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Intracranial recordings and human memory

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Recent work involving intracranial recording during human memory performance provides superb spatiotemporal resolution on mnemonic processes. These data demonstrate that the cortical regions identified in neuroimaging studies of memory fall into temporally distinct networks and the hippocampal theta activity reported in animal memory literature also plays a central role in human memory. Memory is linked to activity at multiple interacting frequencies, ranging from 1 to 500 Hz. High-frequency responses and coupling between different frequencies suggest that frontal cortex activity is critical to human memory processes, as well as a potential key role for the thalamus in neocortical oscillations. Future research will inform unresolved questions in the neuroscience of human memory and guide creation of stimulation protocols to facilitate function in the damaged brain.

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Introduction

Our ability to act based on personal experience drawn from memory is central to everyday life, and defines our individual identity. Human memory function is susceptible to a wide range of neurological insults. For instance, dementia and associated memory dysfunction are reaching epidemic levels as our population ages [1]. We must understand the *precise* neural mechanisms governing memory to make inroads into the understanding of normal as well as disordered memory. Subdural and depth recordings — termed electrocorticography (ECoG) or intracranial electroencephalography (icEEG) — offer superb temporal and spatial resolution that is unparalleled in the study of human cognition. The present review focuses on the contributions of subdural and depth recordings obtained during the successful encoding and immediate or delayed retrieval of memories in humans. We argue that ECoG/icEEG informs unresolved questions in the study of human memory and is yielding insights necessary for the development of novel interventions to facilitate memory function in the damaged brain. We will use the term ECoG to subsume both subdural (epicortical) and depth (subcortical) recordings.

It is well-known that the hippocampus and surrounding medial temporal lobe (MTL) structures are necessary for episodic memory (long-term memory for personal events) [1,2], and that lateral prefrontal cortex (PFC) is necessary for working memory (active storage and processing in memory) [3,4]. However, working and episodic memory, although often approached as separate topics in psychology, both depend on MTL–PFC interactions. What is the nature of these and other inter-regional interactions, and might they be fractionated depending on the type of memory in question? Furthermore, how do neural networks differentially support encoding and retrieval operations, even within a given type of memory? Might the PFC play a domain-general role in memory — that is, a global role that is not specific to stimulus modality or encoding or retrieval operation — that is comparable and/or complimentary to the role of the MTL?

Lesion studies and functional magnetic resonance imaging (fMRI) reveal the *where* of memory function. Scalp EEG and magnetoencephalography (MEG) reveal the *when* and, for low-frequency spectral activity and event-related potentials (ERPs), the *how* of memory. In contrast, ECoG has superb spatiotemporal resolution and can measure an expanded frequency range of activity, including high-frequency responses and, in rare instances, single-unit activity (SUA). Thus, ECoG can reveal the *how* of human memory across an extended scope of the neurophysiology of memory in humans. For instance, Burke and colleagues [5•] reported the results of a large-scale ECoG study of subsequent memory (SM) — that is, measures of neural activity correlated with or predictive of later remembering (see [6]). Their data reveal that regions previously identified using fMRI fall into two networks that exhibit spatiotemporally distinct patterns of 64–95 Hz gamma band power activity within the first 1.5 s following encoding of each later recalled word — first in the ventral visual pathway and MTL, and then across association regions including left-lateralized inferior frontal, posterior parietal, and ventrolateral temporal cortices. The authors suggest that these networks reflect higher-order visual processes followed by top-down control mechanisms [5•]. Jacobs *et al.* [7] used

MTL depth recordings to reveal that neuronal firing is phase-locked to oscillatory activity in the delta, theta, and gamma frequency bands in humans. Comparable invasive recording has been traditionally restricted to animals; thus, human ECoG recording provides a powerful bridge to the animal literature on memory processing.

Event-related potentials and medial temporal lobe function

Intracranial recordings provide the spatial resolution needed to explore temporal dynamics of memory within subregions of the MTL. Axmacher and colleagues [8] examined SM using ECoG and fMRI, and found that, unlike words that were successfully recalled, words that were later forgotten deactivate the hippocampus at encoding — manifested by a positive direct current response in ECoG and negative blood-oxygen-level dependent (BOLD) response in fMRI. This effect was apparent for words presented both early and late in a list, suggesting a continuum of hippocampal involvement over long and short retention durations. Other studies of encoding as a function of subsequent recall demonstrate that the successful encoding of words is associated with an early (300–400 ms) negative ERP in the rhinal cortex, followed by a late (500 ms or later) positive hippocampal ERP [9,10]. Viewing encoding as a function of subsequent recognition, as opposed to recall, several studies suggest that SM is linked to negative ERPs in the hippocampus. In preparation for immediate recognition, a negative ERP is observed 300–500 ms after stimulus presentation and again upon presentation of the probe at retrieval [11]. In preparation for delayed recognition, a late hippocampal negative ERP is observed following stimulus presentation [12–14]. The differential ERP effects observed in hippocampal activity depending on whether SM is measured by recall or recognition suggest that the hippocampus plays a selective role in recollection (i.e. specific memory, in contrast to strength-based familiarity; see [15]). However, additional data indicate that there is more to the human MTL story than ERPs. For instance, negative-polarity ERPs have been shown to correlate with high-gamma activity [14] (see section on high-frequency responses, below).

Intracranial recordings have also informed the long-standing debate over the difference between recollection and familiarity [15]. Staresina *et al.* [16•] demonstrated that the perirhinal cortex and hippocampus are qualitatively dissociable at retrieval, revealing that the magnitude of the ERP in each MTL subregion region differs between the successful recognition of an item versus a source detail (e.g. background color), versus correct rejection of an item. The hippocampus shows enhanced ERP activity during the retrieval of source information as compared to item retrieval or correct rejection [16•]. Rutishauser *et al.* [17] used microelectrodes to record activity of single neurons (SUA) in the hippocampus and amygdala. Encoding is associated with sustained local SUA — with the highest spike rate observed during encoding of items later recollected (here, retrieved with correct source information), followed by items considered familiar (retrieved without source information), and the lowest SUA rate observed for items not recognized — supporting a continuous strength model of retrieval. Together, the high spatiotemporal resolution of ECoG provides evidence supporting both a continuous strength model of hippocampal function [16•,17] and a dual-process model of retrieval by MTL subregion [16•].

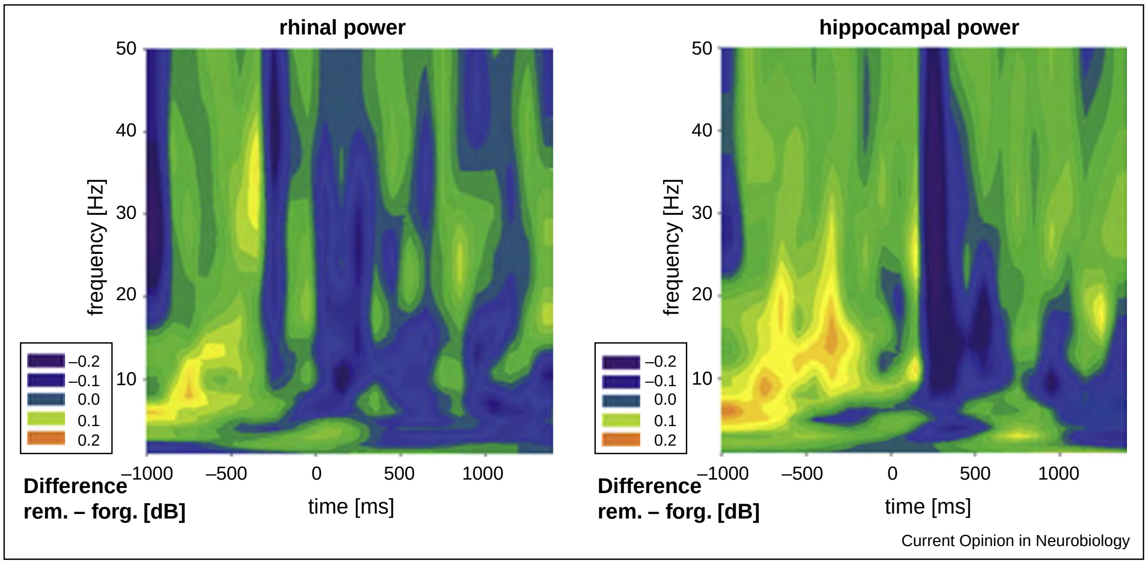
Low-frequency responses and memory

The animal literature has provided robust evidence of oscillations in the theta frequency band (3–8 Hz) at encoding in MTL structures (e.g. [18]). In humans, direct intra-MTL depth recordings and/or cortical surface recordings have shown that presentation of a subsequently remembered stimulus resets theta activity or alters theta power in the hippocampus, rhinal cortex, and/or amygdala [10,12–14,19,20], as well as temporal, frontal, and/or parietal–occipital association cortices [21–23,24••]. Shifts in other frequency bands tend to co-occur with these shifts in theta. Specifically, theta and alpha phase resets in temporal, parietal, and occipital cortices [21]; theta, alpha, and beta phase resets [12] or power decreases [20] in the MTL; and right cortical theta power increases in the midst of widespread gamma increases [25] have been linked to SM. Employing SUA measurements, Rutishauser *et al.* [19] reported that theta phase resets are tightly coupled with local spiking activity — that is, theta phase-SUA coupling (see [26]). Critically, hippocampal theta phase-SUA coupling predicts subsequent long-term recognition as well as participants' confidence in their responses at retrieval. Suthana and colleagues [27] found that stimulation of the entorhinal cortex during encoding resets the theta phase in the hippocampus and enhances spatial memory, suggesting a causal role for hippocampal theta activity in SM.

Patterns of theta and successive alpha band power increases in the hippocampus and rhinal cortex just before stimulus presentation have also been shown to predict subsequent recognition [28] (Figure 1). Fell *et al.* [28] proposed that this pattern reflects the coupling of activated contextual information (theta) and top-down control processes (alpha). This intracranial finding demonstrates the importance of preparatory membrane excitability in successful encoding.

There is activity in multiple frequencies occurring simultaneously during memory encoding and retrieval. Successful encoding in humans has been linked to two distinct hippocampal oscillations at the edges of the theta band. Lega *et al.* [29] found that the 'slow-theta' exhibits higher power at stimulus presentation and is selectively coupled with power in the gamma frequency band.

Figure 1



Normalized power difference plots for the contrast of subsequently remembered > forgotten words in the rhinal cortex (left) and hippocampus (right) reported in [28]. Power increases are shown primarily in the theta and alpha bands before stimulus presentation at encoding.
Adapted from [28] with permission.

(See Box 1 for a description of interactions between different frequency bands, that is, cross-frequency coupling.) This pattern is also observed just before recall; taken together, Lega *et al.* [29] argue that this 3 Hz activity may be the human analogue of the theta oscillations observed in animals. At retrieval, Watrous *et al.* [30••] showed that coherence between MTL, PFC, and parietal cortex is increased for correctly retrieved source information. Spatial memory is linked to 1–4 Hz oscillations while temporal memory is linked to 7–10 Hz oscillations in these regions, supporting a multiplexing mechanism wherein different frequency bands support distinct memory operations (Figure 2). Although multiplexing is not specific to memory, these results suggest that the phenomenon of frequency multiplexing within and across regions may be central to human memory capacity [31].

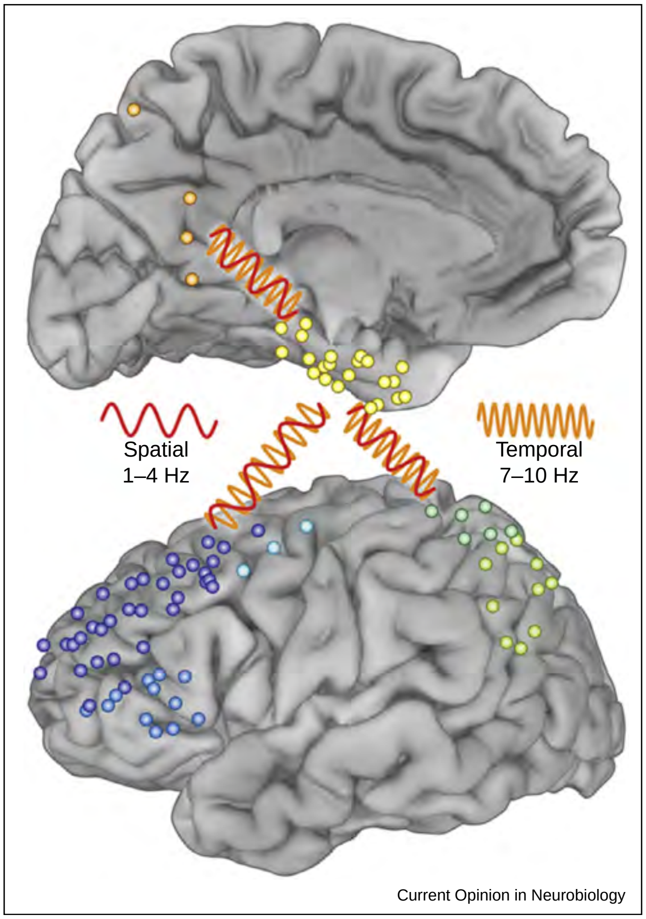
Box 1 Phase-amplitude coupling in memory

Cross-frequency coupling refers to interactions between different frequency bands; it can refer to the coupling of different phases or amplitudes, or the phase of one frequency and the amplitude of another (that is, phase-amplitude coupling). Coupling between higher-frequency amplitude and lower-frequency phase has been linked with a variety of cognitive and motor functions [62–64], and proposed as a mechanism for the short-range coding and inter-regional communication and integration of information [51,52]. Axmacher and colleagues [44] reported that successful maintenance of multiple items in working memory is associated with enhanced coupling between theta phase and beta and low-gamma (14–50 Hz, peak at 28 Hz) amplitudes in the hippocampus (also [46]). Furthermore, memory load modulates theta phase to incorporate additional envelopes of higher-frequency activity, with theta peaking at 7 Hz. At retrieval, Foster *et al.* [33] reported that recognition of remote autobiographical memories correlates with enhanced coupling between theta phase and high-frequency amplitude. The magnitude of phase-locking between the hippocampus and retrosplenial cortex in the theta band peaks 300–400 ms before high-frequency (70–180 Hz) peak amplitude.

Phase-amplitude coupling also supports communication pathways between the thalamus and frontal cortex during successful memory encoding and retrieval. Staudigl *et al.* [49] revealed that successful retrieval is linked to thalamus-frontal synchrony and enhanced coupling between inter-regional beta phase and 55-80 Hz gamma amplitude. Furthermore, they found that the beta activity modulated patterns of gamma power.

Evidence from multiple studies indicates that theta is involved in timing coordinated activity within and across regions during successful encoding and retrieval. Within the hippocampus, theta power first increases and later decreases following presentation of stimuli that are subsequently recognized [14]. Fell *et al.* [13] showed that synchrony between the hippocampus and rhinal cortex varies as a function of frequency, with increased synchrony in delta and theta bands, but increased followed by decreased synchrony in the low-gamma band (28–46 Hz); phase-locking within each region also varies over time as a function of frequency. Using both subdural and depth recordings to examine network activity, Burke *et al.* [24••] showed that theta and gamma power increase in a posterior-to-anterior direction with time over widespread cortical as well as hippocampal regions. Importantly, while some spectral modulations co-occur with local

Figure 2



Individual subdural recording sites from the patients studied in [30••]; blue, prefrontal; green, parietal; orange, precuneus; yellow, parahippocampal. The red oscillation (1–4 Hz) represents coherence between brain regions during spatial memory and the orange oscillation (7–10 Hz) represents coherence between these regions during temporal memory.
Adapted from [30••,31] with permission.

inter-regional synchrony and others with local or global asynchrony, synchronous activity for verbal SM is hubbed in the left PFC. An outstanding question in the intracranial recording of memory concerns whether the PFC may serve a domain-general, causal role as part of an MTL–PFC network, or whether the role of neocortical regions is dictated by domain-specific representations at encoding and/or cognitive operations at retrieval.

Anderson and colleagues [32] showed that increased theta power in the MTL precedes increased theta power in the PFC during successful recall, and serves to synchronize the two regions. Two studies reported that retrieval of remote autobiographical memories (that is, memories encoded before entering the laboratory) is associated with theta band coherence between the MTL and other regions — such as phase-locking between the MTL and retrosplenial cortex [33]. Steinvorth *et al.* [34] showed that layers of the entorhinal cortex that project outward to the cortex exhibit theta activity during retrieval that is synchronized with theta activity in the frontal and temporal cortices. Layers that project inward to the hippocampus, however, show increased gamma activity. Taken together, these findings suggest that theta is important in long-range communication during successful retrieval.

High-frequency responses and memory

Activity in gamma and higher-frequency bands (50–500 Hz) is important for representing information within neural regions. Notably, activity in frequency ranges above 70–80 Hz correlates with local spiking activity [35,36], suggesting that these high-frequency responses reflect SUA. High-frequency power increases [37] and oscillatory activity [38••] have been shown to represent individual stimuli in the neocortex, and gamma band activity is sensitive to differences between stimuli [39]. High-frequency signals are less than a microvolt in amplitude at the scalp, placing them in the noise range of scalp EEG recording. Thus, reliable data in high-frequencies is generally limited to subdural or depth recording (cf. [22]). Importantly, ECoG studies demonstrate that low-frequency and high-frequency activity often share an inverse relationship [5•,20,24••,25,38••,39,40•]. Likewise, while measures of high-frequency amplitude show overlap with the BOLD measures of fMRI, low-frequency activity is anatomically dissociated with BOLD measures [41].

Intracranial recordings reveal an important role for high-frequency responses in successful episodic memory encoding and retrieval. Sederberg and colleagues [42] demonstrated that SM is linked to power increases in the 28–100 Hz gamma range in subdural and depth electrodes in the hippocampus, temporal cortex, and PFC at encoding (also [5•,20,22]), and that this pattern is reinstated just before correctly recalling words. Kucewicz *et al.* [38••] reported that encoding images induces oscillations from 50 to 500 Hz within the primary visual cortex as well as limbic and higher cortical regions, consistent with the visual processing stream (also [5•]), and successful recall is linked with increased 50–500 Hz oscillatory activity in widespread higher cortical regions. Within the hippocampus, Park *et al.* [40•] revealed a role for high-gamma (51–100 Hz) but not low-gamma, delta, or theta, in successful encoding during navigation. Axmacher *et al.* [14] found that 70–90 Hz high-gamma power is selectively increased during processing of unexpected items at multiple points during encoding in preparation for a recognition test. In addition to subserving encoding in conjunction with synchronization and desynchronization in the theta band, this high-gamma activity is also correlated with the hippocampal N500 ERP. Foster *et al.* [43] showed that 70–180 Hz power peaks in the hippocampus-connected posteromedial cortex after 400 ms during retrieval of autobiographical memories.

Gamma and higher-frequency band power responses have also been used to study working memory, suggesting a complex picture of working memory function that involves oscillations and sequenced spiking activity. Axmacher *et al.* [44] demonstrated that maintenance of multiple items in working memory is linked to the coupling of neural assemblies in the 25–100 Hz gamma range with theta phase in the hippocampus. Furthermore, increasing the number of items (i.e. memory load), is associated with modulating this cross-frequency coupling by increasing the length of theta cycles to incorporate additional pockets of higher-frequency power increases (Box 1). Indeed, Roux and Uhlhaas [45] argued that 'theta-gamma' (gamma range: 30–200 Hz) coupling subserves the organization of items maintained in sequence (also [46]), while alpha-gamma coupling may also support the active inhibition of task-irrelevant processes integral to complex working memory.

Inter-regional coherence and memory

Memory is supported by both the local connectivity of MTL subregions, and the distributed connectivity of the MTL to other cortical and subcortical regions [1]. Intracranial recordings can provide insight into the dynamics of both short-range and long-range communication. Fell and colleagues reported that successful encoding is associated with hippocampus–rhinal cortex coherence in the delta and theta bands [13,47] and, in the gamma band, with early hippocampus–rhinal cortex synchronization and later desynchronization [13,48] (also [49]). Comparable patterns of within-theta and within-gamma bands also occur over left cortical regions [24••]. Synchronization within theta and gamma bands is both multiplexed and dissociable throughout the MTL and cortex in SM [24••]. At retrieval, multiplexing occurs as a function of the source being retrieved — with spatial and temporal information traveling along different frequency bands but within comparable MTL–PFC-parietal networks (Figure 2) [30••,31]. Anderson *et al.* [32] suggested that one mechanism of coherence between the MTL and PFC is supported by synchronous activity in the theta band during successful recall.

Intracranial recordings of human cognition also suggest *how* communication might occur between synchronized regions. Staudigl and colleagues [50] recorded activity in a patient with intrathalamic depth electrodes as well as frontal cortex coverage with scalp EEG. They found that successful retrieval is associated with increased synchrony between the thalamus and PFC in the beta band as well as coupling between beta oscillations and gamma power. Indeed, it has been has proposed that coupling between the phase of lower frequencies and the amplitude of higher frequencies enhances local cortical processing, facilitating transmission of information across synchronized brain regions (Box 1) [51,52].

Intracranial recordings and reinstatement

Episodic retrieval often involves the reinstatement of neural activity patterns elicited during encoding [53]. This phenomenon is frequently studied using fMRI, limiting precise timing of these spatially localized patterns. Several ECoG studies report data from both the encoding and retrieval phases of long-term memory paradigms. Kucewicz *et al.* [38••] recorded 50–500 Hz activity and reported a dissociation such that encoding of pictures induces more oscillatory activity in the occipital and parahippocampal cortices than retrieval, consistent with a model of bottom-up visual processing. Retrieval, in contrast, induces more high-frequency activity in the temporal and frontal cortices than encoding, consistent with top-down cognitive processing. Ekstrom and colleagues [54] recorded SUA and local field potentials in the hippocampus and entorhinal cortex during a navigation task and at subsequent recognition. Their data reveal a dissociation between SUA and power increases in broadband potentials, theta and gamma (30–100 Hz) bands, with increased SUA at encoding and increased local field potential activity at retrieval. Reinstatement may be specific to a subset of neurons in these MTL regions.

Context reinstatement — that is overlap of perceptual, conceptual, and/or categorical details based on similarity between encoding and retrieval — is evident in association cortices. Manning and others identified semantic components of neural activity during the encoding of words and reported that the resultant power spectra are reactivated in temporal and frontal cortices according to semantic clustering on subsequent free recall [55,56•,57]. Overlap in neural activity between encoding and recall is not only similar, but also predictive of recall of items similar in context [55,56•]; this pattern is more evident in the cortex than in the hippocampus [57]. Morton *et al.* [56•] further reported that reactivation occurs at all frequencies studied (2–100 Hz) in the temporal cortex but does not occur at any frequency in the occipital cortex. Finally, these studies as well as [29] and [42] reported that reactivation of neural activity observed at encoding occurs just before retrieval, revealing that context reinstatement may be part of preparing to retrieve information and not part of retrieval itself.

Open questions and directions in intracranial recordings and memory

Intracranial recordings offer unparalleled spatiotemporal resolution in the study of human memory and capture high-frequency band responses, effectively bridging the study of memory across human and animal species, and raising the possibility of answering important, unresolved questions in the neuroscience of memory. ECoG studies of working and episodic memory in humans demonstrate the relationships between neuronal spiking and high-frequency activity with oscillations of different frequency bands, which regions interact to support memory and how these regions interact at different stages of memory processing, and the precise source of ERPs generated in memory performance. Recent ECoG data suggest that the PFC is a key hub for successful encoding in humans [24••], providing evidence that the frontal cortex plays a domain-general, causal mechanism in memory networks, Furthermore, emerging subcortical depth recordings in both animals and humans suggest that the driving source of neocortical oscillations may be thalamic [50,58].

Subdural and depth recordings also shed light on multiple questions posed in the psychology of memory. For instance, ECoG provides support on the neural level for multiple models of recollection-based versus familiarity-based retrieval [15–17], and Hanslmayr and Staudigl [59] argued that encoding and retrieval data support Endel Tulving's principle of encoding specificity [60]. ECoG data also indicate that the relationship between successful encoding and retrieval operations – that is, reinstatement – is both spatially and temporally complex.

Intracranial recordings will also provide guidance on how to create stimulation protocols to facilitate function in the damaged brain (see [27,61]). For instance, what is the precise nature of MTL–PFC interactions, and which mechanisms of inter-regional interaction play a *causal* role in successful memory formation and/or retrieval? Much of the extant neocortical data support a role of the PFC in the representation of encoded information, but suggest that the PFC may be a hub for multiplexing and successful encoding of stimuli (see [24••]). Might the PFC support memory processes in a *domain-general* way, irrespective of the type of encoding modality or retrieval operation? Finally, because of its fine spatiotemporal resolution, ECoG offers the means for determining the oscillatory and phase parameters of potential therapeutic stimulation, as well as the precise location and timing of application to best facilitate function (also [61]). If there is a causal and domain-general frontal mechanism governing memory function, and if the source of that mechanism is indeed thalamic, these regions may present alternative stimulation sites — allowing possibility of memory facilitation for patients with MTL damage.

Conflict of interest statement

Nothing declared.

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