What is the contribution of iEEG as compared to other methods to cognitive neuroscience?

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Abstract

Intracranial electroencephalography (iEEG) enables us to record and modulate macro and micro neuronal responses in both cortical and subcortical regions of the human brain with high spatial and temporal precision, offering significant methodological advantages over other non-invasive imaging and stimulating technologies. Leveraging these technical strengths of iEEG, in combination with sophisticated multivariate analytical approaches, researchers have obtained unprecedented insights into many long-standing problems in cognitive neuroscience. This chapter aims to illustrate these contributions, focusing on human memory. In particular, we describe how iEEG could advance our understanding of (1) the dynamic and transformative nature of short-term and long-term memory representations; (2) the role of hippocampal high-frequency neural activities, especially ripple activities, in memory formation, consolidation, and retrieval; (3) the information coding scheme of single-neuronal activity in the hippocampus and other brain regions; and (4) the common and different neural mechanisms between humans, primates and rodents. Moreover, we briefly discuss how iEEG studies can contribute to developing the state-of-the-art brain-computer interface and closed-loop brain stimulation. We conclude by summarizing the strengths and limitations of the iEEG method and providing practical guidance on how to choose between iEEG and other methods.

Introduction

It is generally accepted that human brain functions, such as perception, attention, decision, learning, and memory, are supported by dynamic and interactive neuronal activities. At the microscopic level, neuronal activities can be well characterized by two main types of electrical activity, i.e., neuronal spikes and postsynaptic potentials. The neuronal spikes are the action potentials that travel along the axons of the neuron in an all-or-none form, with a very short duration of approximately one millisecond. Multiple spikes, which result in a spiking train and a highly intricate temporal pattern, serve as the code of brain information (Zeldenrust et al. 2018; Azarfar et al. 2018). Because of the brief timing and opposite electrical currents flow in the intracellular and extracellular spaces, the neuronal spikes can only be recorded with a sensor near enough to the neuron. In contrast to the spikes, the postsynaptic potentials (PSPs) are changes of the potentials in the membrane of the neurons (Purves et al. 2001), which have a longer duration ranging from tens- to hundreds- of milliseconds. The resultant electrophysiological signals, termed the local field potential (LFP), could propagate and thus be recorded both within and outside the skull.

For ethical reasons, most human studies rely on non-invasive brain imaging techniques, including electroencephalogram (EEG), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). These methods provide either an indirect (e.g., fNIRS, PET, or fMRI) or a coarse (e.g., EEG and MEG) measure of neuronal responses. The intracranial EEG (iEEG) recordings, which are mainly applied in drug-resistant epilepsy patients for clinical purposes, provide a rare opportunity to directly record neuronal responses inside the human brain (see also chapter 2 for a detailed description of epilepsy patients and electrodes implantation). iEEG could record both LFP and neuronal spikes with macroelectrodes and microelectrodes, respectively. Specifically, there are two types of macroelectrode recordings, i.e., Electrocorticography (ECoG) and Stereoelectroencephalography (sEEG). Whereas ECoG recordings place electrodes on the surface of the brain, the sEEG uses depth electrodes penetrating the brain to target deep brain structures. Similarly, using microelectrode arrays or microwires on the tips of the depth electrodes, iEEG can be used to record single-unit activities from the surface and deep structure of the brain (see also chapters 19 and 20 for a detailed description of iEEG signal characteristics). Compared with the non-invasive brain imaging methods, iEEG could offer several critical methodological advantages to better uncover the neuronal mechanisms of human cognition. In this chapter, we will summarize these methodological advantages and discuss how they could be leveraged to address long-standing problems in cognitive neuroscience, with a focus on learning and memory. We will conclude by providing practical guidance on how to choose between iEEG and other non-invasive methods.

The methodological advantages of iEEG

High spatial-temporal resolution

fMRI and PET are well-known for their high spatial resolution (1-3mm) and whole-brain coverage. However, they indirectly measure neuronal responses (e.g., blood flow or metabolism rate), with the temporal resolution at the level of seconds. The temporal resolution of EEG/MEG rivals the iEEG, but their spatial resolution is largely degraded by the volume conduction. The irreversible problem in untangling the sources that contribute to the observed EEG/MEG signals

further impedes research from precisely localizing the origins of signals, especially those from deep brain areas.

The iEEG has both high spatial and temporal resolutions. The grid and/or strip electrodes placed on the subdural of the cortex are ~2mm in diameter and covers ~4mm² in the cortical surface. Meanwhile, each depth electrode has about 6-20 contacts, with a diameter of ~1mm and a length of ~2mm for each contact. Given the diameters of the electrodes and their adjacency to neurons, it is assumed that iEEG could record the local field potentials from neural populations within a few millimeters (Engel et al. 2005; Mukamel and Fried 2012). The microwire electrodes used for single-unit recordings are about 40μm in diameter (Kreiman 2007), with a spatial resolution of less than 1mm. In addition, with a sampling rate ranging from ~1000-3000Hz for macroelectrodes and ~30kHz for microelectrodes, iEEG is able to observe the rapid change of local neural activities at a millisecond to submillisecond level.

In summary, due to the high spatial and temporal resolution, iEEG is one of the best methods to characterize the dynamic changes of neural processes and representations across time and brain regions.

High signal-to-noise ratio

Since iEEG could directly record the neuronal responses around its origin, it could yield a greater signal-to-noise ratio (SNR). In contrast, the EEG and MEG record brain signals at the scalp, which is far away from the origins. In addition, the iEEG recordings are less sensitive to environmental noise and artifacts. For example, the fMRI and MEG are both sensitive to the magnetic field change in the recording environments. A slight head movement could result in motion artifacts and introduce challenges in an accurate spatial registration for fMRI and MEG. For both EEG and MEG, body movement, eye blink, or muscle tension could introduce external noise into the recorded signals. In contrast, the iEEG is less sensitive to movement or magnetic field changes. As a result, its signal-to-noise ratio (SNR) is about 20-100 times higher than scalp EEG (Ball et al. 2009). The high SNR of iEEG helps us distinguish the task-related neural activities more meticulously.

High-frequency activity

High-frequency activity (50Hz-150Hz) is the neural oscillations generated by the local neuronal population (Ray et al. 2008), which is characterized by high frequency and low amplitude activities with high temporal resolution. Given the local properties of high-frequency activity and the skull acting as the low-pass filter, these high-frequency activities cannot be easily detected by non-invasive imaging methods, including fMRI, PET and EEG. Although the MEG has been believed to contain neural activities up to about 100Hz (Hansen et al. 2010), its signal-to-noise ratio for high-frequency activities is lower than iEEG in general. This makes the iEEG the optimal way to unveil how high-frequency activities during both online (wake) and offline (sleep) periods.

Direct electrical stimulation of the human brain

In addition to recording the neural activities from the brain, iEEG electrodes can also be used to deliver precise electric pulses to specific brain areas. As compared with the transcranial stimulation systems, such as tDCS/tACS and TMS, the direct brain stimulation by iEEG

electrodes enjoys greater specificity. For example, it could target the medial temporal lobe (MTL), a region that is critical for declarative memory (Jacobs et al. 2016), or the orbitofrontal cortex that is involved in mood state (Rao et al. 2018). In cognitive studies, different stimulation parameters have been applied. In general, the electrical pulses are with a width of 100-300 μ s, a current amplitude of 0.5-6mA, and stimulation frequency can be either at a low-frequency range (e.g., 2-5Hz) or at high frequencies (e.g., 50Hz, 60Hz, or 130Hz) (Suthana et al. 2018).

Table 1. Summary of the methodological advantages of iEEG as compared to common non-invasive imaging methods

Imaging features	iEEG	MEG	EEG	fMRI
Neural electrophysiological activities	Yes	Yes	Yes	No
Temporal resolution	<1ms	<1ms	<1ms	~5s
Spatial resolution	<1cm	~10cm	~10cm	~1mm
High-frequency oscillations	Up to 150Hz	<100Hz	<70Hz	No
Spike activities	Yes	No	No	No
Signal-to-noise ratio	High	Relatively low	Relatively low	High
Deep brain activities	Yes	No	No	Yes
Direct brain stimulation	Yes	No	No	No

Characterize the dynamic and transformative nature of neural representations

The information processing in the brain is highly dynamic, showing fast and prominent changes in neural processes and representations in different brain regions. Intracranial EEG recordings could directly measure brain activities from a wide range of frequencies from 0.5 Hz up to 150Hz with a high temporal resolution, which is ideal for characterizing the dynamic information processing at a fine spatio-temporal scale. Using this approach, many studies have uncovered the dynamic and transformative nature of neural representations, particularly during short-term and long-term memory, which have profoundly changed our perspective of human memory.

For example, the classic persistent activity model postulates that the initially formed neural patterns persist during the short-term maintenance period (Fuster and Alexander 1971; Curtis and D'Esposito 2003). With high temporal resolution, a recent iEEG study showed that the neural patterns of visual items experienced rapid changes from visual formats to abstract semantic formats, and the latter was more robustly maintained during short-term memory (Liu et al. 2020) (Fig. 1A-B). This study further revealed that the neural representations of memory items were

dynamically reactivated during the maintenance period and coupled to the phase of hippocampal low-frequency activities.

Regarding the maintenance of multiple items in the short-term memory, the theta-gamma coding scheme posits that individual items are represented by the synchronized activation of different subsets of neural assemblies at the gamma frequency range and the phase of theta oscillations. In particular, the hippocampal theta oscillation acts as a glue that tightly links items to its different phases in support of short-term memory maintenance (Lisman and Jensen 2013). Using EEG/MEG, studies have found that the theta-gamma coupling during the short-term memory maintenance period (Sauseng et al. 2009; Fuentemilla et al. 2010; Kamiński et al. 2011). On the other hand, fMRI studies have shown that the short-term memory information is stored in distributed brain regions, including the sensory cortex and higher-order brain regions, e.g., the frontal and parietal lobes (Bettencourt and Xu 2016; Christophel et al. 2017). However, the dynamic interactions among these regions and the unique role of the hippocampus in theta-gamma coding cannot be addressed using non-invasive recordings. Using iEEG recordings, studies showed that the theta-gamma coupling is not only observed in the hippocampus (Axmacher et al. 2010; Leszczyński et al. 2015), but also in multiple neocortical sites (Bahramisharif et al. 2018) during multi-item short-term memory (Fig.1C). It further shows that the interactions between hippocampal and cortical regions increase with working memory loads (Boran et al. 2019). Leveraging the high spatiotemporal resolution, several iEEG studies have revealed the directional interactions between MTL and cortical regions at various processing stages (Axmacher et al. 2008b; Chaieb et al. 2015; Johnson et al. 2018; Dimakopoulos et al. 2021). Specifically, the hippocampus replay preceded that in the sensory cortex during the maintenance period, whereas a reversed pattern was observed during the encoding period (Dimakopoulos et al. 2021).

Intracranial EEG studies could also shed light on the subprocesses of memory formations at a higher spatial resolution. For example, ERP analysis of EEG/MEG signals revealed that a late positive complex (LPC) component starting from ~500 ms post-stimulus onset, and an FN400 component with a peak around 400 ms, are both associated with memory retrieval (Woodruff et al. 2006; Voss and Federmeier 2011). Using iEEG, Fernández and colleagues found that the memory-related ERPs included at least two different subprocesses that were executed sequentially (Fernández et al. 1999). The intracranial ERPs diverged between subsequent remembered and forgotten items from about 300 ms in the anterior parahippocampal cortex, followed by the reversed polarity in the hippocampus from about 500 ms post-stimulus onset, suggesting a dynamic interaction between MTL subregions.

Intracranial EEG studies could provide a detailed picture of the transformative nature of long-term memory representations. Guided by Tulving's mental time traveling perspective of episodic memory (Tulving 2002), extant studies have provided evidence that retrieval involves the reinstatement of neural activation during encoding, which enables humans to vividly re-experience the past (Staresina et al. 2012, 2016; Ritchey et al. 2013; Yaffe et al. 2014). Nevertheless, there is now increasing neural evidence to suggest that memory is rather a constructive process (Bartlett et al. 1932; Barry and Maguire 2019) which involves a substantial transformation of neural representations. For example, an fMRI study found that item-specific encoding-retrieval similarity was not significant and lower than the neural pattern similarities within the encoding and retrieval stages (Xiao et al. 2017), suggesting the neural representations

were transformed from encoding to retrieval. A recent iEEG study took advantage of its high temporal resolution to systematically delineate the dynamic transformation of neural representations from encoding to maintenance and retrieval period (Liu et al. 2021a) (Fig. 1D-F). It showed that neural representations of memory items were highly dynamic during encoding, evolving rapidly from visual to abstract semantic representations. Interestingly, greater encoding dynamicity predicted better subsequent long-term memory performance. After encoding, these neural representations experienced continuous transformation during maintenance and retrieval, and only abstract semantic representations are reactivated in successful long-term memory retrieval.

Recent iEEG studies have provided a more detailed description of the temporal dynamics of the hippocampus and cortical region during memory retrieval, which emphasized the role of the hippocampus in driving the cortical activities during retrieval. Specifically, The high-frequency activities (gamma band activity in the range of 40-50Hz) in the hippocampus preceded the decreased oscillatory power in the alpha/beta band in the anterior temporal lobe during memory retrieval (Griffiths et al. 2019). In the long-term memory recognition task, the reinstatement of item-context associations occurred within the first second of retrieval in the hippocampus, followed by the reinstatement of item-specific information in the lateral temporal lobe from ~1s to ~3s of retrieval (Pacheco Estefan et al. 2019). The same study also revealed that the phase synchronization between the hippocampus and lateral temporal lobe preceded the item-specific reinstatement in the lateral temporal lobe.

Fig. 1 Dynamic and transformative memory representations during encoding, maintenance, and retrieval. (A) Higher-order visual representations and abstract semantic representations during early and late encoding clusters, respectively. Left: visual representational formats observed in the iEEG data during encoding of visual objects via using an eight-layer visual deep neural network model (AlexNet, see Krizhevsky et al. 2012). Right: Semantic and abstract semantic formats during encoding of visual objects via using Chinese word embedding model (see Song et al. 2018). Dashed frames indicate the encoding time clusters, during which the neural activities were reinstated during the short-term maintenance period. (B) Abstract semantic representations from the late encoding cluster are better maintained in the short-term memory. (C) Items learned in a sequential order were locked to different phases of low-

*frequency oscillations in the neocortex. P1/P2/P3 indicates the positions (order) of items in a three-item sequence. (D) Illustration of examining the continuous representational transformation of memory items across task stages. (E) Abstract semantic representations of visual items are reinstated during successful retrieval. (F) Continues transformation from encoding to maintenance and retrieval. Cross-stage transformation was examined by comparing the within-stage versus between-stage item-specific pattern similarity. EES: encoding-encoding similarity; EMS: encoding-maintenance similarity; MRS: maintenance-retrieval similarity; ERS: encoding-retrieval similarity; WI: within-item similarity; BI: between-item similarity. *: $p < 0.05$. (A-B), adapted from Liu et al. (2020). (C), adapted from Bahramisharif et al. (2018). (D-F), adapted from Liu et al. (2021).*

The role of hippocampal ripple activities in memory

The ripple activities were first discovered in the rodent hippocampus with the frequency range between ~140-200Hz (O'Keefe and Nadel 1978; Buzsáki et al. 1992). They are co-incident short-lived fast oscillatory patterns that are generated by the pyramidal cell ensemble in the CA1 (Csicsvari et al. 2000). Animal studies have implicated the hippocampal sharp-wave ripples (SWRs), the co-occurrence of ripples and sharp waves, in memory consolidation (Wilson and McNaughton 1994; Diba and Buzsáki 2007; Fernández-Ruiz et al. 2019). Specifically, rodent studies have observed that the sequential firing of hippocampal places cells during spatial navigation was replayed during the post-learning wakeful rest (Wilson and McNaughton 1994; Diba and Buzsáki 2007), as well as during sleep (Nádasdy et al. 1999), in particular, slow-wave sleep stage (Lee and Wilson 2002). Strikingly, these replays were often accompanied by hippocampal SWRs. Selective disruption of hippocampal SWRs via electrical stimulation during sleep could impair memory formation (Girardeau et al. 2009; Ego-Stengel and Wilson 2010). Using a similar method to interrupt SWRs during the encoding stage, a later study also found impairment of memory formation and memory-based decision making, suggesting an important role of hippocampal SWRs in memory encoding, consolidation, and retrieval (Jadhav et al. 2012).

In light of these inspiring findings from animal studies, it is natural to ask whether there are ripples in the human hippocampus and, if so, does hippocampal ripples only support spatial memory as extensively examined in animal studies, or it also supports other types of declarative memory in humans? Due to its high frequency and deep origin, it is a challenge to confidently isolate hippocampal ripples by non-invasive imaging methods (see recent efforts by Liu and colleagues, Liu et al. 2021b). Using iEEG recordings, several studies have investigated the functional role of hippocampal ripples in humans. First, iEEG studies have observed ripples in the human hippocampus (Fig. 2A-B), although at a lower frequency band (80-140Hz) than that found in the rodent hippocampus (Clemens et al. 2007; Axmacher et al. 2008a). Hippocampal ripples are found during an attention-demanding cognitive task, autobiographic memory recall, wakeful rest, and sleep (Fig. 2C), and the duration, rate, and peak frequencies are surprisingly consistent across states (Chen et al. 2021; Norman et al. 2021). Notably, the ripple rate during non-rapid eye movement (NREM) sleep is higher than during other task states and sleep stages. Ripple rate is also higher in the CA1 than CA2 and CA3 (Fig. 2D). The coincidence of individual ripples between every two hippocampal channels decreased sharply with increasing distance (Jiang et al. 2019; Norman et al. 2021), suggesting a local nature of the hippocampal ripples.

Second, iEEG studies have shed light on the functional role of ripples in memory formation and consolidation. For example, several iEEG studies have associated ripple activities during sleep with post-sleep performance. For example, the number of ripples that occurred in the rhinal cortex instead of the hippocampus predicts memory performance during the post-sleep stage (Axmacher et al. 2008a). Using representational similarity analysis, an iEEG study further revealed that the replay of memory representations was time-locked to hippocampal ripples during the NREM sleep (Zhang et al. 2018) (Fig. 2E), and predicted subsequent long-term memory. These results suggest that hippocampal ripples contribute to memory consolidation via memory replay. In addition to memory consolidation, emerging human iEEG studies have shown that ripples during wakeful state predict successful encoding (Norman et al. 2019) and memory retrieval (Kucewicz et al. 2014; Vaz et al. 2019; Norman et al. 2021). During encoding, hippocampal ripple rates were significantly higher for novel stimuli than that for familiar stimuli, and higher ripple rates predicted better subsequent memory performance (Norman et al. 2019; Henin et al. 2021). During memory retrieval, hippocampal ripples modulated the high-frequency activities in the neocortex, which supported memory reinstatement (Vaz et al. 2019; Norman et al. 2019; Sakon and Kahana 2021). Together, these studies highlight an important role of ripples during both wakefulness and sleep in memory (Joo and Frank 2018).

Third, several iEEG studies have started to uncover the underlying mechanisms of hippocampal ripples in triggering cortical reinstatement. For example, an iEEG study found that ripples were locked to the phase of delta oscillation (0.5-4Hz) during sleep within the hippocampus (Axmacher et al. 2008a), resembling the coupling between the hippocampal ripple and neocortical slow oscillation (SO). By simultaneously recording MTL ripples using iEEG and slow-wave oscillations using scalp EEG, one study showed that MTL ripples and spindle activities were both time-locked to the upstate of neocortical SOs (Clemens et al. 2007). The neocortical SO-spindle coupling also coordinates the MTL ripples during NREM sleep. In turn, MTL ripples mediate the information flow from the MTL to the neocortex (Helfrich et al. 2019). Consistently, another iEEG study found that neocortical spindle occurred earlier than the hippocampal spindles, followed by the hippocampal SWRs, especially for the long but not short ripples (Ngo et al. 2020) (Fig. 2F-G). These results suggest a top-down control from the neocortex to the hippocampus via sleep spindles, which potentially initiates the memory replay in the hippocampus. The hippocampal ripples then further drive the neocortical reinstatement of memory content.

Fig. 2 Hippocampal ripple and memory reinstatement. (A) Depiction of hippocampal electrodes in epilepsy patients. (B) Example of ripple activities recorded from hippocampal electrodes. (C) Ripple rates across awake tasks and sleep stages. (D) the effect of anatomical locations on ripple rates in memory-selective tasks. (E) Memory replay during NREM sleep is precisely locked to ripples. (F) ripple activities with short (mean $\pm$ SEM: duration = 0.046 ± 0.001 s) and long durations (mean $\pm$ SEM: duration = 0.059 ± 0.002 s). (G) Directional interactions from neocortex to hippocampus during the occurrence of ripples, especially long ripples. PDC: partial directed coherence in the 12-16Hz spindle range. NC: neocortex; HIPP: hippocampus; Positive PDC value indicates the information flowing from NC to HIPP and vice versa for negative PDC values. (A-C) adapted from Chen et al. (2021); (D) adapted from Norman et al. (2021); (E) adapted from Zhang et al. (2018); (F-G) adapted from Ngo et al. (2020).

The information coding scheme of human single-neuronal activities

Using microelectrodes, iEEG recordings are capable of capturing signals from single neurons, providing direct observation of information processing at the cellular level. Nevertheless, due to technical and ethical challenges, it is extremely difficult to record single neuronal activity in the

human brain. Several studies have seized this rare opportunity to uncover the information coding scheme of single-neuron activities in humans. In particular, a series of studies have examined the role of MTL neurons in signaling memory content, temporal context, and novelty, as well as in supporting memory formation and maintenance.

A classical finding from human single-unit studies is the discovery of the “concept cells”, a subset of MTL neurons that are selectively firing to specific persons or items (Quian Quiroga et al. 2005; Quian Quiroga 2012). For example, a subset of neurons showed increased firing rate to all photos of Jennifer Aniston with different views or backgrounds while showing very weak or no firings to the photos of other famous actresses, landmarks, animals, or objects. More interestingly, these neurons not only fired to the visual images but also the written or auditory names of the actress, suggesting an invariant, amodal conceptual representation (Quian Quiroga et al. 2009) (Fig. 3A). These cells were initially named “Jennifer Aniston” cells and are now termed “concept cells” (Quian Quiroga 2012). The proportion of modality-invariance neurons increases from the parahippocampal and perirhinal cortex to the entorhinal cortex and peaks in the hippocampus (Quian Quiroga et al. 2009), which resembles the increased visual invariance along the ventral visual pathway in non-human primates (Serre et al. 2007).

Are these concept cells also involved in the short-term maintenance when the stimuli are no longer presented on the screen? According to animal models, one potential neural mechanism of short-term memory maintenance is the persistent activation of neurons that are initially reactivated during the perception stage (Fuster and Alexander 1971; Curtis and D’Esposito 2003). This hypothesis was tested by two independent human single-unit studies, which both showed that the concept cells in the MTL fired during the encoding phase showed continuous firing during the maintenance period (Kamiński et al. 2017; Kornblith et al. 2017). Although a similar persistent activity was found in the medial frontal cortex, it was associated with the working memory load instead of memory content. It should be noted that persistent activities are generally obtained by averaging spikes across time and trials. When examining individual trials, recent studies have found that the neuronal spikes in support working memory occurred in a sparse, transient, and dynamic manner (Lundqvist et al. 2018; Miller et al. 2018).

In addition to the concept cells, human single-unit studies have also observed cells that signal visual categories, novelty, familiarity, confidence, temporal context of memory items in the MTL and other brain regions (Rutishauser et al. 2006, 2015, 2018). For example, by separating the neuronal responses according to subjects’ behavioral responses in a recognition task, one study has found two types of neurons, with one showing greater firing to the novel than familiar stimuli, whereas the other showing the opposing pattern (Rutishauser et al. 2015) (Fig. 3B). In addition, neurons in the posterior parietal cortex could signal the subjective confidence level of memory decisions regardless of familiarity (Rutishauser et al. 2018). Another study found that in a memory-based decision task, neurons in the medial frontal cortex could signal the abstract task goals according to the task demands (Minxha et al. 2020). Umbach and colleagues discovered “time cells” in the human hippocampus and entorhinal cortex, which signal the temporal positions of items within encoding/retrieval tasks and predict the temporal clustering of items during memory retrieval (Umbach et al. 2020). Another study also identified time cells in the hippocampus, which track the successive temporal information during sequential learning and replay during the post-encoding gaps (Reddy et al. 2021). A recent iEEG study had demonstrated the existence of “boundary cells” in the MTL, which fired increasingly when a boundary was

detected. The neural state changes elicited by the boundary at the population level also predicted temporal order memory (Zheng et al. 2021).

Single-unit recordings have also contributed to the understanding of associative learning and memory. Different items in the same episodic memory would rely on overlapping neuronal networks. This is achieved by the plasticity of concept neurons, whose firing properties can be reshaped by associative learning (Ison et al. 2015; Reddy et al. 2015). For example, A single neuron firing to a specific item during the pre-learning period showed an expanded preferred response to the associated items that co-occur with the preferred items after a few trials of learning (Ison et al. 2015). Once the associative memory is formed, effective memory cues would trigger a predictive firing of MTL neurons before the re-appearance of items (Reddy et al. 2015).

Fig. 3 Examples of memory-selective cells observed by human single-unit recordings. (A) Concept cells, which invariantly and selectively fire to specific concepts, for example, the picture or the written name of the television host Oprah Winfrey. **(B)** Memory-selective cells during the recognition task. first column: novelty cells; second column: familiarity cells; third column: cells

signal confidence level; fourth column: the average firing rate of these three types of cells during a recognition task. (A) adapted from Quiñ Quiroga et al. (2009); (B) adapted from Rutishauser et al. (2018).

The common and different neural mechanisms between humans, primates, and rodents

Our understandings of the neuronal mechanisms of cognition have been largely advanced by animal studies. A critical question is how the findings from animal studies could inform the neural mechanisms of human cognition, given the apparent difference in brain structure and functions between animals and humans. This question is challenging to address due to different neural imaging techniques, e.g., cellular recording in animals and non-invasive imaging in humans. Human intracranial EEG associated with single-unit recordings bridges the gap, providing unprecedented insights into the shared and unique neural mechanisms between humans, non-human primates, and rodents.

Existing studies have revealed that humans and rodents share similar encoding schemes during spatial navigation, memory encoding, and consolidation. For example, A well-known finding in rodents is the grid cell in the entorhinal cortex (Hafting et al. 2005). Similarly, several iEEG studies also revealed grid-like representations in the human entorhinal cortex (Jacobs et al. 2013; Maidenbaum et al. 2018; Chen et al. 2018), and this hexadirectional modulation was associated with spatial memory performance (Maidenbaum et al. 2018; Chen et al. 2018; Jun et al. 2020). Another well-documented neural code of spatial/temporal information is the phase precession (O'Keefe and Recce 1993). Phase precession refers to the time of neurons responding to the specific locations occurring progressively earlier to the phase of local theta frequency oscillations (~5-10Hz), so the spatial or temporal information could be connected into an ordered sequence within theta cycles. This phenomenon was well observed in the hippocampal place cells (O'Keefe and Recce 1993) and entorhinal grid cells in rodents (Reifenstein et al. 2012). Consistently, a recent iEEG study had observed the phase precession in the human hippocampus and entorhinal cortex when participants were performing the spatial navigation tasks (Qasim et al. 2021). In addition, as described above, both rodents and human studies have implicated the hippocampal SWRs in memory consolidation (Buzsáki et al. 2013; Buzsáki 2015; Khodagholy et al. 2017; Fernández-Ruiz et al. 2019; Ngo et al. 2020; Skelin et al. 2021).

Despite these similarities, researchers have also revealed important differences between humans and non-human animals. For example, a human iEEG study showed that hippocampal theta oscillations during navigation and memory processing are at a lower frequency (1-4Hz) as compared with that in rodents (4-10Hz) (Watrous et al. 2013; Jacobs 2014). This slower theta frequency might enable a higher working memory capacity, according to the theta-gamma coding scheme (Lisman and Jensen 2013). Similarly, the frequency of human SWRs is also lower than that found in rodents (Clemens et al. 2007; Axmacher et al. 2008a). More importantly, it is reasonable to argue that the modality-invariance conceptual cells found in the human hippocampus (Quiñ Quiroga et al. 2005, 2008) might not be possible for rodents. Nevertheless, more studies are definitely required to test this hypothesis. Finally, it usually takes much longer time to train animals than humans to perform certain cognitive tasks, and this overtraining might have introduced additional cognitive and neural processes. For example, one rodent research has revealed two types of temporal order representation in the hippocampal–entorhinal system: in addition to the temporal flow that is formed automatically with one-shot

learning, there are also representations of stable event sequence which are increased in well-practiced structured events (Tsao et al. 2018). Future studies are definitely required to address these issues.

iEEG based brain-computer interface and closed-loop brain stimulation

With the superb SNRs and high temporal resolution, the iEEG recordings could promote the development of brain-computer interfaces (BCI), a next-generation of rehabilitative technologies to restore impaired cognitive functions. For example, in a recent iEEG study, Chartier and colleagues recorded the neural activities from the human sensorimotor cortex while participants were speaking. They found the neural code that gives rise to the complex articulatory kinematics trajectories underlie fluent speech production (Chartier et al. 2018). These results were then used to develop the neural decoders that could synthesize the audible speech from the cortical activity (Anumanchipalli et al. 2019). In another instance, ECoG has been applied to measure signals from the motor cortex, which have then been used to control the prosthetic hands and arms. Compared to scalp EEG, the BCI using ECoG could achieve more accurate operation with fewer training trials (Leuthardt et al. 2004; Yanagisawa et al. 2011; Anderson et al. 2012; Romanelli et al. 2018).

As both a recording and modulation technology, iEEG could also help to develop the state-of-the-art closed-loop brain stimulation system, which could establish a causal relationship between neural activities and behavior and also improve behavioral outcomes. Almost 70 years ago, Wilder Penfield mapped the brain functions by directly stimulating different brain areas during brain surgery (Penfield and Jasper 1954; Penfield and Roberts 2014). Although an increasing number of studies have shown that non-invasive stimulation, including transcranial current or magnetic stimulation, can modulate various brain functions, including perception (Romanska et al. 2015), attention (Li et al. 2017), decision (Xue et al. 2012), cognitive control (Cai et al. 2016), working memory and long-term memories (Marshall et al. 2004; Fregni et al. 2005; Brunoni and Vanderhasselt 2014; Lu et al. 2015), the exact mechanisms are less clear due to low spatial specificity. For example, one study directly tested the effect of the tACS via using the iEEG recordings but failed to find any effects of applied low-frequency tACS on brain rhythms (Lafon et al. 2017). Still, transcranial stimulations so far cannot directly target deep brain structures.

To circumvent these issues, researchers have applied direct electrical brain stimulation (EBS) on epilepsy patients. The studies on memories have found inconsistent results, with some studies showing memory enhancement (Suthana et al. 2012; Inman et al. 2018; Kucewicz et al. 2018), whereas others are showing memory impairment (Lacruz et al. 2010; Jacobs et al. 2016; Merkow et al. 2017; Goyal et al. 2018). The mixed results might be explained by the interacting effect of ongoing brain states and stimulation (Silvanto et al. 2008). For example, Ezzyat and colleagues showed stimulations during a state of low encoding efficacy could promote memory and otherwise could impair memory (Ezzyat et al. 2017). To address this issue, they developed a closed-loop stimulation scheme, in which the stimulation was triggered by a neural state that indicates subsequent memory forgetting. Using this novel approach, they have revealed a robust enhancement effect of hippocampal stimulation on long-term memory (Ezzyat et al. 2018) (Fig. 4).

Fig. 4 Closed-loop brain stimulation using iEEG to modulate memory performance. (A) Illustration of the closed-loop stimulation. First, a classifier is trained using an independent data set. Second, the spectral decomposition analysis is performed during online recording. Third, apply the pre-trained classifier to the spectral decomposed data. Fourth, an electric pulse is triggered if the decoding evidence reaches the threshold. **(B)** The number of successfully recalled items in the stimulation (Stim) vs. no stimulation (NoStim) condition. The stimulation was applied to the lateral temporal lobe. **(C)** Lateral temporal lobe stimulation increased classifier evidence during memory encoding. This figure is adapted from (Ezzyat et al. 2018).

Summary and a practical guidance

So far, we have provided an overall description of the methodological advantages of iEEG and illustrated its implications in addressing fundamental questions in cognitive neuroscience. Compared with the non-invasive brain imaging methods, the ability of iEEG to directly record single-neuron spikes and LFP with greater spatial-temporal resolution and SNRs are unprecedentedly rare and precious. Nevertheless, it is important to notice its limitations when planning your studies. First of all, due to ethical issues, iEEG recordings are typically performed in drug-resistant epilepsy patients for clinical purposes, which makes iEEG less accessible than other non-invasive neuroimaging methods. Second, the electrodes are usually implanted for 2-3 weeks, during which extensive physical examinations are conducted, leaving limited time windows for conducting experiments. It usually takes much longer to collect data from the required number of participants for the above reasons. Third, the electrodes are implanted to localize the seizure onset zone, thus are most likely in or near the epileptic loci. As a result, it is unlikely to get a full brain coverage of electrodes. Moreover, the signals could be smeared by the epileptic spikes, particularly when electrodes are located near the epileptic loci. Thus, iEEG is often less optimal for examining the interactions across wide brain networks. Finally, the implantation schemes are heterogeneous across patients, severely limiting the ability to compare subgroups.

Given these apparent strengths and limitations, it is vital to decide when to choose iEEG recordings over other non-invasive imaging methods. To protect patients' rights, a rule of thumb is always to choose non-invasive imaging methods when they are sufficient to address your research questions. For example, if you are interested in temporal dynamic changes of neocortical brain regions, EEG and MEG can be good options. If you are interested in localizing the brain regions where information is processed or stored, fMRI could be a good choice. Nevertheless, if you are interested in brain oscillations of deep brain regions, such as the medial

temporal lobe or thalamus, iEEG would be a good choice. Moreover, the patients are usually in a less optimal state, cognitively and emotionally, and fatigue is a common symptom in epilepsy (Kwon et al. 2017) (see also chapter 3 for a detailed description of the cognitive status of epilepsy patients). Therefore, it is important to avoid tasks that are either cognitively challenging, may introduce intense arousal and emotional responses, or take an excessively long time (e.g., > 2 hours). Also, it is critical to avoid tasks that might induce a seizure. Finally, the iEEG study should be designed and conducted with potential benefits to the patients whenever possible. For example, in developing the mind-controlled robotic arms for paralyzed patients, intracranial EEG recordings with high SNRs and spatiotemporal resolution might be better than other non-invasive imaging methods. Similarly, deep brain stimulation protocols can be conducted to suppress seizures or improve cognitive functions (see also chapter 11 for a detailed description of iEEG experimental design and brain stimulation). Still, studies that could potentially localize the brain regions involved in essential brain functions, such as motor, language, memory, could be conducted to aid surgical planning. Together, iEEG studies are suggested when researchers need to record neural activities at high spatial-temporal resolutions from deep brain structures and should be conducted with careful considerations to patients.

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