Direct brain recordings fuel advances in cognitive electrophysiology

Joshua Jacobs & Michael J. Kahana

Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104, USA

Direct correspondence to:

Dr. Joshua Jacobs
University of Pennsylvania
3401 Walnut Street
Room 333C
Philadelphia, PA 19104
Phone: 215-746-3500
Fax: 215-746-6848
E-mail: `jojacobs@psych.upenn.edu`

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Abstract

Electrocorticographic brain recordings from patients with surgically implanted electrodes have recently emerged as a powerful tool for examining the neural basis of human cognition. These recordings measure the brain's electrical activity directly, and thus provide data with a higher temporal and spatial resolution than other human neuroimaging techniques. Here, we review recent research in this area and, in particular, we explain how electrocorticographic recordings have informed the neural basis of human working memory, episodic memory, language, and spatial navigation. In some cases this research has identified human brain patterns that were unexpected on the basis of studies in animals.

Brain oscillations and cognition

Neuronal oscillations are a fundamental component of normal brain function. In both humans and animals, neuronal oscillations appear in distinct spatiotemporal patterns that show active brain regions, indicate the types of neuronal computations that occur, and reveal how information flows through the brain. For ethical reasons researchers typically examine these patterns only in animals. However, in the past decade researchers have increasingly examined electrocorticographic (ECoG) recordings of brain oscillations from patients with surgically implanted electrodes. These recordings measure the brain's oscillatory activity with a higher spatial and temporal resolution than other human brain data. During ECoG monitoring, patients are typically conscious and capable of performing complex cognitive tasks. Thus, researchers can use these recordings to study detailed electrophysiological correlates of a wide range of cognitive processes [1, 2].

Here we review recent research using ECoG recordings of brain oscillations to analyze the neural basis of cognition. First, we outline the patterns of oscillations that appear in human ECoG recordings and describe how these signals relate to neuronal spiking. Then, we describe how this research expands our understanding of the neural basis of four complex cognitive domains: working memory, episodic memory, language, and spatial navigation.

Human electrocorticographic recordings

Clinical teams use surgically implanted electrodes to diagnose and treat neurological conditions where brain activity must be probed with a high spatial and temporal precision. Doctors use this procedure in a variety of situations, such as performing deep-brain stimulation when treating Parkinson's disease or mapping functional or damaged regions while examining epilepsy or tumors. Here our focus is on ECoG recordings from patients undergoing invasive monitoring for drug-resistant epilepsy. In this procedure, clinical teams implant ~40–120 electrodes in widespread regions of a patient's brain to identify epileptic foci for potential surgical resection (Fig. 1A). Electrodes remain in place throughout a patient's ~1–3-week hospital stay. During this period patients often have significant free time to perform cognitive tasks. Implanted electrodes include both grid and strip electrodes (Fig. 1B,C), which record ECoG signals from the cortical surface,

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and depth electrodes (Fig. 1D), which penetrate the cortical surface to record field potentials from deep brain structures. In this review we use the term 'ECoG' to refer to both surface and depth recordings. On occasion clinicians implant epilepsy patients with microelectrodes that record individual action potentials (Fig. 1E). We discuss microelectrode recordings only briefly because this procedure is rare and has been reviewed recently [3].

Unlike noninvasive techniques, such as scalp electroencephalography (EEG) or magnetoencephalography (MEG), ECoG recordings measure the brain's electrical activity directly. Thus, they are considered the clinical "gold standard" for accurately identifying seizure foci [4]. For the same reasons that ECoG recordings are useful to clinicians, these data are beneficial for researchers. ECoG reliably measures neural patterns with a resolution of ~4-mm^2 [5]. In contrast, each MEG or EEG sensor records from a relatively large region of cortex. Noninvasive recordings, even with advanced source-localization techniques, sometimes miss patterns that are clearly visible in ECoG data [6]. Furthermore, noninvasive techniques have difficulty isolating activity from deep brain structures and are more susceptible to muscle artifacts than ECoG [7].

Each ECoG electrode measures the combined synaptic activity across the nearby population of neurons, rather than recording individual action potentials [8, 1]. Due to this aggregation, ECoG recordings provide researchers with a measure of the electrical activity that is synchronized across large numbers of neurons. These recordings typically observe oscillations. Neuronal oscillations appear as sinusoidal changes over time in the voltage observed from an electrode (Fig. 1F,G). They appear at frequencies from <0.1 Hz to 500 Hz and are visible at multiple spatial scales, from scalp EEG to intracellular recordings [9]. Researchers believe that oscillations play a critical role in large-scale neuronal computations. When an individual neuron oscillates, it undergoes rhythmic variations in its level of excitability [10]. Animal recordings and computational models indicate that oscillations facilitate communication in large neuronal networks because they cause constituent neurons to become excited synchronously [11, 12]. Generally, slower oscillations synchronize large neuron groups across broad brain regions and faster oscillations coordinate smaller, localized neuronal assemblies [13, 9]. However, there are also examples of relatively fast oscillations synchronizing widely separated brain regions [14, 15]. Distinct physiological processes generate oscillations at various frequencies and brain regions [13]. However, in particular, in-

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hibitory interneurons play a critical role in the generation of many oscillations [16, 17]. Thus, the appearance of an oscillation in an ECoG recording indicates that interneurons are especially active [8] and firing synchronously [18].

Detailed electrophysiological studies in animals show that neuronal oscillations have a number of interesting functional properties. Generally, the presence of an oscillation indicates that a brain region has an increased level of activity relative to baseline [9, 10]. In addition, when groups of neurons oscillate together synchronously, they are more effective at exchanging information [11, 12]. Furthermore, oscillations underlie phase coding, a phenomenon in which individual neurons encode information by spiking at a particular phase of ongoing oscillations [19, 10].

Researchers have used spectral analyses to measure properties of ECoG oscillations as patients perform controlled tasks to characterize the functional role of brain oscillations in cognition. This work showed that, in particular brain regions, the amplitudes of oscillations at certain frequencies correlated with distinct aspects of behavior. For example, research showed that the amplitude of human theta oscillations increased during memory tasks [20, 21], which is consistent with animal research implicating theta in synaptic plasticity [22]. During human and animal sensorimotor processing, there was a focal increase in the amplitude of gamma activity in the neocortical region that corresponds to the body part that feels a percept or performs a movement [1]. In addition to amplitude changes, some oscillations exhibit phase resets following salient external events [23]. Researchers have also identified more-complex oscillatory phenomena in humans, such as phase–amplitude coupling [24, 25, 26] and inter-region oscillatory phase synchrony [27, 28, 29, 30].

In particular, attention plays a general role in modulating neuronal oscillations throughout a wide range of behaviors. After a percept is presented, the oscillatory patterns that appear in a patient's brain are greater in amplitude if the stimulus is actively attended, rather than if the stimulus is ignored [31, 32]. In addition, research in animals indicates that attended stimuli are represented by more-distinctive patterns of oscillations than unattended stimuli [33]. These results suggest that attention modulates brain oscillations in a manner that allows downstream regions to determine the relevant stimuli for the current task [32].

In addition to spectral analyses of oscillatory power and phase, other work has examined ECoG recordings using event-related potentials (ERPs). This technique is designed to measure

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ECoG waveforms that are evoked after important cognitive events. However, in practice, evoked activity can be difficult to distinguish from oscillatory phase resets, because both phenomena often appear as significant patterns in ERP analyses [34]. Distinguishing between these evoked activity and phase resets is an important area of ongoing research [35]. Here we emphasize research findings concerning oscillations rather than ERPs because we have a better understanding of how oscillations relate to the activities of individual neurons [8, 36, 18].

Complementing oscillatory patterns that appear at specific frequencies, researchers have reported broadband power changes in ECoG recordings [37, 38, 1]. These are power changes that appear at many or all frequencies. Miller et al. [39] suggested that broadband ECoG power increases are the direct result of neurons in a region increasing their spiking rate. Supporting this view is the empirical finding that human neuronal spiking rates are consistently positively correlated with broadband power [40] and data from computational models indicating that neuronal spiking appears at various frequencies in ECoG recordings [5, 41]. This work raises the intriguing possibility that standard ECoG grid and strip electrodes can provide an estimate of nonoscillatory neuronal spiking rates, even though these electrodes are much larger than the ones typically used to record action potentials. Thus, developing improved methods for distinguishing broadband power changes from narrowband oscillations is a fruitful avenue for future research.

Finally, in addition to examining human ECoG recordings alone, other studies examined the relation between ECoG oscillations and the spiking of individual neurons. This work indicates that recordings of human brain oscillations can predict both the timing and rate of neuronal spiking (see Box 1) [36, 18, 42, 40]. Furthermore, research in humans and animals has shown that ECoG activity correlates with the blood-oxygenation signal observed with functional magnetic resonance imaging (fMRI) [8, 18, 43, 44, 45]. Scientists have used fMRI to map how the brain encodes diverse types of perceptual and conceptual information [46]. Because the signals measured with fMRI and ECoG share some properties, it suggests that ECoG oscillations can elucidate neural patterns that underlie various cognitive representations (Box 2).

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Glossary

Broadband power. The overall energy, or variance, of a time series. Whereas changes in broadband power appear at many or all frequencies, changes in narrowband power are often specific to a given frequency band.

Gamma oscillation. Rhythmic neural activity in the ~30–100 Hz frequency range. Gamma oscillations have been implicated in a wide range of cognitive processes including perception, attention, and memory.

Phase synchrony. Two or more neural assemblies oscillating together with a consistent phase relationship.

Phase reset. An oscillation exhibiting an altered phase as the result of an external event.

Phase–amplitude coupling. A pattern where one oscillation's amplitude varies with the phase of a slower oscillation. Phase–amplitude coupling is prevalent in human neocortex, where gamma oscillations have greater amplitude at the trough of theta oscillations [25].

Theta oscillation. Rhythmic neural activity at ~3–10 Hz. Theta oscillations have been implicated in memory both at the behavioral level [20, 47] and at cell-level processes [48, 49].

Oscillations and cognition

Over the past decade, researchers examining ECoG recordings of human brain oscillations identified neural correlates of various perceptual, motor, and cognitive processes [1, 2]. Below, we review how ECoG data have informed our understanding of the neural basis of four cognitive processes: working memory, episodic memory, language, and spatial navigation.

Working memory. Working memory—the process of remembering a stimulus temporarily for immediate processing—is critical for many common tasks. Experimentally, researchers often examine working memory using a task where a participant views a short list of items and, after a short delay, is asked to indicate whether a probe item appeared in the list (Fig. 2A). Thus, a trial in this task has three phases: stimulus encoding, memory retention, and memory retrieval.

Examining ECoG activity during stimulus encoding, researchers have identified several distinct neural patterns that have furthered our understanding of how the brain encodes memories. One of the most dramatic occurrences of these is a post-stimulus phase-reset of theta oscillations (Fig. 2B). Because individual neurons activate at particular theta phases (see Box 1) [36], these phase resets indicate that neurons across the brain spike in precise spatiotemporal patterns during stimulus processing. This is consistent with models of cortical processing derived from animal studies that involve large-scale synchronous neuronal activity [42]. In addition, viewing a stimulus causes an increase in the amplitude of gamma-band activity at many sites [50, 38]. This stimulus-induced gamma activity is often coupled to the phase of simultaneous theta oscillations [24, 51]. This is consistent with Canolty et al.'s finding that phase–amplitude coupling between theta and gamma oscillations underlies various neural processes [25]. Generally, the appearance of gamma-band activity indicates that a brain region is active [10, 18]. Thus, because some locations selectively exhibit gamma activity when particular stimulus types are perceived, these patterns identify brain regions that support different classes of cognitive representations [52, 50, 38, 53, 54, 55, 56]. Furthermore, these patterns also encode detailed information regarding the identity of the specific stimulus that is viewed (see Box 2). This supports the view that gamma-band activity is a rich information source that can be used to decode specific cortical network states [57, 58, 59, 51].

After a person encodes a stimulus, their next task is to retain it in memory. ECoG recordings indicate that the set of brain regions that support working-memory maintenance is different from the areas involved in perception. In fact, some regions involved in memory maintenance were traditionally thought to support language [60]. During memory retention, one study found that different cortical regions exhibited phase synchrony between oscillations in the beta band (~16–30 Hz) [27]. Notably, other human studies also reported cortical phase synchrony in the beta frequency band [29, 30], rather than in the gamma range where these patterns typically appear in animals [61, 12]—the different frequencies of these phenomena may be an important difference between humans and animals. Researchers have also examined the neural basis of memory retention by identifying ECoG patterns that correlate with memory load (the number of stimuli remembered at any moment). In particular, the amplitude of gamma activity at many electrodes increases linearly with memory load (Fig. 2C), revealing specific brain regions involved

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in memory maintenance [62, 60] and indicating that gamma oscillations play a role in persistent neural representations [63, 10]. In a smaller number of regions, gamma amplitude is inversely related to memory load [64]. This emphasizes the diversity of memory-load–related patterns across the brain. In addition to gamma, theta oscillations are also linked to memory maintenance, as some sites exhibit robust increases in theta power during memory maintenance, relative to baseline (Fig. 2D; [20]).

The final phase of each trial is the retrieval interval, where the participant determines whether a probe stimulus matches one of the remembered list items. After a probe is viewed, theta oscillations at many sites reset in phase again (Fig. 2B,E). However, between the probe and the list items, some sites reset to different phases [65], with varying levels of precision [23]. This supports the theory that the trough phase of hippocampal theta is involved in memory encoding and that the peak is used for retrieval [49]. ECoG recordings can also reveal details of the neural computations involved in comparing a stimulus to the contents of memory: For example, van Vugt et al. found that the amplitude of frontal activity in the delta band (1–4 Hz) correlated with the similarity between the probe and the items held in memory [66]. This establishes electrophysiological support for psychological theories that propose that humans recognize stimuli by computing a graded measure of the similarity between a percept and the contents of memory [67, 68].

Episodic memory.   An issue of significant practical and theoretical interest is why people remember some events easily whereas they are unable to remember others despite much effort [69]. This issue is a core topic in the study of episodic memory (i.e., memory for autobiographical events). Experimentally, one way of probing the neural basis of episodic memory is via the free-recall task. In this task, a person is presented with a list of items and is later asked to recall the list items in any order.

Analyzing brain activity as patients studied lists of items, Sederberg et al. identified patterns of theta and gamma oscillations in widespread brain regions that significantly varied in amplitude according to whether a viewed stimulus would be recalled successfully [21]. Later studies showed that these patterns were especially prominent at gamma frequencies in the left inferior frontal gyrus [70], which is consistent with neuroimaging studies implicating this region in episodic-memory formation [71]. The high spatial resolution of ECoG was critical for identifying this detailed

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pattern, which had not been observed previously with noninvasive recordings. Furthermore, during memory retrieval, theta and gamma activity appeared in the same brain regions as during encoding [72], which supports the view that memory retrieval involves reinstating the patterns of brain activity that appeared during learning [69].

Since a broad literature shows that the hippocampus underlies long-term memory [73, 47], it is important to characterize the electrophysiological activity in this region during memory formation. Towards this end, researchers have identified differing electrophysiological patterns in animals and humans. In animals, hippocampal theta oscillations reliably increase in amplitude during memory encoding [74, 47]. In contrast, human hippocampal recordings show that successful memory encoding is associated with decreased activity at many frequencies [70]. A subsequent study by Axmacher et al. further illustrated the complex role of the hippocampus in human memory, showing that hippocampal activity (measured via slow voltage shifts) is positively correlated with successfully remembering stimuli that are retained for long durations and is negatively correlated with remembering stimuli that are retained for short durations [75]. One potential explanation for this result is that humans use different physiological processes to remember items that are retained for different lengths of time [76].

Empirical and theoretical work indicates that memories are initially stored in hippocampus and later transferred to neocortex [73]. This predicts that there is communication between hippocampus and neocortex during memory encoding [77]. To the extent that neuronal oscillations reveal inter-region communication [63, 9], human ECoG data support this theory. When a stimulus is successfully memorized, Fell et al. observed increased gamma-band coherence between rhinal cortex and hippocampus [14]. Furthermore, when a memory is retrieved, there is elevated gamma synchrony in regions projecting to hippocampus [78]. This pattern also appears outside of controlled experiments, demonstrated by the finding that the level of rhinal–hippocampal coherence observed during sleep predicted whether dreams would be subsequently remembered [79]. Together, these findings show that cortico–hippocampal interactions play an important role in human memory and, more broadly, demonstrate that neuronal oscillations are not only informative about the activity within individual brain areas, but they also show how information is transferred between regions.

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Language. Human ECoG recordings are especially useful for studying auditory linguistic processes because electrodes are frequently implanted in brain regions that are critical for listening and speaking. Analyses of ECoG recordings during listening and speaking have provided support for the traditional view that language comprehension is supported by Wernicke's Area and that language production involves Broca's Area [1, 80, 54]. However, ECoG studies have also implicated more widespread cortical networks in both language comprehension and production, as we discuss below.

After hearing a word, there is a dramatic increase in the amplitude of ECoG gamma activity in regions near Wernicke's Area, including the superior temporal gyrus (STG) and cortex surrounding the superior temporal sulcus (STS) [80, 1]. ECoG recordings revealed that this language-related activity flows from the posterior STG, to the middle STG, followed by the STS. In STG, gamma activity generally encodes low-level acoustic properties of a sound [80]. However, by the time this activity reaches the STS, its amplitude and duration encode lexical information [80, 54]. These findings are consistent with a model proposing the sequential processing of linguistic information along the STG–STS pathway [81]. In addition to temporal-lobe activations, linguistic processing also involves neuronal activity outside the temporal lobe, as one ECoG study reported that parietal and frontal gamma activity varied in amplitude according to whether a syllable is recognized [82].

ECoG studies of language provided evidence to support theories from fMRI that semantic information is represented throughout bilateral cortical regions, but that lower-level linguistic information is represented unilaterally [81, 46]. One study found that when a patient performed a lexical-decision task, task-related gamma activity appeared only in the temporal cortex of the language-dominant hemisphere. In contrast, a picture-naming task, which required deeper semantic processing, activated bilateral temporal regions [38]. In addition to temporal regions, semantic information is also represented in frontal cortices. This was shown by ECoG recordings from patients performing a semantic-decision task, which revealed frontal gamma oscillations that appeared at different latencies according to whether a patient was presented with semantically related or unrelated stimuli [83].

A recent study by Sahin et al. investigated ECoG recordings from Broca's Area to examine the role of this region in speech and grammar. Examining recordings while participants were shown

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words that they were asked to imagine speaking, the authors identified three ERP components representing different linguistic properties of the to-be-produced word [84]: The ERP component at ~200-ms encoded the word's lexical properties (whether it was rare or common), the ~320-ms component indicated the word's grammatical properties (whether it was inflected), and the ~450-ms component correlated with the word's phonological properties (number of syllables). Because these ERP components have different spatiotemporal characteristics, this research indicates that Broca's Area contains a series of spatially distinct networks that sequentially perform different linguistic computations. Furthermore, the early timing of the lexical ERP component is important evidence that Broca's Area plays a role in word comprehension.

ECoG recordings during speech indicates that frontal regions, like Broca's Area, are involved in language production [1, 54]. Analyzing the temporal dynamics of ECoG speech patterns has led to additional insights. Frontal gamma activity becomes elevated ~800 ms before speaking, which suggests that this activity relates to speech–motor planning rather than direct motor output [54]. During speaking, gamma activity in the mouth region of motor cortex is synchronized with activity both in frontal regions and Wernicke's Area [85], which indicates that speech articulations are directly driven by multiple cortical regions, in addition to Broca's Area.

Spatial navigation. Spatial navigation is an essential behavior for nearly all humans and animals. Because spatial processing is such an innate function, understanding its neural basis can reveal important similarities and differences between human and animal neurophysiology. Although patients undergoing clinical monitoring for epilepsy are confined to a hospital bed, researchers can nonetheless study brain activity during spatial cognition using computer-based virtual-navigation tasks [86, 87].

During navigation, the human brain exhibits several oscillatory patterns that are analogous to patterns observed in animals. When a rodent is moving, theta oscillations appear prominently in the hippocampus [47]. Similarly, when humans navigate virtual environments, theta oscillations in widespread regions increase in amplitude [86, 87]. The amplitude of these oscillations positively correlates with navigation performance [88], indicating that this pattern has a causal role in spatial cognition [47]. In particular, the unique ability of human intracranial recordings to measure activity from deep brain structures allowed researchers to compare and contrast the

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properties of hippocampal oscillations in humans and animals. Researchers have identified two potential interspecies differences in the properties of hippocampal theta. In rodents, hippocampal theta oscillations reliably appear at 4–8 Hz [47]; however, in humans the prominent hippocampal oscillation appears at a slower frequency of 1–4 Hz [89, 90, 87, 36, 91, 88, 92]. Furthermore, whereas hippocampal theta activity in animals stays elevated for relatively long durations [19, 47], theta oscillations in humans often appear transiently [86, 87] and sometimes not at all [93]. Because human 1–4-Hz hippocampal oscillations have similar behavioral properties as the 4–8-Hz hippocampal theta oscillations observed in rodents [87, 94], it suggests that human 1–4-Hz hippocampal activity is functionally equivalent to rodent hippocampal theta. In contrast, human neocortical theta oscillations typically appear at 4–8 Hz [86, 36]. However, because a recent study provided evidence of 1–4-Hz oscillatory coherence between hippocampus and neocortex [91], it suggests that human neocortex could exhibit theta-like activity at multiple frequencies [95].

Beyond hippocampus, human navigation-related brain oscillations also appear in widespread neocortical regions [86, 87]. Neuroimaging and lesion studies have shown that the right hemisphere of the neocortex plays a unique role in spatial cognition [96]. To link hemisphere-lateralization research with electrophysiological findings, a recent study compared the prevalence of navigation-related ECoG oscillations throughout the brain [94]. This study found that navigation-related gamma activity was especially prevalent in the right hemisphere, compared to the left. This supports the view that the right hemisphere is important for spatial processing and adds to literature indicating that gamma oscillations and fMRI activations identify similar neuronal patterns [8, 18].

Conclusions and future directions

Human ECoG recordings have implicated brain oscillations in various types of brain functions, including both cognitive and sensorimotor processes [1, 2]. Although oscillations at many frequencies have been found to correlate with cognitive processes, the theta and gamma bands are most frequently found to covary with cognitive demands. Theta and gamma oscillations each have distinct physiological and computational properties (Box 1). Thus, these oscillations provide insight into the neuronal processes that underlie different aspects of human cognition: Theta oscillations are more-closely associated with temporally precise neuronal spiking, rather than changes in firing

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rate [36, 18, 43]. This suggests that cognitive processes that correlate with theta activity, such as movement during navigation [86] and working-memory retention [20, 97], are supported neurally by temporally precise spiking patterns, rather than by firing-rate changes. In contrast, gamma-band activity is correlated with both elevated neuronal firing rates [58, 8, 39, 18, 12] and precisely timed spiking activity [10, 36]. Thus, cognitive variables that relate to gamma activity, such as memory load [62, 64], are likely associated with neuronal computations that involve both firing-rate coding and temporal coding. Beyond theta and gamma, an emerging pattern is broadband ECoG power—this phenomenon is an indication of cognitive processes that involve firing-rate changes but not temporally precise oscillatory spiking [5]. More generally, these patterns show that ECoG recordings can be used to elucidate the neuronal patterns that support different human cognitive processes. Because ECoG recordings reveal this information with a greater precision than noninvasive techniques, they allow researchers to draw insights into human cognitive electrophysiology at a level of detail that rivals direct animal brain recordings. This has revealed unique human electrophysiological patterns that do not appear in animals [27, 97, 36, 94, 84], as well as similarities between human and animal brain activities [8, 86, 47, 87, 18, 6, 43].

There are several exciting developments underway in the study of cognitive electrophysiology with ECoG data. Perhaps the most important of these is the study of oscillatory interactions across regions [29, 28] and of interactions between oscillations at different frequencies within the same region [24, 25, 98]. To the extent that oscillations at different frequencies have distinct functions, cross-frequency interactions appear to play a critical role in linking physically disparate neuronal networks [95]. Thus, an important area of future research is identifying how oscillatory interactions, across both regions and frequencies, relate to cognitive processes. Another emerging research trend is the use of real-time "closed loop" systems that vary the parameters of an experiment according to instantaneous brain activity [99, 100]. This research seeks to determine whether recordings of brain activity can be used to alter human behavioral performance, and thus this work has the potential to distinguish the ECoG signals have a causal role in behavior.

Box 1: Oscillatory activity and neuronal spiking

Some epilepsy patients undergoing intracranial monitoring are implanted with special depth electrodes that have microwires extending from their tips (Fig. 1E). These microwires record single-neuron action potentials, which allows researchers to examine the relation between neuronal spiking and simultaneous brain oscillations.

Research in animals shows that brain oscillations provide a neuronal timing signal that allows neurons to encode information by spiking at a particular phase of an oscillation—a phenomenon called phase coding [19, 10]. To examine the prevalence and properties of phase coding in humans, one recent study examined how neurons in widespread regions varied their instantaneous firing rate according to the phase of ongoing oscillations [36]. This work found that many neurons were *phase locked* to oscillations, a phenomenon in which they increased their firing rate at a particular phase of these oscillations. Figure 3A shows the activity of a neuron that exhibits this phenomenon by spiking just before the peak of the theta oscillation. The properties of neuronal phase locking varied between high- and low-frequency oscillations. Neurons phase locked to oscillations at frequencies slower than 10 Hz had various preferred phases, whereas neurons phase locked to oscillations faster than 10 Hz had preferred phases near the oscillation's trough. This indicates that oscillations faster than ~10 Hz reveal specific times (the trough of the oscillation) when many neurons are active, whereas slower oscillations cannot predict population spike times with this level of precision.

In addition to examining the timing of individual action potentials, a different set of studies examined the relation between the rate of neuronal spiking and the amplitude of oscillatory activity. In some cases, neuronal firing rate is well predicted by the amplitude of simultaneous oscillations (Fig. 3B). However, the details of this relation dramatically vary according to the oscillation and brain region being examined. Oscillations at high frequencies (>10 Hz) in sensory cortex correlate positively with neuronal spiking [18] and a similar, but weaker, pattern appears in hippocampus [43]. In contrast, low-frequency oscillations exhibit varied correlations with single-neuron spiking: In neocortex, theta- and alpha-band oscillatory power is negatively correlated with neuronal spiking [18], but in hippocampus these oscillations do not correlate with spiking rate [43]. Overall, this work shows that ECoG recordings provide a temporally precise indication

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of neuronal spiking, which may complement techniques like fMRI that measure neuronal activity with less precision [8, 18, 45].

Box 2: Brain oscillations reveal neuronal correlates of specific cognitive representations

Research on human brain oscillations has generally sought to identify broad cognitive processes that are correlated with the properties of different neural signals. For example, research on the hippocampal theta oscillation has characterized oscillatory activity that increases in amplitude during memory and navigation [47, 87]. However, in addition, Freeman found that gamma oscillations could be used to reveal specific cortical network states [57, 58]. Examining oscillatory activity in sensory cortices, Freeman observed that the identity of a percept was encoded in the landscape of gamma-band activity. This indicates that cortical recordings of brain oscillations can predict sensory inputs, because individual stimuli were associated with distributed patterns of gamma activity that had different spatial topographies. These stimulus-specific patterns are important theoretically because they suggest that gamma oscillations can identify neuronal patterns that underlie specific cortical-network states.

Following this line of work, Jacobs and Kahana [51] examined stimulus-specific activity in human ECoG recordings. This study measured gamma-band oscillatory brain activity from 37 patients memorizing lists of letters. After each letter was presented, the amplitude of oscillatory activity at many sites varied according to the identity of the viewed letter. As an example of this phenomenon, Figure 4 depicts the amplitude of high-gamma activity observed at a site from left temporal cortex. At this site, an overall increase in gamma activity appeared ~100 ms after the letter appeared; and, subsequently, the amplitude of this signal varied with the viewed letter's identity. Significant numbers of electrodes exhibiting stimulus-specific activity appeared in occipital and temporal regions. Furthermore, at some sites in occipital cortex these patterns encoded visual features of the viewed letter's shape, which is consistent with previous observations that activity in sensory regions encoded perceptual features of stimuli [61, 18, 46]. This work shows that human ECoG recordings can reveal detailed information about the state of a cortical network. Because

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gamma-band activity appears in widespread brain regions [52, 10], going forward, stimulus-specific gamma patterns may be used for mapping the neural basis of various specific cognitive states.

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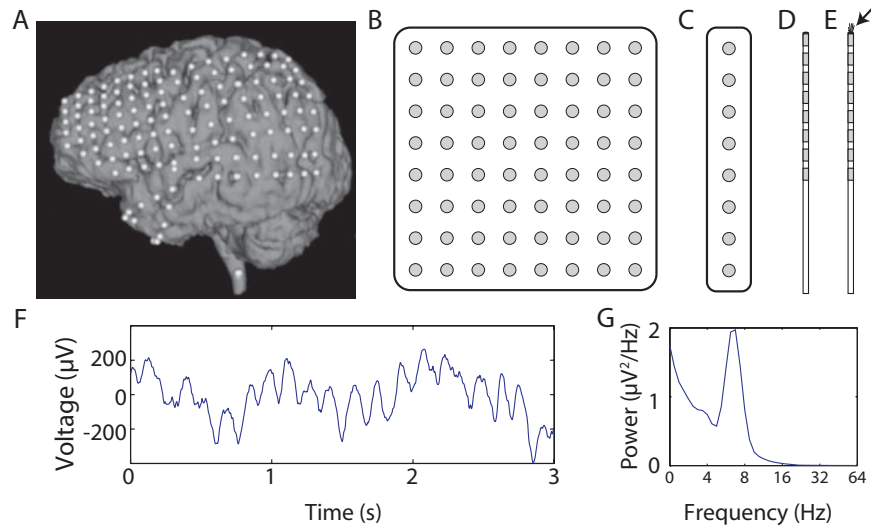
Figure 1: **Performing electrocorticographic recordings in humans .** **A.** An MRI image of one patient's brain with the locations of implanted ECoG electrodes indicated with white dots. Modified, with permission, from Ref. [54]. **B.** An illustration of an 8×8 electrode grid; gray shading indicates electrodes' conductive surfaces. (Illustrations not to scale). **C.** A illustration of an 8-electrode strip electrode. **D.** A depth electrode with eight contacts. **E.** A depth electrode with microwires extending from the tip to record action potentials (marked by the arrow). **F.** A recording of ECoG activity from the right temporal gyrus. **G.** The power spectrum of the recording from Panel F, which shows that this trace exhibits a robust theta oscillation.
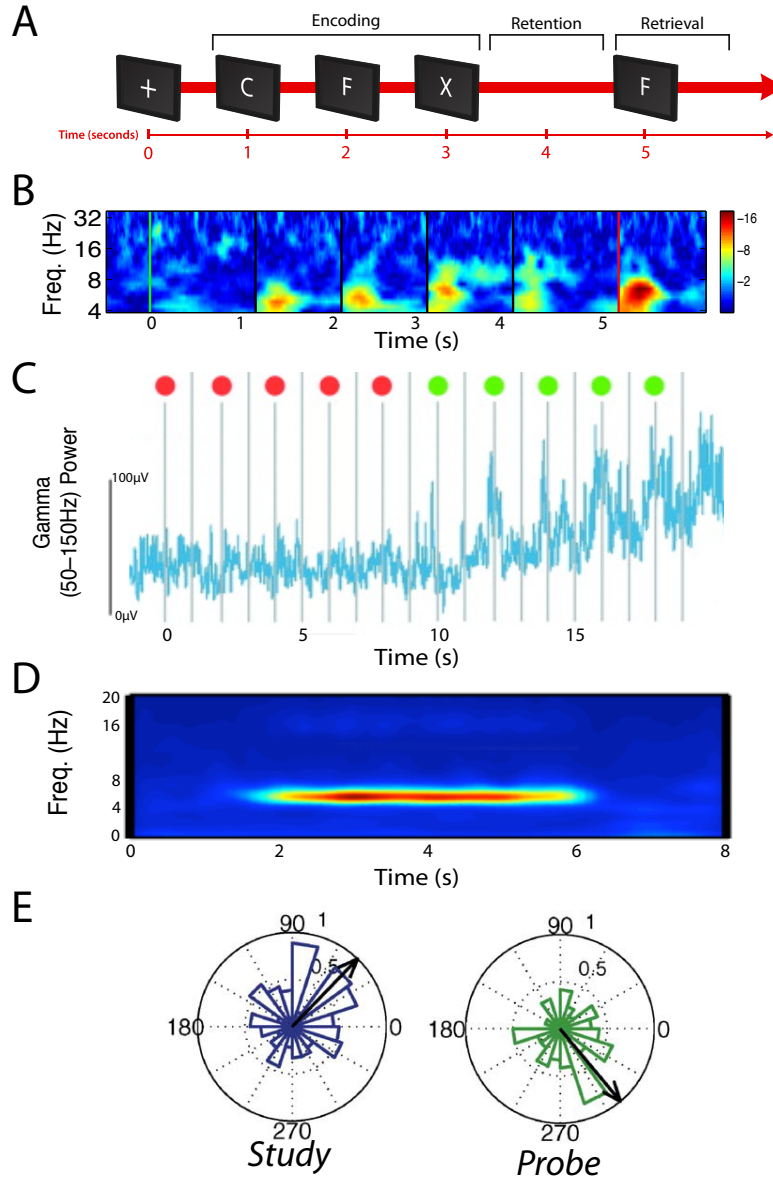
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Figure 2: **Oscillatory brain activity in human working memory. A.** Schematic of a working-memory task. **B.** Phase-reset analysis of ECoG activity from an electrode in one patient's right subcallosal gyrus during this task. The color at each frequency and timepoint indicates the z score from a Raleigh test evaluating the uniformity of the ECoG phase distribution (computed across trials). Warm colors indicate significant phase resetting. Modified, with permission, from Ref. [23]. **C.** Gamma power from a Broca's Area electrode in a different patient performing a variant of this task where each stimulus is preceded by an indication of whether the item should be remembered (green dot) or ignored (red dot). This electrode's gamma power is correlated with memory load, as this activity increases following stimuli that are remembered. Modified, with permission, from Ref. [60]. **D.** Normalized oscillatory power at a site from one patient's in the parahippocampal gyrus that exhibited elevated theta activity during memory retention. Red coloring indicates elevated oscillatory power relative to baseline. Modified, with permission, from Ref. [97]. **E.** An electrode from a right frontal cortex that resetted to different phases between viewing study items (left) and viewing cues (right). Each plot is a circular histogram that indicates the number of trials where different theta phases were observed 100 ms after stimulus onset (0°indicates the peak phase of theta, and 180°is the trough). Black arrow indicates the mean theta phase. Modified, with permission, from [65].
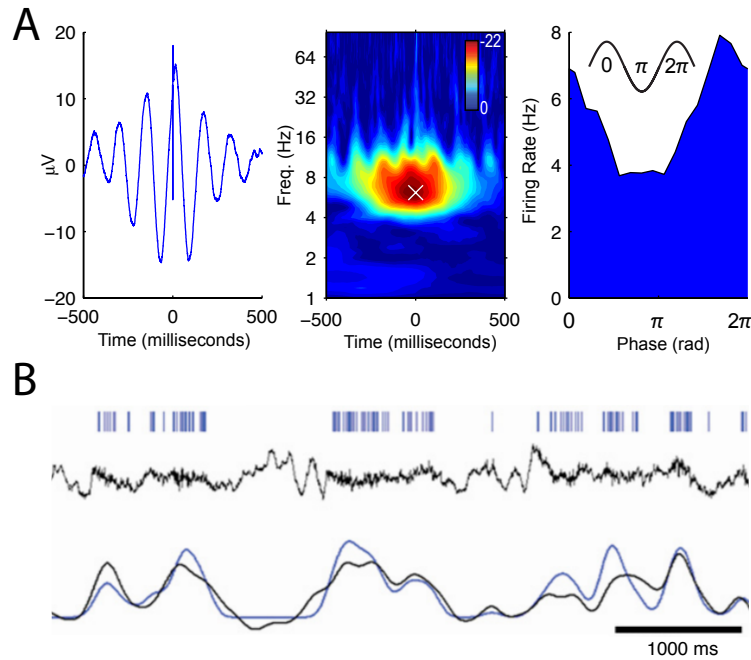
Figure 3: **The relation between oscillatory brain activity and neuronal spiking. A.** The activity of a neuron from the right superior temporal gyrus that spiked just before the peak of the theta oscillation. Left panel, average local-field potential (LFP) computed relative to each spike. Middle panel, z score from a Rayleigh test, which measured LFP phase uniformity at the time of each spike, as a function of frequency and time offset. White '×' indicates the frequency of peak phase locking. Right panel, firing rate of this cell as a function of instantaneous theta phase at the frequency of peak phase locking. Adapted, with permission, from Ref. [36]. **B.** The activity of a neuron from one patient's auditory cortex whose spiking was tightly coupled to the amplitude of simultaneous gamma oscillations ($r = 0.84$). Ticks in top row indicate individual action potentials. Middle row depicts the LFP signal filtered to only include frequencies below 130 Hz. Bottom row indicates LFP gamma power (black) and neuronal firing rate (blue), showing that these two measures are closely related. Adapted, with permission, from Ref. [18].
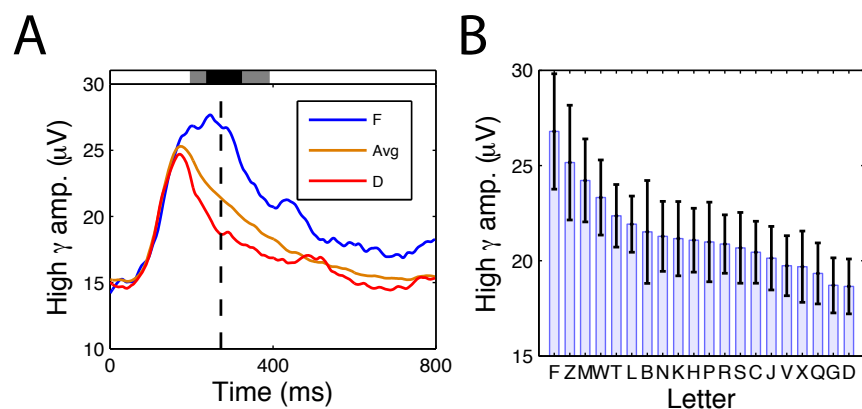
Figure 4: **Gamma-band correlates of specific cognitive representations. A.** The activity of an electrode from left-temporal cortex that exhibited significant variations in high-gamma (65–128 Hz) amplitude according to the identity of the stimulus that was viewed. Blue line indicates the gamma amplitude after viewing 'F,' red indicates the gamma amplitude after viewing 'D,' and orange indicates the mean gamma power across all letters. Shaded rectangles indicate timepoints where this effect is significant (gray indicates $p < 0.05$, black indicates $p < 10^{-5}$). **B.** Right panel indicates the mean high-gamma power for each letter at the timepoint of peak letter-related differences (indicated by the black dashed line in left panel). Modified, with permission, from Ref. [51].