rodriguez E et al (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2:229–239
13. Buzsáki G, Anastassiou CA, Koch C (2012) The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. Nat Rev Neurosci 13:407–420
14. Pesaran B, Vinck M, Einevoll GT et al (2018) Investigating large-scale brain dynamics using field potential recordings: analysis and interpretation. Nat Neurosci 21:903–919
15. Engel AK, Moll CKE, Fried I et al (2005) Invasive recordings from the human brain: clinical insights and beyond. Nat Rev Neurosci 6:35–47
16. Bronstein JM, Tagliati M, Alterman RL et al (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 68:165–165
17. Weiss D, Klotz R, Govindan RB et al (2015) Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease. Brain 138:679–693
18. Zavala BA, Jang AI, Zaghloul KA (2017) Human subthalamic nucleus activity during non-motor decision making. eLife 6. https://elifesciences.org/articles/31007
19. Helfrich RF, Fiebelkorn IC, Szczepanski SM et al (2018) Neural mechanisms of sustained attention are rhythmic. Neuron 99:854–865.e5
20. Helfrich RF, Lendner JD, Mander BA et al (2019) Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans. Nat Commun 10:3572
21. Mayberg HS, Lozano AM, Voon V et al (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45: 651–660
22. van Westen M, Rietveld E, Figee M et al (2015) Clinical outcome and mechanisms of deep brain stimulation for obsessive-

compulsive disorder. Curr Behav Neurosci Rep 2:41–48
23. Crone NE, Miglioretti DL, Gordon B et al (1998) Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. Brain 121(Pt 12): 2301–2315
24. Edwards E, Soltani M, Deouell LY et al (2005) High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. J Neurophysiol 94: 4269–4280
25. Ray S, Maunsell JHR (2011) Different origins of gamma rhythm and high-gamma activity in macaque visual cortex. PLoS Biol 9: e1000610
26. Flinker A, Korzeniewska A, Shestyuk AY et al (2015) Redefining the role of Broca's area in speech. Proc Natl Acad Sci U S A 112:2871–2875
27. Dubey A, Ray S (2019) Cortical electrocorticogram (ECoG) is a local signal. J Neurosci 39:4299–4311
28. 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
29. Holdgraf CR, de Heer W, Pasley B et al (2016) Rapid tuning shifts in human auditory cortex enhance speech intelligibility. Nat Commun 7:13654
30. Li G, Jiang S, Paraskevopoulou SE et al (2018) Optimal referencing for stereo-electroencephalographic (SEEG) recordings. NeuroImage 183:327–335
31. Kanth ST, Ray S (2020) Electrocorticogram (ECoG) is highly informative in primate visual cortex. J Neurosci 40:2430–2444
32. Johnson EL, Knight RT (2015) Intracranial recordings and human memory. Curr Opin Neurobiol 31:18–25
33. Eichenbaum H (2017) Prefrontal-hippocampal interactions in episodic memory. Nat Rev Neurosci 18:547–558
34. Zheng J, Anderson KL, Leal SL et al (2017) Amygdala-hippocampal dynamics during salient information processing. Nat Commun 8:14413
35. Zhang H, Fell J, Axmacher N (2018) Electrophysiological mechanisms of human memory consolidation. Nat Commun 9:4103
36. Vaz AP, Inati SK, Brunel N et al (2019) Coupled ripple oscillations between the medial temporal lobe and neocortex retrieve human memory. Science 363:975–978
37. Rutishauser U (2019) Testing models of human declarative memory at the single-neuron level. Trend Cog Sci 23:510–524
38. Fried I, Rutishauser U, Cerf M et al (2014) Single neuron studies of the human brain: probing cognition. MIT Press
39. Cash SS, Hochberg LR (2015) The emergence of single neurons in clinical neurology. Neuron 86:79–91
40. Groves DA, Brown VJ (2005) Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 29:493–500
41. Boëx C, Seeck M, Vulliémoz S et al (2011) Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure 20:485–490
42. Miatton M, Van Roost D, Thiery E et al (2011) The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy Behav 22:759–764
43. Carrette S, Boon P, Sprengers M et al (2015) Responsive neurostimulation in epilepsy. Expert Rev Neurother 15:1445–1454
44. Noachtar S, Borggraefe I (2009) Epilepsy surgery: a critical review. Epilepsy Behav 15:66–72
45. Devinsky O, Vezzani A, O'Brien TJ et al (2018) Epilepsy 4:1–24
46. Rao VR, Lowenstein DH (2015) Epilepsy. Curr Biol 25:R742–R746
47. 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
48. Meisel C (2020) Antiepileptic drugs induce subcritical dynamics in human cortical networks. Proc Natl Acad Sci U S A 117: 11118–11125
49. Talairach J, Bancaud J, Bonis A et al (1962) Functional stereotaxic exploration of epilepsy. Confin Neruol 22:328–331
50. Tandon N, Tong BA, Friedman ER et al (2019) Analysis of morbidity and outcomes associated with use of subdural grids vs stereo-electroencephalography in patients with intractable epilepsy. JAMA Neurol 76:672–681
51. Schalk G, McFarland DJ, Hinterberger T et al (2004) BCI2000: a general-purpose brain-computer interface (BCI) system. IEEE Trans Biomed Eng 51:1034–1043
52. Kam JWY, Szczepanski SM, Canolty RT, et al (2016) Differential sources for 2 neural signatures of target detection: an electrocorticography study. Cereb Cortex 28(1):9–20

53. Gray CM, König P, Engel AK et al (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338:334–337
54. Miller KJ, Sorensen LB, Ojemann JG et al (2009) Power-law scaling in the brain surface electric potential. PLoS Comput Biol 5: e1000609
55. Miller KJ, Zanos S, Fetz EE et al (2009) Decoupling the cortical power spectrum reveals real-time representation of individual finger movements in humans. J Neurosci 29: 3132–3137
56. Canolty RT, Edwards E, Dalal SS et al (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science 313: 1626–1628
57. Brunet N, Vinck M, Bosman CA et al (2014) Gamma or no gamma, that is the question. Trends Cogn Sci (Regul Ed) 18:507–509
58. Hermes D, Miller KJ, Wandell BA et al (2015) Gamma oscillations in visual cortex: the stimulus matters. Trends Cogn Sci (Regul Ed) 19: 57–58
59. Ray S, Maunsell JHR (2015) Do gamma oscillations play a role in cerebral cortex? Trends Cogn Sci (Regul Ed) 19:78–85
60. Bruns A (2004) Fourier-, Hilbert- and wavelet-based signal analysis: are they really different approaches? J Neurosci Methods 137:321–332
61. Foster BL, Rangarajan V, Shirer WR et al (2015) Intrinsic and task-dependent coupling of neuronal population activity in human parietal cortex. Neuron 86:578–590
62. Haller M, Case J, Crone NE et al (2018) Persistent neuronal activity in human prefrontal cortex links perception and action. Nat Human Behav 2:80–91
63. Voytek B, Kayser AS, Badre D et al (2015) Oscillatory dynamics coordinating human frontal networks in support of goal maintenance. Nat Neurosci 18:1318–1324
64. Donoghue T, Haller M, Peterson EJ et al (2020) Parameterizing neural power spectra into periodic and aperiodic components. Nat Neurosci 23:1655–1665
65. Bastos AM, Schoffelen J-M (2015) A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. Front Syst Neurosci 9:175
66. Aru J, Aru J, Priesemann V et al (2015) Untangling cross-frequency coupling in neuroscience. Curr Opin Neurobiol 31:51–61
67. Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. Trends Cogn Sci (Regul Ed) 14:506–515
68. Gerber EM, Sadeh B, Ward A et al (2016) Non-sinusoidal activity can produce cross-frequency coupling in cortical signals in the absence of functional interaction between neural sources. PLoS One 11:e0167351
69. Tort ABL, Kramer MA, Thorn C et al (2008) Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. Proc Natl Acad Sci U S A 105: 20517–20522
70. Quian Quiroga R, Panzeri S (2009) Extracting information from neuronal populations: information theory and decoding approaches. Nat Rev Neurosci 10:173–185
71. Vyas S, Golub MD, Sussillo D et al (2020) Computation through neural population dynamics. Annu Rev Neurosci 43:249–275
72. Stokes MG, Kusunoki M, Sigala N et al (2013) Dynamic coding for cognitive control in prefrontal cortex. Neuron 78:364–375
73. Stokes MG (2015) "Activity-silent" working memory in prefrontal cortex: a dynamic coding framework. Trends Cogn Sci (Regul Ed) 19:394–405
74. Cunningham JP, Byron MY (2014) Dimensionality reduction for large-scale neural recordings. Nat Neurosci 17:1500–1509
75. Kobak D, Brendel W, Constantinidis C et al (2016) Demixed principal component analysis of neural population data. eLife 5:e10989
76. Kriegeskorte N, Mur M, Bandettini P (2008) Representational similarity analysis - connecting the branches of systems neuroscience. Front Syst Neurosci 2:4
77. Timme NM, Lapish C (2018) A tutorial for information theory in neuroscience. eNeuro 11:5(3):ENEURO.0052-18.2018. doi: 10.1523/ENEURO.0052-18.2018. PMID: 30211307; PMCID: PMC6131830
78. Borchers S, Himmelbach M, Logothetis N et al (2012) Direct electrical stimulation of human cortex—the gold standard for mapping brain functions? Nat Rev Neurosci 13:63
79. Foster BL, Parvizi J (2017) Direct cortical stimulation of human posteromedial cortex. Neurology 88:685–691
80. Fox KCR, Shi L, Baek S et al (2020) Intrinsic network architecture predicts the effects elicited by intracranial electrical stimulation of the human brain. Nat Hum Behav 4:1039–1052

81. Suthana N, Haneef Z, Stern J et al (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 366:502–510
82. Titiz AS, Hill MRH, Mankin EA et al (2017) Theta-burst microstimulation in the human entorhinal area improves memory specificity. eLife 6:e29515
83. Hermes D, Miller KJ, Noordmans HJ et al (2010) Automated electrocorticographic electrode localization on individually rendered brain surfaces. J Neurosci Methods 185:293–298
84. Groppe DM, Bickel S, Dykstra AR et al (2017) iELVis: an open source MATLAB toolbox for localizing and visualizing human intracranial electrode data. J Neurosci Methods 281:40–48
85. Blenkmann AO, Phillips HN, Princich JP et al (2017) iElectrodes: a comprehensive open-source toolbox for depth and subdural grid electrode localization. Front Neuroinform 11:14
86. Dykstra AR, Chan AM, Quinn BT et al (2012) Individualized localization and cortical surface-based registration of intracranial electrodes. NeuroImage 59:3563–3570
87. Stolk A, Griffin S, van der Meij R et al (2018) Integrated analysis of anatomical and electrophysiological human intracranial data. Nat Protoc 13(7):1699–1723
88. Oostenveld R, Fries P, Maris E et al (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869
89. Holdgraf C, Appelhoff S, Bickel S et al (2019) iEEG-BIDS, extending the Brain Imaging Data Structure specification to human intracranial electrophysiology. Sci Data 6:102
90. Faraut MC, Carlson AA, Sullivan S et al (2018) Dataset of human medial temporal lobe single neuron activity during declarative memory encoding and recognition. Sci Data 5:180010
91. Boran E, Fedele T, Steiner A et al (2020) Dataset of human medial temporal lobe neurons, scalp and intracranial EEG during a verbal working memory task. Sci Data 7:1–7
92. Johnson EL, Helfrich RF (2016) How brain cells make memories. Front Young Minds 4
93. Ram B, Helfrich RF Waves of percetion. Front Young Minds 5
94. Chiong W, Leonard MK, Chang EF (2018) Neurosurgical patients as human research subjects: ethical considerations in intracranial electrophysiology research. Neurosurgery 83: 29–37
95. Ammanuel SG, Kleen JK, Leonard MK et al (2020) Interictal epileptiform discharges and the quality of human intracranial neurophysiology data. Front Hum Neurosci 14:44
96. Buzsáki G (2015) Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 25: 1073–1188
97. Szczepanski SM, Crone NE, Kuperman RA et al (2014) Dynamic changes in phase-amplitude coupling facilitate spatial attention control in fronto-parietal cortex. PLoS Biol 12:e1001936
98. Saxe R, Brett M, Kanwisher N (2006) Divide and conquer: a defense of functional localizers. NeuroImage 30:1088–1096
99. Anumanchipalli GK, Chartier J, Chang EF (2019) Speech synthesis from neural decoding of spoken sentences. Nature 568:493–498
100. Pasley BN, David SV, Mesgarani N et al (2012) Reconstructing speech from human auditory cortex. PLoS Biol 10:e1001251
101. Oganian Y, Chang EF (2018) A speech envelope landmark for syllable encoding in human superior temporal gyrus. Sci Adv 5:388280
102. Fiebelkorn IC, Pinsk MA, Kastner S (2018) A dynamic interplay within the Frontoparietal network underlies rhythmic spatial attention. Neuron 99:842–853.e8