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Promises and limitations of human intracranial electroencephalography

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Intracranial electroencephalography (iEEG), also known as electrocorticography when using subdural grid electrodes or stereotactic EEG when using depth electrodes, is blossoming in various fields of human neuroscience. In this article, we highlight the potentials of iEEG in exploring functions of the human brain while also considering its limitations. The iEEG signal provides anatomically precise information about the selective engagement of neuronal populations at the millimeter scale and the temporal dynamics of their engagement at the millisecond scale. If several nodes of a given network are monitored simultaneously with implanted electrodes, the iEEG signals can also reveal information about functional interactions within and across networks during different stages of neural computation. As such, human iEEG can complement other methods of neuroscience beyond simply replicating what is already known, or can be known, from noninvasive lines of research in humans or from invasive recordings in nonhuman mammalian brains.

Inspired by the reports of electrical signals recorded directly from the brains of rabbits, cats, dogs and monkeys[1,2], Hans Berger (1873–1941) performed the first recordings of human electrical brain activity with electrodes attached to the scalp surface in patients with skull bone removed or healthy individuals with little hair (for example, bald men)[3]. He called his method electroencephalography, nowadays referred to as scalp EEG. When the EEG recordings are obtained with intracranial electrodes, we refer to it as intracranial EEG (iEEG). It may be either in the form of electrocorticography (ECoG) using strips or grids of electrodes implanted in the subdural space or stereotaxic EEG (sEEG) using wires of electrodes penetrating the brain and targeting predefined deeper sites (for example, hippocampus) without open craniotomy (Fig. 1).

Today, combined with neuroimaging and computational tools, human iEEG has become increasingly more amenable to scientific explorations, and its popularity among neuroscientists is on a steady rise (Fig. 2). As such, human iEEG provides the opportunity to confirm and extend cognitive neuroscience research from other modalities. This review is intended to provide an overview of the promise and limitations of human iEEG for complementing other methods of scientific inquiry in cognitive neuroscience.

Clinical rationale for invasive recordings with subdural or depth electrodes

Most human iEEG studies are conducted in patients with epilepsy. About 1% of the world's population has epilepsy, and approximately one-third of these patients have medication-resistant epilepsy[4]. These patients experience breakthrough seizures while on medications. Those with focal epilepsy can gain freedom from seizures if the source of their seizures can be identified and surgically removed[5]. iEEG monitoring is often needed to identify the precise origin of seizures. Before the patient is implanted for invasive monitoring, clinicians use noninvasive diagnostic tools to form a hypothesis about the approximate origin of patient's seizures. Scalp EEG recordings are used to determine (if possible) the laterality and approximate lobar origin of seizures; structural brain MRI is used to detect anatomical abnormalities that are often associated with seizures; brain positron emission tomography (PET) with fluorodeoxyglucose is used to determine focal hypometabolic tissue; and neuropsychological evaluations are used to detect lateralizing cognitive deficits (for example, verbal memory deficits associated with seizures involving the left medial temporal lobe). Invasive implantation of electrodes is planned if clinicians have a high confidence that the patient suffers from focal epilepsy, though the exact focus is often not known.

If the laterality of seizures is unknown, or if the seizure onset zone is hypothesized to be in the deeper structures of the brain (such as the hippocampus or the insula), the sEEG approach is preferred. In these cases, each patient is often implanted with 5–15 depth electrodes, unilaterally or bilaterally (each consisting of 10–14 recording contacts). These electrodes often target the limbic structures (medial temporal lobes, cingulate, orbitofrontal and insular regions), but since they penetrate the brain from its lateral surface, they also offer recordings from the lateral sites as well (Fig. 1). If the preoperative evidence is strong enough to suggest laterality and lobar origin of seizures, but the extent of the epileptic tissue is unknown, the ECoG method with subdural electrodes is preferred. In these cases, grids and strips of electrodes are placed over the suspected lobe to confirm the precise extent of the pathologic brain tissue and to delineate the safe boundaries of cortical resection.

Because clinical needs dictate the pattern and type of implantation in each patient, and given that most patients with epilepsy have limbic or frontal lobe seizures, most of the implanted electrodes will cover these regions of the brain. Recordings from occipital and parietal lobes are by comparison quite rare. In a study of 2,200 patients with epilepsy, clinical noninvasive data suggested focal origin in approximately 62%. In this subgroup of patients, about 66% were suspected to have temporal lobe epilepsy while 24% were suspected to have frontal lobe, 3% occipital lobe, 2% parietal lobe and 3% multilobar epilepsies[6]. The high percentage of cases of suspected temporal lobe epilepsy explains why most human iEEG reports are from the temporal or frontal lobes.

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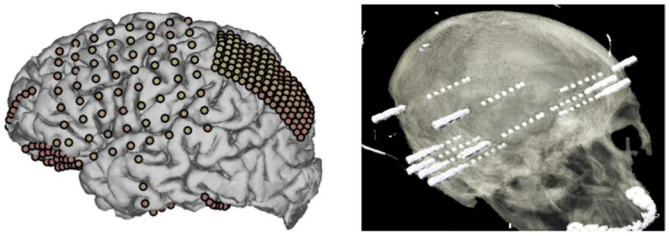


Fig. 1 | Two methods of intracranial EEG: electrocorticography and stereo-EEG. While grids and strips of subdural electrodes (left) provide a large coverage over the bare surface of the cerebral cortex, they are often implanted in one hemisphere and do not reach deeper brain structures (for example, hippocampus or insula). By comparison, depth electrodes (right) can enable bilateral monitoring of superficial and deep cortical structures, but only the most superficial and deep contacts will be within the cortical gray matter while the rest of the contacts are in the white matter. ECoG electrodes have a circular plate shape while depth electrode contacts have a cylindrical shape. The diameter of subdural plate electrodes is often 1.2 to 3 mm while the diameter of depth electrodes is 0.86–1.1 mm with 2.29 or 2.41 mm height. The distance between the centers of two adjacent electrodes (subdural or depth) is often in the range of 4 to 10 mm. The total area of the brain covered with electrodes can be in the range of 1 mm^2 to 15 mm^2. Lastly, it should be noted that the number of electrodes and the coverage areas are defined according to the patient's clinical needs. Because most patients have seizures originating from medial temporal and frontal lobes, it is exceedingly rare to find coverage outside these regions of the brain. This often explains the relatively small number of subjects in iEEG publications reporting data from nontemporal and nonfrontal sites.

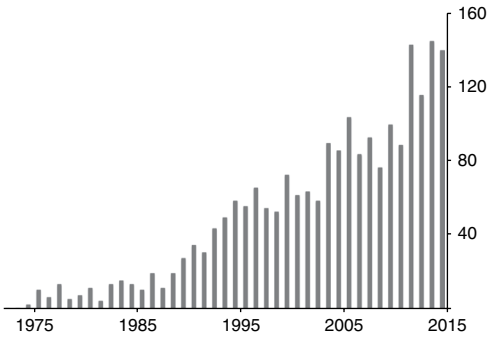


Fig. 2 | Recent surge in the number of iEEG publications. Number of publications in PubMed using the search terms "sEEG," "depth electrodes," "iEEG," "ECoG" or "electrocorticography."

Once intracranial electrodes are implanted in the operating room under general anesthesia, the patient is transferred to a hospital room to be connected with wires to a recording rig for continuous streaming of raw electrophysiological data from the implanted electrodes. The patient's antiepileptic medications are gradually discontinued and, if needed, analgesic medications are administered. Given the wires connecting the electrodes to the recording rig, the patient is literally tethered to bed for several days. To determine the source of seizures, one often needs to record for several days to capture several seizures. It is during these days of monitoring and in this clinical setting that neuroscience experiments are conducted.

Characteristics of human iEEG

Limited accessibility and clinical setting. One of the main limitations of the iEEG method is that it is only possible in clinical settings at a few hospitals and by specially trained teams of clinicians and investigators. This introduces a significant limitation of accessibility. Furthermore, the experimental subjects have a pathological condition (see Box 1). Clinical and hospital constraints do not permit experimental setups for sophisticated psychophysics measurements, and the experiments often suffer from low numbers of trials and simplicity of design. Moreover, the location of electrodes is decided clinically and, once implanted in the operating room, cannot be changed—unlike in animal recordings, in which the investigator may penetrate the cortex many times until responsive neurons are found.

Sparse sampling. Since clinical needs dictate the pattern and type of implantation in each patient, parietal, occipital and inter-hemispheric areas are much less frequently implanted with iEEG electrodes. Moreover, those brain areas that are covered with electrodes are often probed with electrodes that are 5–10 mm apart. Thus, unlike in functional MRI, excellent global coverage across the whole brain is not possible.

Corticocentric bias. Except in studies of amygdala and hippocampus with depth electrodes in patients with epilepsy or in the subthalamic nucleus in patients with Parkinson's disease[7,8], subcortical structures such as basal ganglia, thalamus, brainstem and cerebellar regions are not implanted for presurgical EEG monitoring because of lack of clinical motivation. As a consequence, there is little study of these subcortical regions using iEEG. Thereby, the field of iEEG fuels the current 'corticocentric myopia' wherein contributions of subcortical structures to cognition and behavior are often not considered[9]. Direct recordings in nonhuman primates and other animal models are needed to fill this gap (for example, refs [10,11]).

Neuronal population activity at millimeter resolution. Electrodes used in sEEG are cylindrical, with a contact length of ~2 mm, diameter of ~1 mm and total surface area of ~10 mm^2 penetrating the cortical layers. Grid or strip electrodes used in ECoG are circular plates with a diameter of ~2 mm and surface area of ~4 mm^2 placed over the bare cortex. Thus, iEEG electrodes capture signals from a relatively large and diverse population of cells. Given the diameter of human iEEG electrodes and the known estimates of the number of neurons per cortical area, one may assume that there are ~500,000 cells underneath or surrounding these electrodes[12].

iEEG signals recorded from such a large and diverse population of cells are understandably complex and carry information in different bands of oscillatory activity—for example, delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–20 Hz) and gamma (21 to ~50 Hz), as well as higher frequency activity known as high-gamma activity or high frequency broadband (HFB) (above 50 Hz). The HFB signal is currently interpreted as a reflection of a nonoscillatory broadband signal[13,14]. Notably, HFB is different than pathological high-frequency oscillations that are seen in epileptic recording sites. The latter, for instance, are associated or coupled with interictal epileptiform discharges and are randomly interspersed with pathological background activity, and they can be present across several adjacent electrodes[15,16], whereas HFBs are time locked to the presentation of specific stimuli or cognitive or behavioral conditions (see Box 1).

HFB activity is a reliable electrophysiological correlate of underlying averaged spiking activity generated by thousands of neurons adjacent to the recording electrode[17–21]. The extent of brain tissue from which the HFB signals are recorded remains largely unknown. However, based on studies in nonhuman brains using research-grade microelectrodes, estimates fall around several hundred micrometers[20,22,23]. Moreover, the number of neurons contributing to the high-frequency signal may be as scarce as ~16% of neurons sampled by a given electrode[24].

HFB signals also correlate with hemodynamic signals detected with functional MRI (fMRI)[21,25–28]. Thus, an increase in the HFB

Box 1 | Pathological brains?

Findings from patients with epilepsy have contributed significantly to our understanding of the brain throughout the history of neuroscience. For instance, experiments in patients with epilepsy led to the finding of somatotopic organization in the postcentral gyrus[86], significance of medial temporal lobe in memory consolidation (patient HM)[87] and lateralization of functions across the hemispheres (split brains)[88].

A major concern regarding iEEG is that recordings are made from patients with longstanding epilepsy. A pertinent question is the extent to which epilepsy-affected brains provide a suitable model for studying normal neural mechanisms underlying various aspects of human cognition and behavior. Are epilepsy brains too pathological to begin with? Will intracranial recordings in epileptic brains reflect the normal neural substrates of human brain function? These are valid questions and must be carefully considered. However, the answer to these questions depends on two important factors: the patient population recruited for the iEEG study and the relative health of the recorded brain areas.

Epilepsy is a heterogeneous disease with diverse severity, clinical appearance and pathogenic mechanisms. At one end of the spectrum, it includes severe epilepsy syndromes, with onset in early childhood, that are associated with bilateral and multifocal epileptiform discharges, diffuse slowing of baseline brain activity, mental deterioration and behavioral regression. At the other end of the spectrum, it includes focal epilepsies in high-functioning adult patients, who have normal intelligence and a few localized deficits depending on the focal brain network that is involved[89–92]. In addition, the cognitive and behavioral burden of the disease is directly related to factors such as early onset, duration of the disease and seizure control. It is therefore imperative that the iEEG reports are interpreted in light of the severity of the disease and the details of administered medications in the studied patient population. Unfortunately, current iEEG reports vary significantly in the clinical details that they provide (see "Opportunities for growth" for suggestions).

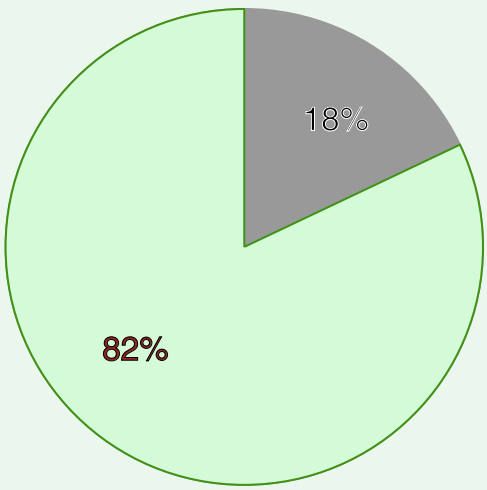
The main goal of invasive recordings is to find a single seizure focus and offer focal resection and thereby freedom from seizures. iEEG monitoring is chosen only if the preoperative workup suggests focality of disease and a high chance of finding the seizure focus – even though most of the time the exact focus is not known before implantation and many times multifocal disease is confirmed only after implantation. Invasive monitoring is mostly avoided in patients with presurgical evidence of known multifocal or diffuse disease. In these patients, intracranial recordings will reveal widespread and bilateral pathological activity.

During invasive monitoring, often many electrodes (100–200 per patient) are implanted across lobes or hemispheres to ensure that the source of seizures is not missed. As a result, intracranial electrodes often cover a large extent of the brain. In a patient with focal disease and with a relatively large number of implanted electrodes, many recording sites will be void of epileptic activity while a few will capture the source of seizures.

The ratio of epileptic to nonepileptic electrodes will naturally depend on the total number of implanted electrodes and the location of electrodes across the brain. For instance, in a patient who reports flickering stars in the right visual field every time he has a seizure and shows scalp EEG evidence of epileptic discharges in the left posterior quadrant of the head, one may choose to implant strips and grids of ECoG electrodes covering a large extent of the occipital and ventral temporal cortices in the left hemisphere. In this patient, one may find that a small piece of cortex in the pericalcarine area is epileptic while the rest of implanted sites are void of pathological epileptic discharges. In another patient with limbic seizures (for example, rising nausea) and scalp EEG evidence of bilateral discharges but no MRI or PET abnormality, one may implant the hippocampi, amygdalae, anterior and posterior cingulate, as well as orbitofrontal and insular cortices bilaterally with the sEEG method. In this patient, a few electrodes in the medial temporal lobe regions may show epileptic activity while others will be void of such activity. An electrode needle with 14 recording contacts will target the insula, traversing the frontal lobe. While the first couple of electrodes capture insular activity, the other contacts along the electrode needle will provide valuable recordings from structures such as the claustrum.

To be conservative, one often concentrates signal analysis on the channels that are free of pathological activity (i.e., without pathological slowing of background activity and without epileptiform discharges). This is especially important when the analysis is focused on power in the HFB because transient and paroxysmal pathological high-frequency oscillations are often present in epileptic tissue (see main text), and it is important to ensure that these oscillations are not mixed with induced time-locked physiological HFBs.

An issue that is often discussed in the clinical epilepsy literature, but has yet to be settled, is to what extent the focal epileptic activity in one region of the brain affects normal activity in the rest the brain. It has been known that isolated epileptic discharges (which correspond to large-amplitude intracellular depolarization with evoked action potentials in a group of neurons) and subclinical subtle seizure activity in the same region cause transitory cognitive impairment, with the type of deficit dependent on where in the cortex the epileptic activity arises[93–95]. It has been hypothesized that focal epileptic discharges (i.e., seizures or isolated interictal discharges) cause material and site-specific deficits in cognitive functions that are mediated by a focal network of the brain in the hemisphere in which the discharges occur[95]. As such, specific material deficits in a patient can indirectly be used to highlight



Box Fig. 1 | Ratio of electrodes in epileptic and nonepileptic tissue. In 100 patients implanted with ECoG or sEEG electrodes at Stanford Medical Center, we reviewed the iEEGs in each patient and labeled pathological electrodes that contained epileptic activity (i.e., recorded seizures or epileptiform spikes). We used the total number of electrodes implanted in these patients to calculate the ratio of pathological (gray) to nonpathological (green) sites. In patients with focal epilepsy, sites with pathological activity are clustered in a few electrode contacts. The extent of nonpathological electrodes will depend on the density, form and size of implanted intracranial electrodes. In a patient with wide coverage and a focal epileptic zone, nonpathological sites will be covered across a large region of the brain.

Box 1 | Pathological brains? (continued)

the brain network that is affected by seizures. In fact, for many decades, neuropsychological preoperative evaluation of patients who are candidates for epilepsy surgery has been used successfully in clinical practice to highlight dysfunction in specific domains of cognition and thereby provide functional information about the possible lobe and hemisphere of origin of the patient's seizures[96]. For instance, patients with left temporal lobe seizures are expected to score lower on verbal memory tests and those with frontal lobe seizures do poorly in executive function tests[96]. Cognitive dysfunction in these patients is directly correlated with the frequency of interictal epileptiform discharges and is greater with generalized than with focal discharges, but more specific with the latter[95,97]. The subsequent treatment of a discharging focus leads to modest improvement in patient's cognition[98].

Given the current state of our knowledge about focal epilepsy and the effect of epileptic activity on the rest of the brain, we believe epilepsy-affected brains can be used as a proxy for normal human brains only if the confounding effects of epilepsy on the acquired intracranial electrophysiological data are minimized by rigorous measures. Such measures include (i) acquiring data from nonepileptic tissue—i.e., brain tissue without epileptic signals (see Box 2); (ii) obtaining data several hours outside the window of seizures; (iii) excluding trials in which epileptic discharges were occurring; and, most importantly, (iv) documenting that the observed findings in a patient are anatomically and functionally consistent across other patients with other types of epilepsy and seizure foci. It would be beneficial to show that findings in subjects with epilepsy are akin to findings reported in noninvasive studies of healthy subjects. This will naturally not be possible if the findings are novel and unreported in literature. Such reliable results from iEEG will have the potential to yield unique information about human cognition and subjective experience.

power in a recording site reflects the local engagement of the cortical tissue underneath or around the electrode. There is strong evidence that, unlike slow oscillatory activity, the HFB signal has a remarkably localized anatomical precision and originates from the cortical tissue immediately around or underneath the recording electrode (for human iEEG evidence, see for example refs [27,29–33], and for direct measures from nonhuman primate studies, see for example refs [18–20,22]).

While HFB activity appears to reflect responses of local populations of cells around or underneath a recording electrode,

Box 2 | Handling iEEG signals with care

For the reader of iEEG literature, it is important to be aware of potential problems that may degrade the value of the findings:

1. **Electrode localization**. An important advantage of the iEEG method is that the anatomical coordinates of the recording site can be identified with great precision. However, one must be cautious about the reported anatomical coordinates of the electrodes. Especially in ECoG, when the electrode hardware is implanted after a relatively large craniotomy, the brain of each patient will necessarily be shifted in space from its preoperative coordinates. Therefore, reconstructing the location of electrodes on the subject's preoperative brain MRIs (as is often done) may be problematic. One way of avoiding this issue is to construct the 3D location of the electrodes using postoperative MRIs. Another way is to use methods that account for the shift and take great deal of care to ensure correct alignment between the two series of images[99,100].
2. **Data processing**. Multiple steps are involved in handling complex iEEG signals, and each step can cause data distortion. Processing signals obtained from patients with healthy and pathological signals mixed across recording sites can also be problematic if the data processing has not been performed correctly. While the precise steps taken in the processing of data may vary across labs and research aims, several key steps are commonly applied to the raw iEEG data before the actual statistical analyses are performed: concatenating several data files (for example, across blocks or conditions across days); downsampling of the data, most commonly from 1,000–10,000 to 250–1,000 samples per second, and thus changing the temporal resolution of the reported data; identifying and removing artifacts and noise or pathological signals (notch filtering, excluding signals from electrodes with abundant pathological activity and common-averaging or rereferencing to remove a common signal).
3. **Defining a baseline**. The control condition in electrophysiology is the baseline, which is commonly defined as the average pre-stimulus signal (usually ~100–200 ms before onset of the trial). Normalizing the raw signal to the baseline activity is important given that the electrodes do not homogenously cover all pixels of the brain and they may vary in shape, size or distance from each other. Correcting for baseline prevents the signal of interest from being conflated with average noise. Thus, differences between conditions during stimulus presentation can be accurately compared and contrasted. Depending on the hypotheses that are being tested, it is exceedingly important to ensure that the right baseline is chosen. For instance, shorter baselines will be problematic for slow oscillations (too few waveforms per unit of time), or the task design may not allow using pre-stimulus phase as the baseline.
4. **Multiple comparisons**. One of the most salient attributes of intracranial EEG is the ability to measure signals within a specific frequency range, such as delta, theta, alpha, beta and gamma oscillations, as well as the broadband signal. One can either process the amount of activity in each bandwidth (i.e., the amplitude of the filtered signal) or look at the interaction and coupling of activity across frequencies. One may study the association of multiple frequencies across different bands of activity or across neural systems. One may study the sustained versus transient burst of activity or coupling within or across certain frequencies or neural systems. The richness of the iEEG data is a true blessing, but it can also be a curse and lead to spurious findings. In a large amount of data with different frequencies, multiple sites and different measures of power and phase, almost any pattern can be interpreted as a 'result', and multiple-comparisons correction becomes close to infinite. Having an a priori hypothesis with a mechanistic approach linking the work to previous literature and existing theories, showing consistency of the same findings across subjects, and selectivity and specificity of the finding to a given experimental condition, region or network are must-haves before a result can be taken as a serious finding. Combining passive recordings with active electrical stimulations and thus proving causality will be the ultimate means by which to beat the curse of pseudo-findings in the iEEG literature.

low-frequency oscillations in the theta, alpha and beta frequency bands may serve as carrier frequencies that are used by distant nodes within large-scale networks to communicate[34]. Notably, low-frequency oscillations may control the excitability of local neuronal populations, as evidenced by the coupling between the higher frequency activity and slow oscillations during cognitive tasks[34]. Here we remind the reader that locking to phases of higher frequencies is technically difficult because a small amount of jitter in precision abolishes locking. The measure of coupling between the phase of slow oscillations and the power in higher frequencies (particularly HFB) or the rate of neuronal spikes (cross-frequency, or spike phase, coupling), as well as the measure of coupling of phases of two oscillatory rhythms (phase–phase locking) can inform about important aspects of the functional dynamics of brain activity, such as the directionality of information flow across a network (for recent reviews, see refs [35,36]). Cross-frequency interactions may also be important for folding nodes into a common network or for integration of interactions across different cognitive networks[37]. As relevant examples, in a recent study it was found that theta phase (4–8 Hz) and HFB coupling in the human prefrontal cortex were predictive of trial-by-trial response times[38]. In another study HFB power modulated by the phase of an ongoing 2–5 Hz oscillations remained elevated throughout the period of attentional allocation in the prefrontal, parietal and visual cortices, and the strength of this phase–amplitude coupling predicted reaction times to detected targets on a trial-by-trial basis[39].

Millisecond temporal resolution. Given that the sampling rate of human iEEG data is typically in the range of 1,000–3,000 Hz, the intracranial signal contains temporal information with millisecond resolution—though downsampling and temporal smoothing can hamper the resolution of the signal (see Box 2). Conventional scalp EEG and magnetoencephalography have similar temporal resolution to iEEG; however, the iEEG signal is highly localized and the source of the signal is spatially better defined. Observation of fast dynamics of activity between precisely localizable populations of neurons across distinct brain regions can inform neuromechanistic accounts of perceptual and cognitive functions. Moreover, knowing the exact onset of activations or deactivations in a region of the brain can inform us about the details of possible neural computations taking place in the targeted brain area. For instance, finding tens of milliseconds of lag time between activations in region A and region B suggests that neural computations in A precede computations in B (and activity in A may even be causing activity in B). Precise temporal information can also help us understand the pattern with which different regions of the brain interact with each other. In a recent study[40], it was found that within the first 300 ms of object presentation, several different subregions in the human inferior temporal and lateral parietal cortex become activated together, but in different time windows, clearly providing a detailed account of recurrent information flow between the inferior temporal and lateral parietal regions. A different study of object recognition targeted at neuronal populations in ventral visual cortex illustrates how iEEG's millisecond resolution can inform mechanistic accounts of perceptual processes. When subjects viewed incomplete images of the objects, neural responses in the human inferior temporal cortex required ~100 ms more processing time than when they viewed whole objects. This pattern of time information clearly suggested that recognition of partially presented objects depends on recurrent signals not only from feedforward but more likely from feedback connections, as also proposed by attractor network or Bayesian inference models[41].

High signal-to-noise ratio. A clear advantage of working with the iEEG signal is the exceedingly high signal-to-noise ratio (SNR). Compared to imaging studies, the SNR of iEEG is indisputably higher. For instance, local energy consumption increase owing to a typical task-related response in fMRI is as little as 1%[42]. By contrast task-related increases in the local field potentials can be as high as ~300%[43]. Sources of SNR in imaging studies of the brain include field of view, scan parameters, magnetic field strength, slice thickness and noise stemming from the subject (cardiac and respiratory pulsations, head motion), which vary in time. These are largely absent in iEEG recordings. Compared to that of scalp EEG, SNR of iEEG data can be as much as 100 times higher[44]. This is in part because of an approximately tenfold higher amplitude of iEEG signal compared to scalp EEG signal and substantially reduced problems electromagnetic noise from the recording room, physiological noise from cardiac signal or muscle contractions, or skin potentials (for example, skin cells on the scalp or ionic potential of sweat glands) with intracranial recordings. Of critical importance for the field of brain–machine interface, the SNR of iEEG recordings remains stable and strong over many months, without negative correlation between decoding performance and the time between model generation and model testing[45] (see Box 2 for important steps in signal processing to increase the SNR).

Selectivity of iEEG signals. Since the iEEG signal is conveyed by the 'forest' of neurons and their neuropil, one might question whether the forest signal is specific and selective enough, and if so, at what level and to what extent. Many recent studies from iEEG laboratories have convincingly shown selective rise of HFP power across a multitude of experiments. In this context, it is important to know that the reported iEEG findings are based on a comparison between the induced changes of the electrophysiological activity after the onset of a stimulus and the baseline pre-stimulus activity in the same recording site (usually ~200 ms before onset of the trial). This is in stark contrast to some functional imaging data in which the reported results are based on subtraction of two signals during two different cognitive conditions (for example, increased hemodynamic responses to numbers minus responses to colorful images (see Box 2). In this regard, selectivity of the iEEG responses may be more meaningful. As examples, intracranial recordings in the human lateral temporal lobe (in areas commonly known to be part of the language system) have shown heterogeneous patterns of neuronal population response, clearly revealing that language processing in this part of cortex is not spatially homogenous over the span of a centimeter[29]. A different study using a high-density grid of electrodes in human subjects listening to natural and continuous speech showed that the acoustic properties of the phonemes were mediated by population responses distributed across millimeters of the brain[30]. In another study, recording from a grid of electrodes in the human temporal cortex, speech representations and identification of individual words were decoded directly from the iEEG signals during single-trial sound presentations[46]. Thus, the selectivity profile of HFB responses across millimeters of the brain enables us to get closer to a neuromechanistic view of cortical processing that otherwise could not be studied with methods that lack the anatomical precision of the recorded signals or their temporal resolution.

It goes without saying that acquiring single-unit data from the vicinity of implanted iEEG electrodes[7,8] can provide more granular information about the computations performed in a given brain region. For instance, the timing at which spiking activity occurs often clusters relative to certain phases of oscillatory activity, as extracted from the local field potential. Such spike–field coherence can provide another tool for decoding neural computations and inter-regional connectivity. For instance, it has been shown that successful memory formation in humans is better predicted by a coordination of spike timing with the local theta oscillation rather than the phase of these oscillations or the average firing rate of neurons per se[47]. Moreover, the strength of spike–field coupling as a function

of task set suggests that temporal codes are important in sculpting and orchestrating perceptual and cognitive functions across large-scale networks[37]. Examples of such temporal coding have been found in many brain regions, with spiking activity typically coupling to phases of inter-regional slow oscillatory activity[48,49].

Simultaneous sampling of many sites. Implantations in human subjects often include many electrodes and broad coverage for simultaneous recordings across a wide range of regions. The number of ECoG electrodes (for example, an 8 × 8 cm grid of electrodes) or the number of sEEG electrodes (for example, 10–15 cannulas containing 10–14 electrodes) can total to 150–200 different recording sites. Such a broad spatial coverage over large-scale networks has two advantages. First it allows one to examine the involvement of a larger mantle of the cerebral cortex and identify distinct patterns of responses across multiple cortical locations at various time points during a cognitive experiment, or to map large-scale gradients (for example, in the visual hierarchy) within a given region of the brain and in the same individual brains. Second, it allows one to identify functional relationships between nodes of the same functional network that are incidentally covered by clinical electrodes. As such, processes in large-scale networks can be linked to more local processes, and the local processes can be understood in the context of their large-scale role in the network. For instance, in a recent iEEG study (Fig. 3), simultaneous recordings from ventral temporal cortex and dorsal parietal regions explored the timing and profile of responses in discrete neuronal populations during simple arithmetic processing (for example, 2 + 2 = 4)[40]. Electrodes in anatomically consistent inferior temporal and intraparietal sulcus regions showed similar profiles of time-locked HFB responses during the addition of numerals. Notably, the HFB responses were relatively weak to the presentation of the first digit in the equation and increased substantially after the following operator and second digit were presented. Such a precise timing and differential selectivity profile of responses across the temporal and parietal sites can provide important information about the flow of information between the two sites during an experimental condition[40].

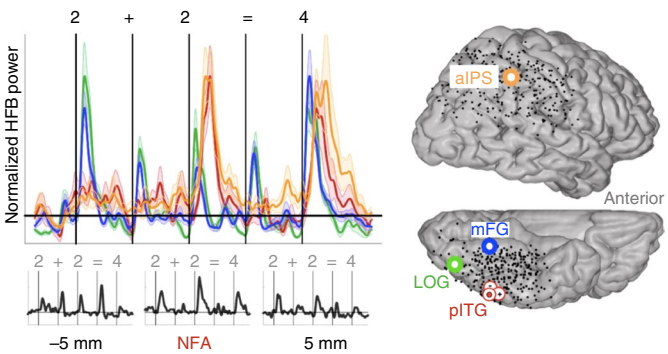


Fig. 3 | Simultaneous recording with broad coverage for tracking the spatiotemporal profiles of activity of populations of neurons during a particular cognitive task. In a group of subjects, simultaneous iEEG recordings in the lateral parietal and inferior temporal regions tracked HFB responses in each electrode site while the subjects were making true/false judgments on an arithmetic task in which operands (numerals 1–9) and operators (+ and =) were visually presented one symbol at a time (for example, "2", "+", "2", "=", "4"). Nonselective HFB responses in lateral occipital gyrus (LOG) and medial fusiform gyrus (mFG) contrasted with the selective HFB responses to numerals in the posterior inferior temporal gyrus (pITG, red) and anterior intraparietal sulcus region (aIPS, top left). Note the stronger responses in the pITG and aIPS after the presentation of the second numeral following the "+" sign and the opposite profile of HFB responses in the LOG and mFG sites. Also of interest was the finding of HFB response selectivity across the three adjacent pITG sites (bottom left). Neuronal populations that are ~5 mm apart show clearly different profiles of responses. Note the most selective responses to numbers in the number form area (NFA) that was for the first time reported in Shum et al.[85] in a different set of subjects. This figure has been recreated using data from Daitch et al.[40].

Understanding the temporal dynamics of neuronal responses in different nodes of a specific brain network is of great importance for generating a neuromechanistic account of human brain function at the systems level. For example, neuroimaging studies have shown that the posterior cingulate cortex (PCC) and angular gyrus (AG) are engaged in autobiographical memory functions and are also connected at rest[50]. However, on the basis of these data, it was almost assumed that a large area of PCC should be connected to a large area of AG. In a recent ECoG study, simultaneous recordings from PCC and AG in human subjects showed that, on a trial-by-trial basis, responses in both PCC and AG during memory retrieval are coupled with zero time lag (i.e., both areas are engaged around the same time and one does not drive the other), and more importantly, the entire AG was not functionally coupled with the entire PCC at rest. Instead, using the same metrics validated in previous studies[51,52], it was found that the coupling at rest occurred between those discrete populations of neurons in the PCC and AG that were coactivated during the experimental task[53]. In summary, simultaneous iEEG recordings from distinct nodes of functional brain networks provide data with high temporal resolution and reliable anatomical precision of signal sources. Such data are presently not obtainable with noninvasive methods in humans.

Exploring causality. Another characteristic of iEEG data is that it can provide information about the causal importance of a given cortical site (and its connected network) in a given cognitive condition or behavior. Implanted electrodes can not only record signals from a specific population of neurons but also deliver electrical pulses to that population. Direct electrical stimulation of the human brain confers the ability to record and stimulate the human brain at specific sites and hence test the causal importance of a given population of neurons (and their interconnections) for a particular function while a subjective report of the human participant is instantly available. The fact that humans can explain their subjective experience during electrical stimulation of their brain makes the intracranial experiments in humans unique. For instance, in patients undergoing awake brain surgery, stimulating the right inferior parietal regions triggers a strong intention and desire to move the contralateral hand, arm or foot, whereas stimulating the left inferior parietal region provokes the intention to move the lips and to talk[54]. When stimulation intensity is increased in parietal areas, participants believe they have really performed these movements, although no electromyographic activity is detected[54]. Other findings include that stimulation of the anterior cingulate cortex can induce complex physical and autonomic states (chest or neck vibrations and increased heart rate, respectively) coupled with emotions (feeling of anticipated anxiety and foreboding) along with a strong motivational state (for example, "I want to push harder and harder," " I want to fight against it")[55]. Further, stimulation of the brain in a patient with implanted electrodes in the dorsal frontal cortex can cause a feeling of mirth[56], and stimulation of the AG has led to illusory transformations of the patient's own body experience[57]. In a study of the human fusiform face form area (FFA), stimulation of the FFA caused distortions of perceived faces, and these changes of perception were modality specific and thus applied only to faces[43]. These effects occurred only when the right FFA, but not the FFA in the language-dominant left hemisphere, was stimulated[58]. These are just a few examples among many other cortical stimulation studies[59] that go far beyond correlative approaches and can offer evidence about the link between the brain and a human's subjective experience.

Direct electrical stimulation of the brain has a great therapeutic potential, especially when coupled with real-time recordings from the surface of the brain or from a subcortical structure in a closed-loop circuit. This is evident in the current practice of responsive neurostimulation[60] to control pathologically driven activity such as seizures (NeuroPace) or abnormal beta-band activity with movement in Parkinson's disease[61], or recent investigations into the possibility of modulating cognitively driven activity to treat neuropsychiatric disorders[62] or simply devising cognitive prosthetic devices[63].

The human brain model. From our discussion thus far, it could be argued that iEEG is currently the method with the most suitable combination of anatomical precision, temporal resolution and simultaneous coverage of multiple nodes of interest to study the human brain. The method promises further insights into human brain function beyond what we have learned, or can learn, from noninvasive studies of the human brain. One advantage of human iEEG studies over those conducted in laboratory animals such as monkeys or rats is that humans can perform tasks based on verbal instructions, and they do so with minimal training and in the absence of ongoing reward or task-cueing. Such an approach allows more ecologically valid and ethologically relevant experiments than are possible in most animal species, also avoiding the potential confound of overtraining. Moreover, to develop animal models for specific cognitive functions requires a perfect phenotype that matches the human counterpart, but these phenotypes are often absent for uniquely human faculties such as language. As an example, a recent human iEEG study revised the old model of language processing and differentiated the neuromechanistic accounts of speech from language processing[64]. It showed that our current models of lateralized speech processing may not be entirely accurate after all. The traditional model of language processing proposes that speech production and language processing occur in the language dominant (mostly left) hemisphere, and that the coupling from language perceptual sensory (lateral temporal) sites to production (inferior frontal) sites occurs primarily in the language-dominant hemisphere. Instead, the iEEG recordings revealed a clearly bilateral rather than unilateral speech sensory–motor coupling. As another example, an iEEG study in human subjects revealed that conscious and subjective perception of visual phosphenes (induced by electrical stimulation of the primary visual cortex) occurs only when stimulation in the primary visual cortex is accompanied by HFB responses in the temporoparietal junction area (TPJ)[65]—suggesting that the outbound distribution of signals from the primary visual cortex to the TPJ may be necessary for human conscious visual perception. This study illustrates not only the knowledge that can be gained from subjects who are able to report whether or not they are consciously aware of their percepts, but also the advantages of a data-driven approach employing broad coverage of the brain with hundreds of electrodes.

Lastly, invasive recordings in pathological regions in the human brain provides important human-specific information about the pathophysiological mechanisms at play. For example, none of the available animal models of Parkinson's disease accurately reproduces all of the symptoms of the human disease, and animal models of Parkinson's disease or epilepsy do not reproduce the gradual pathological changes that occur in the brain over the course of decades[7]. Thus, testing pathophysiological hypotheses directly in the human brain provides complementary information to studies in animal models.

Opportunities for growth

Partnership between electrophysiologists working on human and primate brain models. The macaque monkey is the primary animal model for human brain function. However, comparisons of brain function in humans and nonhuman primates have been thus far mainly indirect due to differences in methodological approaches. There are only few direct comparative studies across primate brains, and they have used a combination of invasive recordings and fMRI (for example, refs [66,67]). Thus, comparative electrophysiology in monkey and human subjects will be a fruitful approach for establishing not only the validity of the nonhuman primate brain as a model for human brain function, but also for studying evolutionary aspects of cognition. Such an approach will require recordings in tasks that result in common behavior across primate species and from sites that are functionally similar. As noted, the recorded iEEG signal is the sum of local field potentials generated from large populations of cells that are localized under or around the recording electrode. This signal is too crude to discern a distributed code among many cells within a small region. While recent studies with multicontact microelectrodes that are chronically implanted in epilepsy patients have great promise for deciphering the laminar source of signals that we record with ECoG and sEEG recordings[68,69], much more granular research with microelectrodes in nonhuman models (for example, refs [66,70]) will provide a great opportunity to uncover the neuronal mechanisms in greater detail. In nonhuman primates, laminar recordings across the layers of cortex can provide further details of local circuitry, including detailed consideration of signals arising from feedforward and feedback pathways (for example, refs [71,72]), and simultaneous recordings of interconnected nodes of a large-scale network can inform about mechanisms of interareal communication (for example, ref. [10]). Notably, sophisticated and identical behaviors can be established in nonhuman primates in tasks motivated from human cognitive psychology, thereby taking our mechanistic models from the coarse sampling of human iEEG all the way to the microcircuitry of laminar recordings in nonhuman primates (for example, ref. [10]).

Common platforms and more data sharing. Many innovative ideas can be fostered by establishing common platforms for acquiring data across laboratories so that a larger pool of subjects can be recruited to perform the same task. Moreover, sharing the acquired data with the rest of the world will make the iEEG data more accessible to a larger pool of researchers. Recent efforts by the US National Institutes of Health and National Science Foundation make it easier to share research data with the public using their platforms.

Better reporting. It is important that scientific journals require iEEG findings to be accompanied by detailed reports of the patient demographics, especially the source of seizures, duration of epilepsy, frequency of seizures, type of seizures, educational level and antiepileptic medications in use, as well as details of neuropsychological evaluations and IQ. Such detailed documentation will allow the reader to evaluate the cohort in which the data was collected and provide context to position the results and their interpretation.

Technical and analytical improvements. Several areas of iEEG practice have unfortunately not been modernized for decades, partly because any innovation must pass the regulatory hurdles of US Food and Drug Administration. As was recently highlighted[73], new technologies are needed to create substantial improvements in both spatial and temporal resolution. With the growing role of engineering (including materials, computing, electronics and hardware)[74], there is great hope that we will reach major milestones in the years ahead.

One major milestone will be the development of wireless intracranial recordings and stimulations in human subjects. At present, intracranial electrodes need to be wired to a recording apparatus. This tethers the patient to a bed and increases morbidity due to

prolonged bed rest. Each wire tail is also an inlet for infectious agents. Wires are furthermore susceptible to movement artifacts.

Another milestone will be the development of new computational systems that will increase the power of current clinical recording systems, which cannot process more than several hundred channels simultaneously. Large channel counts will have implications for every downstream component, including connectors, routing, amplification, signal processing and storage. Multiplexing the signals will be required to transmit all the signals over a single wire or a few wires. Increasing the number of recording electrodes, using finer grained recording sensors[73] and combining conventional iEEG electrodes with microelectrodes will lead to analysis of data across multiple spatial and temporal scales and will improve our understanding of the relationships embedded within the complex network of the human brain during normal and pathological (for example, epilepsy) conditions. For instance, NeuroGrid[75] is a step toward this aim. The largest human probe is currently ~2 cm × 2 cm and has 512 channels, which require several parallelized chips with bulky back-end connections. To record 5 min of a study with 20-µm spatial resolution and 20-kHz sampling rate, the system requires about 12–15 Tb of memory and 320 Gb/s for real-time processing. To increase the size of coverage to several centimeters, the computational requirements, by today's standards, are beyond the range of currently available tools. Signal acquisition of such large-scale data is limited by lack of high-channel-count electrophysiological interfacing electronics. However, in concert with advances in high-speed electronics and data processing capacity, the number of samples recorded per unit of time could substantially increase in the future.

Technical advancements will also lead to better electrical stimulators. In current clinical practice, constant-current stimulators are used to deliver rectangular charge-balanced, biphasic waveforms with minimal risk of tissue damage[76]. More recently, nonrectangular waveforms have been proposed that may usher in new stimulation methods[77].

Technological advances in the field of iEEG will hopefully lead to a newer field of therapeutics (namely, electroceuticals[78]) and newer implantable devices[79]. It will also lead to a more fruitful path in the field of brain–computer interface research[80]. This is especially promising since brain computer interfaces using local field potentials in nonhuman models can even outperform those using spikes and may have an extended lifetime[81]. This will offer a great opportunity for cognitive or motor prosthetics used by disabled patients to convey thoughts or actions[81].

Lastly, the field of iEEG can benefit from incorporating sophisticated network analytical tools from functional imaging methods (for example, dynamic connectivity, clustering and graph theory) that have resulted in findings on the functional architecture of the human brain that would have otherwise gone unnoticed[82–84].

Conclusion

This piece was meant to provide an overview of human iEEG method and its limitations as well as promises. The field of human iEEG has a unique place in studying averaged responses of populations of neurons with high temporal resolution and probing their causal importance for human subjective experience and behavior and their interaction with, and relative time of their engagement compared to, other nodes of the same or different functional networks. As such, iEEG can provide new and unique temporal information that can be complemented by other means of scientific research to construct neuromechanistic accounts of human cognition and behavior. Human iEEG can bring new information to the field of neuroscience, beyond simply replicating what is already known, or can be known, from noninvasive lines of research in humans or from invasive recordings in nonhuman mammalian brains.

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Competing interests
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