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Review

A Neural Chronometry of Memory Recall

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Episodic memory allows us to mentally travel through time. How does the brain convert a simple reminder cue into a full-blown memory of past events and experiences? In this review, we integrate recent developments in the cognitive neuroscience of human memory retrieval, pinpointing the neural chronometry underlying successful recall. Electrophysiological recordings suggest that sensory cues proceed into the medial temporal lobe within the first 500 ms. At this point, a hippocampal process sets in, geared toward internal pattern completion and coordination of cortical memory reinstatement between 500 and 1500 ms. We further highlight the dynamic principles governing the recall process, which include a reversal of perceptual information flows, temporal compression, and theta clocking.

Memory Recall: The Brain's Time Machine

One of the most remarkable capacities of the human mind is to mentally travel back in time and relive past experiences in great detail. Think of how looking at your vacation photograph album, hearing the first notes of an old favourite song, or smelling the perfume of a loved one can reignite entire experiences and associated emotions, sensations, and thoughts. In experimental terms, a scenario in which an external or a self-generated (i.e., internal) reminder elicits a vivid memory is referred to as **cued recall** (see Glossary). Intriguingly, the conversion of a simple cue to a full-blown memory can occur within a few hundred milliseconds. Despite decades of neuroimaging research, however, little is known about the precise temporal dynamics that govern successful memory recall. Is there a particular sequence in which particular brain regions need to engage? Where and when does the conversion from cue to target representations occur? Do the neural codes change from perceiving to retrieving?

In this review, we discuss new results elucidating the neural chronometry of cued recall. After a brief summary of computational models and fMRI work, we delve into recent findings from human electrophysiology, capitalising on direct invasive recordings and time-resolved multivariate pattern analyses. Mounting evidence suggests the following scenario. Within the first ~500 ms after cue presentation, information traverses dedicated cortical pathways and progresses toward the medial temporal lobe (MTL). In the MTL cortex, the cue elicits an initial 'old/new' signal. If the cue is deemed old/familiar, a hippocampal process sets in at ~500 ms, in the first instance geared toward reactivating the hippocampal cell assembly assigned to the initial experience (**pattern completion**). If successful, hippocampal pattern completion triggers the sustained **reinstatement** of the cortical memory trace between ~500 and 1500 ms. This is the time interval in which a full-blown mnemonic representation unfolds, with posterior parietal regions contributing to the maintenance and goal-directed manipulation of the target memory (Box 1). On a mechanistic level, memory recall exhibits distinctive temporal dynamics, including flow reversal, time compression, and theta clocking (Figure 1, Key Figure).

Computational Accounts and fMRI Evidence for Pattern Completion and Reinstatement

The question of how a simple cue can trigger recall of a past experience has a long history in computational models of memory. Following the seminal discovery that intact episodic memory critically relies on the hippocampus [1], theoretical work has tried to link this region's unique physiological properties to its putative role in coordinating memory recall [2–5]. First, the hippocampal circuitry itself enables so-called 'pattern completion' processes [3]. Second, the hippocampus is reciprocally connected with a host of multimodal regions in high-level association cortex [6]. Together, these properties put the hippocampus in a privileged position to orchestrate cued recall. Specifically, it is thought that during the initial experience, a particular set of hippocampal neurons coactivates with and is thereby linked to the cortical sites representing the constituents of the

Highlights

Simple reminders can bring back a host of vivid memories, experimentally epitomised in cued-recall paradigms.

Electrophysiological recordings have elucidated the chronometry with which sensory cues are converted into retrieved memories.

At 500 ms after cue onset, a pattern completion process begins in the hippocampus and triggers the reinstatement of the target memory in the neocortex.

Cortical reinstatement unfolds between 500 and 1500 ms and gives rise to the subjective feeling of recollection.

Reinstatement is governed by intricate temporal dynamics, including the reversal of perceptual processing streams and clocking by theta rhythms.

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Box 1. Parietal Cortex Contributions to Memory Recall

Neuroimaging work has consistently shown engagement of the medial and lateral posterior parietal cortex (PPC) in episodic memory retrieval [94]. Although beyond the scope of the current review, it deserves mention that the PPC comprises structurally and functionally distinct subregions [95–98]. Recall/reinstatement effects in the PPC seem to differ qualitatively from those in occipitotemporal regions [99,100] and prominent views hold that parts of the PPC serve as an amodal **episodic buffer** [97,101] or are deployed for working with memories in a goal-directed fashion once they are recalled [89,96]. Common to these accounts is that the PPC responds to a bottom-up mnemonic signal, and as reviewed in the main text, the most likely candidate to generate this signal is the hippocampus. By varying the interval of maintenance of a recalled episodic detail, fMRI data suggest that hippocampal engagement during successful recall is transient, whereas PPC engagement is sustained and co-varies in time with the maintenance interval [102]. Moreover, a recent fMRI study found that mnemonic decod-ability in the PPC correlated with that in MTL regions [103]. Both of these results are consistent with the notion that a hippocampal memory signal precedes and influences PPC engagement, although it is difficult to infer the exact temporal relationship between these regions based solely on fMRI dynamics. One recent study used fMRI in conjunction with source-reconstructed EEG/MEG and revealed a recall effect in the left precuneus from 600 to 1600 ms after cue onset [104]. Human intracranial recordings from parietal regions are relatively rare compared with MTL coverage. Besides two studies using simple old/new recognition memory paradigms [29,105], one study [106] used an autobiographical memory task, more strongly reliant on recall processes. Pro-nounced engagement of the PPC was observed (high-gamma signal; 70–180 Hz), with an average onset of the parietal response at 600 ms. Together these studies suggest that PPC contributions unfold after the hippocam-pal recall process has begun. We speculate that there might be a push–pull relationship between the hippo-campus and PPC. In particular, the hippocampus initiates cortical reinstatement in a bottom-up, holistic fashion [64], whereas the PPC aids and refines recall by deploying working memory/attentional resources to recover the task-relevant mnemonic features [107] (see Outstanding Questions). Given the extent of the structural and functional connectivity of the PPC not only with the hippocampus [108] but also with a wide network of high-level cortical regions [109–111], this region might be thought of as an additional, third layer in the multi-plexed index for memory reinstatement (hippocampus → EC → PPC). This notion is corroborated by a recent MEG study showing enhanced connectivity between the MTL and precuneus during autobiographical memory retrieval [85]. Experimental disruption of the precuneus via continuous theta burst stimulation diminished both MTL–cortical coupling and memory vividness, pointing to a potential role of the PPC in maintaining hippocampal–cortical communication in the service of successful recall.

Glossary

Autoassociative processes: intra-hippocampal network dynamics based on recurrent connections among neurons, thought to enable pattern completion. We refer to autoassociative process in the hippocampus as pattern completion and to the ensuing activation of the cortical engram as reinstatement, although the hippocampal pattern could also be described as (part of) the engram and a cortical pattern is completed during reinstatement.
Blood-oxygenation level-depen-dent (BOLD) signal: reflecting in-direct and delayed metabolic ef-fects of neuronal activity (leading to certain temporal ambiguity); main dependent measure in fMRI.
Cued recall: experimental para-digm in which participants initially learn stimulus associations (e.g., word/image pairs). Memory is then queried by presenting one stimulus only, with the task to recall the associated material.
Dynamic causal modelling (DCM): analytical approach to infer a causal relationship among two or more brain regions.
Encoding retrieval similarity (ERS): correlation of distributed activation patterns (e.g., across voxels, sensors) between study (encoding) and test (retrieval) of particular stimuli, used to assess memory reinstatement.
Engram: the neurophysiological representation of a memory trace underlying its phenomenology.
Episodic buffer: a component of Baddeley's working memory model, integrating external (perceptual) and internal (mne-monic) information in a limited-capacity temporary store.
Gamma bursts: brief bouts of neural activity in the gamma fre-quency range (>30 Hz), assumed to synchronise cells that code the same content at a given moment in time and therefore assumed to represent mnemonic content during cued recall.
Hippocampal index: theoretical account positing that hippocam-pal cell assemblies formed during an experience point to neocortical representations of that experience.
Intracranial electroencephalog-raphy (iEEG): invasive recordings

experience. The specific configuration of cortical sites (participating regions and activation profiles) forms the so-called **engram** [7]. As the cortical sites disengage/reconfigure to process new incoming information, the reciprocal link between hippocampal neurons and the cortical engram lives on in the form of strengthened synaptic weights, also referred to as the **hippocampal index** [5]. Later presentation of a subset of the engram (i.e., a partial cue) again propagates into the hip-pocampus, where the entire index is activated via **autoassociative processes**, thereby reinstating the complete cortical engram.

A number of recent fMRI studies on cued recall have provided some empirical evidence for these computational accounts of hippocampal pattern completion and cortical reinstatement. Particularly, the advent of multivariate pattern analyses (MVPA) [8], including **representational similarity analysis** and **machine learning** approaches, has yielded great progress in the assessment of memory-guided reinstatement. Not only have these methods consistently shown that cortical reinstatement is stron-ger during successful relative to unsuccessful recall, but activation levels in the hippocampus predict the extent of cortical reinstatement [9–12]. Regarding pattern completion in the hippocampus, fMRI evidence is scarcer, but a recent high-resolution fMRI study showed enhanced similarity of hippocam-pal encoding and retrieval activation patterns for successful versus unsuccessful cued recall [13] (see also [14,15]). Together these findings are consistent with a hippocampal pattern completion process geared toward orchestrating cortical reinstatement. However, given the temporal ambiguity of the **blood-oxygenation level-dependent (BOLD) signal**, most of these findings would also be compatible with hippocampal activity following cortical reinstatement. Thus, to establish whether hippocampal engagement during memory recall indeed initiates reinstatement, real-time (i.e., millisecond preci-sion) temporal resolution is needed.

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Electrophysiological Recordings Elucidate the Neural Chronometry of Recall

Temporal Dissociation of Different Memory Signals

The most widely used method to glean real-time insights into human cognitive processes is noninvasive electrophysiological recordings via electroencephalography (EEG) or magnetoencephalography (MEG). Most early EEG investigations focused on different forms of recognition memory rather than cued recall *per se*. Specifically, event-related potentials (ERPs) were used to distinguish between familiarity-based and recollection-based recognition [16], with the latter being more akin to cued recall. In brief, an early (300–500 ms) frontal ERP has been linked to familiarity-based recognition, whereas a later (>500 ms) posterior ERP has been linked to recollection-based recognition [17]. (Note that we hereafter refer to onset latencies of significant differences between memory conditions or changes from baseline where this information is available.) These data hint toward different mnemonic processes being discernible via human electrophysiological recordings, with recall-related processes unfolding ~500 ms after the reminder. However, given the ambiguities about neural generators of surface electrical/magnetic fields, the underlying brain regions – and the link to hippocampal signals in particular – have remained largely unknown.

One methodological approach that overcomes many of the abovementioned modality-specific limitations is direct invasive recordings from the hippocampus and cortical target sites in human epilepsy patients [intracranial EEG (iEEG)] [18]. The first set of iEEG studies on memory employed simple old/new recognition tests, revealing an initial response peaking around 400 ms in the entorhinal cortex (EC)/perirhinal cortex and distinguishing correctly identified old from new stimuli (for a review see [19]). In the hippocampus, corresponding old/new responses were typically observed later, from ~500 ms onward [20–22]. However, the simple comparison of old versus new stimuli leaves open whether this response reflects a novelty signal or recall of episodic details associated with the old stimulus. An iEEG study designed to distinguish between old/new discrimination and associative retrieval (cued recall) indicated the latter. ERPs were derived for: (i) new items [correct rejection (CR)]; (ii) recognised old items without recalling associative details [item recognition (IR)]; and (iii) recognised old items and recalling associative details [associative recognition (AR)]. Hippocampal ERPs showed an associative recall effect (AR > IR) most pronounced between 500 and 1500 ms [23]. A novelty response (CR vs IR) did not unfold until much later in the trial once the memory decision was made, perhaps reflecting encoding of the novel experience [24]. In any case, a dedicated hippocampal signal distinguishing successful from unsuccessful recall and statistically emerging at ~500 ms has since been demonstrated with complementary measures including action potentials of single hippocampal neurons [25] (Figure 2A, top) and gamma (>30 Hz) power [26,27] (Figure 2A, bottom). While the convergence of the effect across different electrophysiological signals speaks to its robustness, the exact relationship between ERPs, action potentials, and gamma power is still not entirely understood [28] and it would be informative to directly link these different signals in a single study. In sum, studies investigating the temporal profiles of successful recall highlight a process that unfolds ~500 ms after the presentation of a reminder, with invasive recordings directly linking this process to the hippocampus.

It deserves mention that the hippocampal signal usually increases from pre-cue baseline levels prior to 500 ms (Figure 2A). As further elaborated below, this increase might reflect the activation of visually selective neurons responding to the cue from ~270 ms [29] (see also [25,30]) or preparatory processes imposed by the cued-recall paradigm (i.e., participants anticipate memory search demands). In any case, the difference between successful and unsuccessful recall tends not to unfold before 500 ms, at which point sensory cue processing and an initial old/new assessment are likely to be completed.

Timing of Hippocampal Pattern Completion and Cortical Reinstatement

What is the functional significance of this hippocampal process emerging at ~500 ms? As mentioned above, models of memory recall postulate hippocampal pattern completion coordinating reinstatement of the mnemonic engram in the cortex. In a recent iEEG study [26], participants first learned trial-unique nouns paired with one of two colours or one of two scenes. During retrieval, participants were

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of electrical brain activity via cortical grids or depth electrodes.
Machine learning: multivariate classifiers (e.g., support vector machines, linear discriminant analysis) are trained to distinguish, for example, two activation profiles during encoding. The training weights can then be used to assess the extent of the reactivation of encoding patterns during retrieval.
Pattern completion: a partial activation pattern elicits the activation of an entire ensemble of previously linked neurons via autoassociative recurrent connections in the CA3 subfield; used here to denote reactivation processes in the hippocampus.
Reinstatement: used here to denote the reactivation of the cortical engram induced by hippocampal pattern completion.
Replay: dynamic reactivation of temporal activation profiles, initially observed in rodent recordings during post-learning rest intervals; can occur in a forward or backward fashion and at different compression rates.
**Representational similarity analysis:** analysis approach correlating activation patterns across features (e.g., voxels in fMRI, electrodes in EEG) between different experimental conditions or trials.
Source analysis: umbrella term to describe methods that project electrode (EEG) or sensor (MEG) data onto brain space, generating a model of the most likely source of activity observed over the scalp.
Testing effect: the finding that long-term retention is strongly enhanced when memories are repeatedly recalled as opposed to repeatedly restudied.
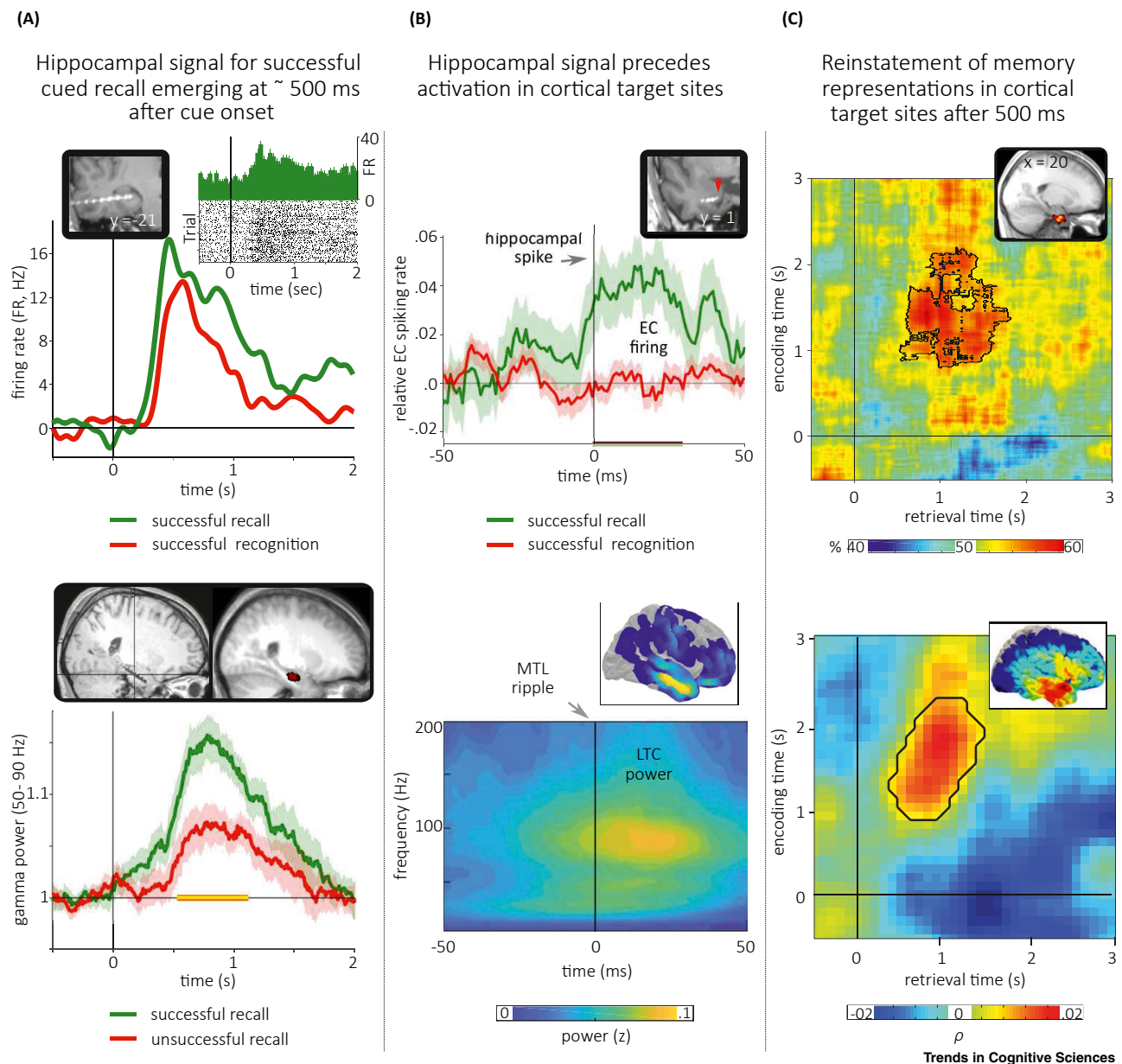
Key Figure

A Schematic of the Neural Chronometry of Cued Recall
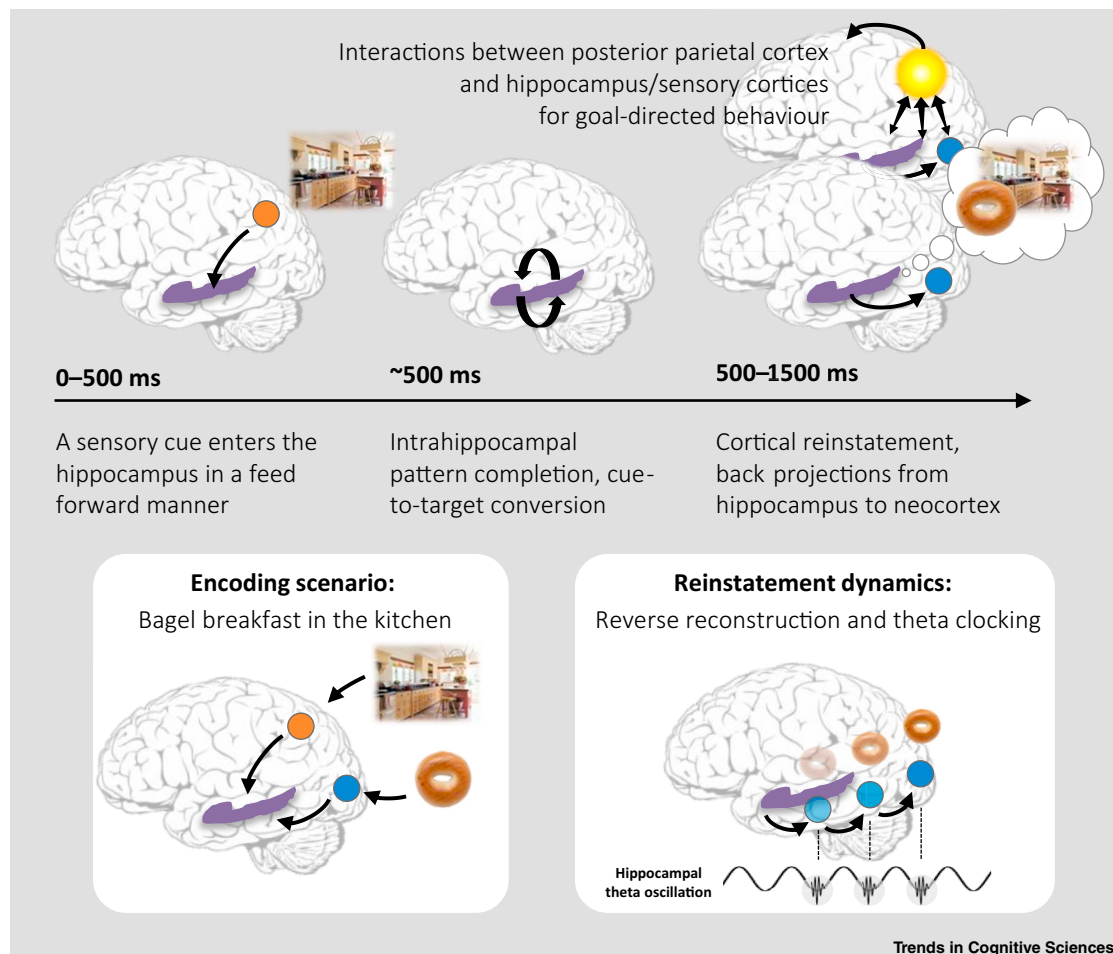
Figure 1. Top left to right: A memory cue enters the hippocampus in a feedforward fashion, followed by pattern completion at approximately 500 ms after cue onset. From 500 ms onward, target memories are reinstated in the neocortex. Memory signals are projected to posterior parietal regions, with reciprocal interactions for maintenance and translation into goal-directed behaviour. Bottom left: Example of a unique event that involves eating a bagel in the kitchen for breakfast. Reinstatement propagates from the hippocampus back to the neocortical regions that coded aspects of the original experience. This reinstatement cascade progresses along a feedback pathway that reconstructs an event in the reverse order from its original encoding. Each stage of this backward reconstruction process is characterised by bursts of neural activity in the reactivated neocortical areas and occurs in time-limited, rhythmic windows defined by the hippocampal theta rhythm.

asked to recall the associated colour/scene when cued with a noun. To assess hippocampal pattern completion, the **encoding-retrieval similarity (ERS)** of the spectral activation patterns was examined. Hippocampal ERS was not only greater for successful than unsuccessful recall between 500 and 1500 ms (with a concurrent increase in gamma power), but also greater for a given noun–image combination with its exact encoding counterpart than with other encoding trials sharing the same image. This suggests that upon receiving a partial cue (the noun), reactivation (completion) of the event-specific hippocampal encoding pattern sets in at ~500 ms during successful recall.

(A)

Hippocampal signal for successful cued recall emerging at ~ 500 ms after cue onset

(B)

Hippocampal signal precedes activation in cortical target sites

(C)

Reinstatement of memory representations in cortical target sites after 500 ms

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Figure 2. Invasive Recordings in Humans Elucidate the Neural Chronometry of Memory Recall.
(A) At ~500 ms after cue onset, a hippocampal signal emerges specifically for successful cued recall. Top: Single-unit example depicting hippocampal firing rates (baseline corrected). Left inset: Placement of microwire bundle used for recordings. Right inset: Raster plot of action potentials for successful recall. Adapted from [25]. Bottom: Gamma power increase for successful versus unsuccessful recall. Left inset: Example depth electrode. Right inset: Hippocampal group coverage. Adapted from [26]. (B) Hippocampal signals precede activation in cortical target sites (cortical signals are aligned to hippocampal signals). Top: For successful recall only, entorhinal cortex (EC) neurons fire within 30 ms of hippocampal spikes. Inset: Example EC microwire placement. Adapted from [25]. Bottom: Lateral temporal cortex (LTC) ripples (80–120 Hz) within 30 ms after MTL ripples. Inset: Group coverage of the LTC. Adapted from [36]. (C) Reinstatement of memory representations in cortical target sites after 500 ms. Top: Population decoding of successfully retrieved target objects from entorhinal cortex (EC) neurons. Inset: Coverage of the EC. Adapted from [25]. Bottom: Reinstatement of encoding representations in the lateral temporal cortex (LTC) as assessed via encoding retrieval similarity (ERS) of spectral power. Inset: Group coverage of the LTC. Adapted from [34].

Invasive recordings have also begun to shed light on the reinstatement of memory engrams outside the hippocampus. The first cortical recipient of hippocampal output is the EC [31]. Computational models suggest that hippocampus-mediated reinstatement is multiplexed, such that the hippocampus points to indices in the EC, which in turn index cortical target sites [32]. The EC might thus serve as the interface between intrahippocampal pattern completion and cortical engram reinstatement [33]. Using simultaneous single-neuron recordings from the hippocampus and EC, a recent study showed that during successful cued recall, entorhinal spikes followed hippocampal spikes within 30 ms [25] (Figure 2B, top). Importantly, at the population level, the mnemonic target could be decoded from entorhinal spiking patterns from 600 to 1500 ms (Figure 2C, top), with hippocampal firing rates predicting the strength of entorhinal reinstatement. Recall-related reinstatement has also been demonstrated in cortical regions further downstream. Using a cued-recall paradigm with concrete noun pairs, another iEEG study [34] showed enhanced ERS during successful recall in the ventral and lateral temporal cortex. Again, this effect was seen between 500 and 1500 ms after cue onset (Figure 2C, bottom). A subsample of patients was implanted with microelectrode arrays in the middle temporal gyrus (MTG), and reinstatement was observed across individual MTG neurons between 500 and 1500 ms [35]. Intriguingly, recent work now tied these reinstatement effects in the temporal cortex to preceding signals in the MTL [36]. Specifically, reinstatement was most prevalent when the temporal cortex and MTL were coupled via ripples (transient bursts of ∼80–120-Hz oscillations; Box 2). Critically, lateral temporal cortex ripples emerged within 50 ms after MTL ripples, similar to the entorhinal neurons spiking after hippocampal neurons mentioned above (Figure 2B, bottom). No MTL-triggered ripples were seen in motor cortex control sites (where target memories should not be represented). Last, cortical >500-ms reinstatement has also been observed via noninvasive EEG/MEG recordings [37–40], and recent advances in source reconstruction methods [41] hold promise that dynamic hippocampal–neocortical interactions can now be investigated comprehensively in healthy participants.

Together, the results from electrophysiological recordings in humans reveal that a hippocampal pattern completion process sets in at 500 ms for successful recall, upon which the hippocampus drives

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Box 2. Ripples during Awake Reactivation and Their Potential Role in Memory Strengthening

One exciting recent development with respect to the timing of memory signatures is the discovery of sharp-wave ripples (SWRs) during awake recall. Ripples are bursts of coordinated neural activity in the high gamma band (80–120 Hz in humans, 150–250 Hz in rodents), originating in the hippocampus and thought to play a prominent role in memory consolidation by coordinating hippocampal–neocortical memory replay [112–114]. Hippocampal ripples were initially identified during sleep and states of immobility in rodents [115] and later in humans [66,116,117]. According to two-stage models of memory formation [112,118], an initially labile memory is reinforced by repeated replay in hippocampal–neocortical circuits. The fast timescale of ripples enables spike-timing-dependent plasticity, resulting in synaptic strengthening of the connections between coactive neural assemblies that represent the different elements of a memory [114]. A recent study found that ripple events in the human brain are not limited to sleep and rest, but additionally occur during cued recall [36]. In this study, MTL ripples in a frequency range from 80 to 120 Hz showed a relative increase during recall periods of a memory task, were coupled to ripples in the lateral temporal association cortex, and temporally co-occurred with the reinstatement of encoding-specific neural patterns (Figure 2B, bottom). These findings strongly suggest a role of ripples in orchestrating the reinstatement of memories between the hippocampus and neocortex and indicate an important parallel between animal and human memory replay and consolidation [117]. The results also open the compelling possibility that memory reinstatement serves a common function irrespective of whether it occurs during sleep or wake; namely, the stabilisation and reorganisation of memories [71,119]. If ripple-mediated plasticity can be induced via awake cued recall, this might provide a plausible physiological basis for why repeatedly recalling a memory is such a powerful means to make memories last, thereby bridging between low-level physiology and cognitive theories of the 'testing effect' [71,120,121]. One fruitful avenue for future work is thus to further investigate the role of SWRs in retrieval-mediated learning, stabilisation, and reorganisation, to identify the parallels as well as the functional differences between sleep and wake ripples [119], and to describe the timing of ripples relative to slower (e.g., theta) oscillations in hippocampal–neocortical circuits.

memory reinstatement in cortical target sites. Of course, some variability in the precise timing of hippocampal engagement is to be expected across events, participants, imaging modalities, and experimental paradigms. However, by aligning the engagement of extrahippocampal regions to hippocampal signals on a trial-by-trial level, the abovementioned studies make a strong case for hippocampal activation preceding cortical reinstatement. We note, however, that conclusive evidence for a causal role would require direct perturbation of the hippocampal response. Great progress has been made recently using direct electrical stimulation of MTL regions during spatial and verbal learning in humans [42–45]. That said, whether perturbation of the hippocampus at different latencies differentially affects cued recall performance remains an open question (see Outstanding Questions). Rodent models have shown that electric or optogenetic manipulation of hippocampal ripples directly impacts spatial memory performance [46,47]. Given that hippocampal ripples have now been linked to successful recall in humans as well [36,48] (Box 2), electrical manipulation of cue-evoked ripples at different time points might be a viable approach to establish the causal role of the hippocampus in orchestrating cortical reinstatement.

It also deserves mention that the observation of a 500 ms latency stems from experimental settings in which participants' attention is fully focused on memory retrieval. In more natural settings, cues are less explicit or noisier, and the 500 ms interval can thus be regarded as a lower temporal bound for hippocampal pattern completion processes. Moreover, averaging across many trials and integrating across multiple participants will obscure trial-by-trial variability in cue-evoked effect latencies (e.g., due to fluctuation in levels of attention [49]). To more closely examine the processes leading up to the moment of recall, researchers have resorted to response-locked (button press or verbal response) instead of cue-locked analyses. Those data show – with equal consistency – that a hippocampal signal and ensuing memory reinstatement sets in ~1 s prior to the response [23,26,34,35,48,50]. Response-locked analyses also allow, in principle, better resolution of the extent of reinstatement needed to terminate memory search given specific task demands. For instance, greater levels of reinstatement are likely to be needed to support the recall of perceptual details as opposed to recalling categorical gist/semantic features [51] (see below).

The Temporal Codes of Memory Recall

As reviewed above, accumulating evidence suggests that hippocampal–neocortical dynamics between 500 and 1500 ms after a reminder reinstate mnemonic patterns. In this section, we zoom in on the temporal dynamics that govern the reinstatement process in this critical time window. We first review the evidence regarding the timeline of memory reactivation for single events and event sequences, before turning to the role of theta oscillations in clocking the reinstatement process.

An Information Flow Reversal between Perception and Memory?

During cued recall, sensory information pertaining to the cue enters the hippocampus in a feedforward fashion. When successfully matched with an overlapping, stored memory trace, hippocampal pattern completion then reinstates mnemonic target content back in neocortex (see computational models discussed in sections above [33]). The cue-to-memory conversion should thus be associated with a reversal of the information flow from a feedforward, cue-driven input process to a feedback, memory-driven output process. In experimental terms, study designs that use cross-category cued recall (e.g., object–scene or word–face associations) are particularly well suited for isolating purely mnemonic target reinstatement from perceptual cue processing.

One fMRI study used cross-category (object–scene) cued recall in conjunction with **dynamic causal modelling (DCM)** to provide empirical support for the hypothesised reversal of information flow from cue to target. The same MTL cortical region was found either to send information to the hippocampus when its preferred category (objects for perirhinal cortex, scenes for parahippocampal cortex) served as the cue or to receive information from the hippocampus when its preferred category was the target [52]. Similar results were obtained from studies employing laminar recordings in monkeys [53–55]. Using object-based cued recall, a feedforward signal was observed across perirhinal cortex layers during the cue period. During the delay period, where the target representation was

presumably recalled, this flow across layers reversed and indicated a feedback signal [55]. Although no recordings were obtained from the hippocampus, one likely scenario is that the switch from cue to target representation was mediated by hippocampal pattern completion. In our timeline of human memory recall, this conversion would occur around 500 ms post-cue presentation.
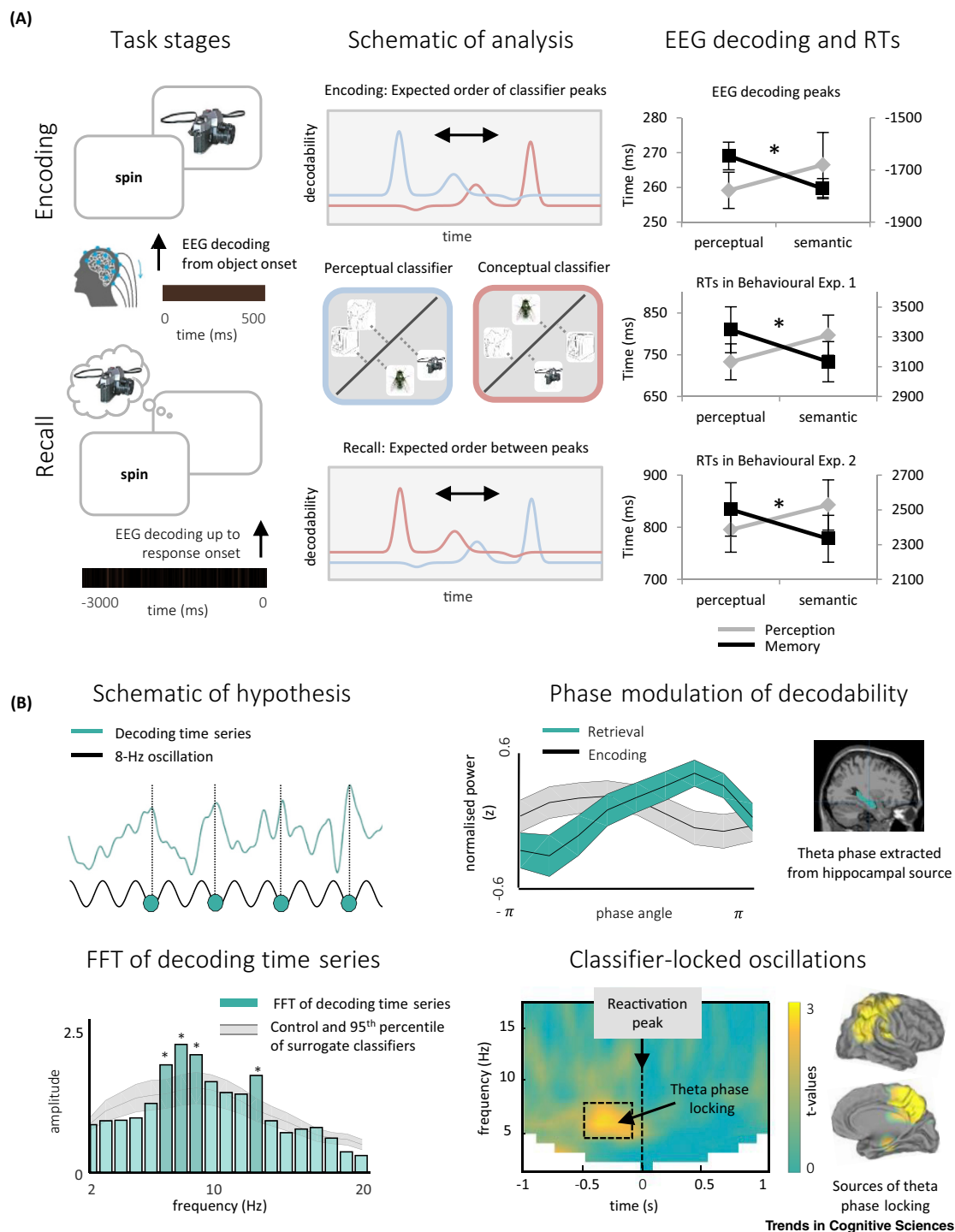
Once a cue has ignited pattern completion in hippocampal circuits, how are the various constituent elements of an episodic memory then reconstructed in the neocortex? Even a static visual image comprises multiple layers of information that are processed along a detailed-perceptual to abstract-semantic gradient (e.g., [56,57]). If remembering entails a reversal of information flow compared with perception, are the various constituent features of a visual stimulus also recreated in reverse order when reconstructed from memory? A recent study using EEG-based decoding and reaction time measures provides direct evidence for this view [51]. Participants either perceived visual objects or recalled them from memory when cued with a reminder word (Figure 3A). Perception followed the well-established forward stream, with perceptual features (photograph vs line drawing) coming online more rapidly than conceptual features (animate vs inanimate), as evident in neural decoding time series and behavioural reaction times. Critically, this relative timing flipped when an object was reconstructed from memory: conceptual information was now classified more rapidly than perceptual information. Cued recall thus appears to trigger a neural processing cascade that temporally prioritises abstract-conceptual over detailed-perceptual information. The findings are consistent with the idea that the MTL preferentially back projects to multisensory areas that contain high-level abstract representations of an event [58]. They are also in line with findings showing that mental imagery with no bottom-up visual input, reliant on the hippocampus [59], tends to recapitulate relatively late stages of visual processing [60,61]. It should be noted, however, that under highly controlled task conditions, mnemonic reinstatement during cued recall can be found even in early visual cortex, suggesting that the back propagation does not terminate at high-level conceptual stages [9]. An interesting question is whether recurrent neural networks [62] can realistically simulate such reinstatement that starts at high levels of the visual hierarchy without direct perceptual input and then back propagates from conceptual to perceptual levels of representation. Such models could potentially make interesting predictions about the degree of perceptual detail that can be achieved by a mnemonic backward reconstruction process that lacks any bottom-up visual input. Future studies will also reveal whether this reverse information processing cascade generalises across different task contexts and different types of memories, including more complex multiple-element episodes as discussed in the following section (e.g., [63,64]).

Temporal Dynamics of Sequence Replay during Memory Recall

Episodes unfold, by definition, across time and contain multiple events. Much work on the **replay** of event sequences has been conducted in rodents, reviewed elsewhere (e.g., [65]). Here we focus on the emerging literature investigating the reactivation of event sequences in humans. While evidence is accumulating for forward and backward replay during periods of inactivity following learning [66,67], very few studies have investigated sequential reactivation during cued recall. In one recent EEG study [68], participants were presented with short movie or sound clips and later asked to mentally replay these clips when cued with a reminder. The neural trajectories that uniquely characterised a clip during its initial perception were replayed in a forward sequence during cued recall, for both visual and auditory memories. A follow-up MEG study [69] used sequences of short movies that together constituted a coherent episode (e.g., a movie of a boat, divers jumping off the boat, divers under water). A critical word stimulus was presented during one of the three sequential clips. During retrieval, participants were asked to mentally replay the full movie to judge when in the sequence the word had appeared. Behavioural reaction times and neural patterns suggested a time-compressed forward skipping through the sequences during recall. This finding is consistent with other, within-event evidence indicative of a time-compressed forward recall process [70].

Interestingly, one of the abovementioned studies on replay during rest periods [66] identified reward as the critical determinant of the direction of replay, with rewarded sequences becoming preferentially replayed in reverse order. The same study also demonstrated that abstract, structural

(A)

Task stages

Schematic of analysis

EEG decoding and RTs

Encoding

Recall

Encoding: Expected order of classifier peaks

Perceptual classifier

Conceptual classifier

Recall: Expected order between peaks

EEG decoding peaks

RTs in Behavioural Exp. 1

RTs in Behavioural Exp. 2

Perception
Memory

(B)

Schematic of hypothesis

Decoding time series
8-Hz oscillation

Phase modulation of decodability

Retrieval
Encoding

Theta phase extracted from hippocampal source

FFT of decoding time series

FFT of decoding time series
Control and 95th percentile of surrogate classifiers

Classifier-locked oscillations

Reactivation peak

Theta phase locking

Sources of theta phase locking

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Figure 3. Temporal Dynamics of Cortical Reinstatement.
(A) Reversal of the information flow between perception and cued recall. Left and middle: Electroencephalography (EEG)-based classifiers are trained to decode perceptual (photograph vs drawing) and conceptual (animate vs inanimate) features while participants visually perceive an object (encoding) or recall it from memory when prompted with a verbal cue. Right: Evidence for the reversal of the perceptual-to-conceptual gradient during perception (primary axis) compared with memory (secondary axis). The top graph shows the participant-level average decoding peaks of the perceptual and

(Figure legend continued at the bottom of the next page.)

information about a sequence is consistently replayed before object-specific information, consistent with the conceptual-to-perceptual gradient of memory reinstatement discussed above. Clearly, more work is needed to establish the conditions that trigger forward and backward sequential replay during awake recall and their respective functional significance for the retention and reorganisation of memories over time (see [51,71] and Outstanding Questions).

Theta Oscillations as a Clocking Mechanism

In this final section, we review the role of brain oscillations in the theta frequency range in the temporal orchestration of the recall process. Theta oscillations (~4–8 Hz) dominate the field potential of the rodent hippocampus and have been identified in human iEEG recordings at similar or slower frequencies [72–74]. Several brain regions, including medial prefrontal and anterior thalamic nuclei, have been discussed as pacemakers of this rhythm, synchronising the hippocampus with larger subcortical and neocortical networks [75]. In the medial temporal lobe, the timing of neural activity within a theta cycle appears to play a central role in the emerging memory codes. In rodents, different neural assemblies that represent different information (e.g., the animal's location in a maze) fire sequentially along a theta cycle, with their order of firing mirroring trajectories the animal has taken in the past [76–78]. Such firing occurs in so-called **gamma bursts**, which group together the cells that constitute a neural assembly [76]. A distinct spatial mnemonic code has thus been identified in rodents that comprises sequential gamma bursts nested into slower theta oscillations.

Based on this animal literature, theta phase coding has been proposed as a computationally efficient mechanism for the ordering and linking of discrete events within a sequence [79,80]. Direct evidence in humans that elements of a reactivated episodic memory are grouped by theta-nested gamma bursts is still missing. During offline periods following learning, replay has been shown to coincide with hippocampal ripples in the gamma band [66], and human iEEG recordings provide initial evidence for ripple-bound memory reinstatement during awake recall [36] (Box 2). The missing link, at present, is the demonstration that ripple events are clocked by the hippocampal theta rhythm during active recall. A recent iEEG study provides encouraging evidence for such clocking in working memory. While participants were mentally rehearsing letter sequences, the elements constituting a sequence could be decoded from neighbouring gamma bursts (>80 Hz) along the theta cycle [81]. In long-term memory, it has been demonstrated that the human brain deploys a theta–gamma code for the encoding of novel event sequences [82] and for binding memories to their encoding context [83]. Theta-to-gamma coupling also generally increases during recall [80]; for example, when participants recognise a stimulus as old [84] or recall autobiographical events [85]. It is therefore conceivable that theta oscillations clock the timing of memory recall signals in human long-term memory.

The most direct demonstration of a theta clocking function in humans comes from recent EEG work using time-resolved decoding of memory reinstatement following the presentation of a reminder [86] (Figure 3B). As expected, decoding of reactivated mnemonic content was maximal 500–1000 ms after cue onset, consistent with the literature reviewed above. Critically, in this time window the neural signatures of memory reinstatement fluctuated rhythmically, waxing and waning at a theta frequency of 8 Hz (Figure 3B, bottom left). The decodability of perceived versus recalled objects was maximal at opposite phases of the theta cycle (Figure 2B, upper middle), consistent with computational models

conceptual classifiers when the object is visually presented (grey) or reconstructed from memory (black). The two bottom graphs show independent replications of the same flip in reaction times (RTs) when human participants classify perceptual or conceptual features of objects that are visually presented or reconstructed from memory. Asterisks indicate a significant classifier type (perceptual, conceptual) × task stage (perception, memory) interaction. Adapted from [51]. (B) Theta phase modulates memory reinstatement. Top left: Memory reinstatement, as indicated by the decodability of an object during cued recall, is expected to fluctuate in a theta rhythm and to be maximal at a specific, recurrent phase of the theta rhythm. A fast Fourier transform (FFT) of the decoding timelines confirms a significant fluctuation at 8 Hz (left bottom). Top right: Significant modulation of object decodability by the phase of an 8-Hz rhythm extracted from virtual sources in the hippocampus. Bottom right: Classifier-locked analysis showing significant phase locking 200–300 ms before maximal classification (i.e., reinstatement) of the recalled object, with source reconstruction suggesting an origin of the phase-locked signal in the hippocampus and parietal areas. Adapted from [86].

that predict a phase separation of information flowing into the hippocampus during encoding and out of the hippocampus during retrieval [87]. This work allows the intriguing possibility that, between those theta states that are optimal for encoding and retrieval, respectively, a transition phase exists that provides the optimal time point for the perception-to-memory flip discussed in the previous section.

Related to the critical time point of this reversal, the same study [86] also suggests an interesting temporal relationship between theta phase and neocortical reinstatement. Time points of maximal memory reactivation were preceded by a theta phase-locked signal by approximately 250 ms (Figure 3B, bottom right). The delay is indicative of an upstream region (e.g., hippocampus) initiating the recall process at the optimal retrieval phase of the theta cycle followed by neocortical reactivation of mnemonic content 200–300 ms later, an interpretation corroborated by **source analysis** (Figure 3B, bottom right). This observation is of interest because human iEEG work points to a similar offset between the processing of a memory cue and hippocampal recall processes. For instance, one study recorded field potentials in the hippocampus and anterior temporal lobe (ATL) while participants encoded and later recalled cross-category associations [27]. The directionality of oscillatory coupling between these regions changed during recall relative to encoding, with ATL engagement following a hippocampal recall signal with a delay of ~250 ms. A study using single-neuron recordings examined the delay between visually selective (VS) and memory-selective (MS) MTL neurons during recognition [29] and found that VS neurons responded approximately 200 ms earlier (from ~250 ms) than MS neurons (from ~450 ms). Similar effects were found in a cued-recall paradigm, where neuron population-based decodability of the cue emerged 140 ms before decodability of the reactivated memory [25]. Finally, a third single-unit study found that the spiking of neurons that encode the identity of a reminder peaks at ~400 ms, while neurons encoding an associated (not visually presented) stimulus spike around 600 ms, again suggesting an offset of 200 ms [88].

Together, electrophysiological recordings support the idea that content reinstatement during memory recall follows reminder-specific processing with a latency of ~200 ms, roughly corresponding to one theta cycle. Some temporal variability is, of course, to be expected empirically and it is unlikely that perceptual versus mnemonic processes occur in an all-or-none fashion at a single instance of a theta cycle. Instead, there might be a gradual build up of both cue processing (within the first 500 ms) and target reinstatement (>500 ms), but this build up might still contain discrete volleys of information progressing via theta rhythms. It could be speculated that these volleys take the form of rapid forward sweeps of incoming sensory information and rapid backward sweeps of mnemonic information (i.e., replay events) during opposing phases of a theta cycle. Once a reminder has been sufficiently processed to initiate a pattern completion process, each retrieval phase of a theta cycle provides a time window for the hippocampus to coordinate the reinstatement of discrete 'parcels' of content in the neocortex, presumably during ripple events. Neocortical areas including the parietal lobe (Box 1) then accumulate this mnemonic evidence, yielding the phenomenology of reinstatement once the evidence surpasses a given threshold [89]. While speculative at this point, the idea is consistent with observations of theta-clocked memory signatures during episodic recall [86], during spatial navigation [90], and during working memory maintenance [91]. It is also consistent with evidence that the theta rhythm is not limited to the hippocampus [75] but rather synchronises larger neocortical networks during both encoding and recall [85,92], presumably facilitating inter-regional communication. During cued recall, coupled theta oscillations in hippocampal–neocortical circuits might thus gate the information flow out of the hippocampus, constituting a clocking mechanism that times retrieval operations to minimise their temporal overlap with concurrent sensory processing.

Concluding Remarks

We reviewed recent progress in elucidating the neural chronometry of memory recall. Intriguingly, most of a memory cue's mnemonic fate is sealed within a single second. For the first ~500 ms, sensory cue information progresses toward the hippocampus. Autoassociative processes in the hippocampus then reactivate the cell assembly assigned to the particular experience. This pattern completion

Outstanding Questions

Are different brain regions causally involved in successful recall at different times? Future studies could use brain stimulation to target, for example, the hippocampus via direct intracranial stimulation and the parietal cortex via transcranial magnetic stimulation (TMS). Is there a double dissociation in the effect of stimulation of these regions at early (~500 ms) vs late (~1500 ms) stages of the recall process?

Within the 500–1500 ms time window of cortical reinstatement, would experimental perturbation at early vs late stages differentially affect the recall of conceptual vs perceptual information, respectively?

Is mnemonic evidence in the posterior parietal cortex (PPC) fed directly by a hippocampal signal or by the sensory areas in which reinstatement occurs? Likewise, is recall terminated by direct inhibition of hippocampal processes or by activity in sensory areas?

Can recall performance be enhanced by presenting cues at specific phases of the ongoing theta rhythm (e.g., by using closed-loop stimulus delivery as a function of theta peaks vs troughs)?

Extant evidence points to forward replay during recall of sequences. Is there also a role of reverse replay in humans, analogous to rodent models? Is forward vs reverse replay differentially likely to occur during cued vs spontaneous recall or sleep vs wake?

What is the speed (i.e., compression factor) of memory recall in humans? Are sequences that occurred within two event boundaries compressed to fit onto a single theta cycle?

Does the recall chronometry described here require a particular retrieval mode? Cued-recall paradigms in the laboratory artificially separate encoding from retrieval intervals, whereas in real life, salient reminders can occur at any time during ongoing experiences, requiring the brain to switch from a

process leads to the reinstatement of mnemonic content in high-level cortical sites from 500 ms onward. Recent work has now begun to unveil the dynamic principles governing this reinstatement cascade. First, mirroring the (re)constructive nature of memory retrieval, the flow of information appears to reverse during recall (feedback) compared with encoding (feedforward). Moreover, the speed of feedback communication might deviate from its encoding counterpart, including temporal compression and jumps at event boundaries. Last, theta rhythms play an integral part in coordinating hippocampal–neocortical communication, effectively gating sensory (external) versus mnemonic (internal) representations and providing discrete time windows for the progression of information from one level to the next.

We assembled much of this intricate clockwork from various experimental approaches across different study populations and species. However, recent advances in our understanding of oscillatory dynamics [93] in conjunction with improved source reconstruction algorithms and the widespread application of multivariate analysis techniques have kickstarted a renaissance of noninvasive human electrophysiology. These developments will spawn a new generation of studies capturing the brain-wide dynamics between the hippocampus and neocortex and opening fine-tuned temporal windows for experimental control of memory recall (see Outstanding Questions).

sensory (encoding) to a mnemonic (retrieval) state.

How does the recall chronometry change for recall of remote autobiographical memories? Most studies reviewed here investigated recent, laboratory-based memories. For remote memories, the timeline might show a general slowing reflecting increased effort or reinstatement might become increasingly imprecise while progressing with equal speed, reflecting the 'gistification' of memories over time.

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