Within and beyond the medial temporal lobe: brain circuits and mechanisms of recognition and place memory - Review Article

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Prefrontal–hippocampal interaction during the encoding of new memories

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Abstract

The hippocampus rapidly forms associations among ongoing events as they unfold and later instructs the gradual stabilisation of their memory traces in the neocortex. Although this two-stage model of memory consolidation has gained substantial empirical support, parallel evidence from rodent studies suggests that the neocortex, in particular the medial prefrontal cortex, might work in concert with the hippocampus during the encoding of new experiences. This opinion article first summarises findings from behavioural, electrophysiological, and molecular studies in rodents that uncovered immediate changes in synaptic connectivity and neural selectivity in the medial prefrontal cortex during and shortly after novel experiences. Based on these findings, I then propose a model positing that the medial prefrontal cortex and hippocampus might use different strategies to encode information during novel experiences, leading to the parallel formation of complementary memory traces in the two regions. The hippocampus captures moment-to-moment changes in incoming inputs with accurate spatial and temporal contexts, whereas the medial prefrontal cortex may sort the inputs based on their similarity and integrates them over time. These processes of pattern recognition and integration enable the medial prefrontal cortex to, in real time, capture the central content of novel experience and emit relevancy signal that helps to enhance the contrast between the relevant and incidental features of the experience. This hypothesis serves as a framework for future investigations on the potential top-down modulation that the medial prefrontal cortex may exert over the hippocampus to enable the selective, perhaps more intelligent encoding of new information.

Keywords

Hippocampus, prefrontal cortex, recognition memory, spatial memory, classical conditioning

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Introduction

Established literature suggests that memories of daily experiences, so-called episodic memories, depend on the inter-connected network of the hippocampus and neocortex (Eichenbaum, 2000; McClelland et al., 1995; Squire, 1992). Studies using rodent models of episodic memory showed that the hippocampus rapidly encodes new information via modifications of highly plastic synaptic connections between local neurons (Bittner et al., 2015, 2017; Whitlock et al., 2006). Within a few hours, these modified synaptic connections become stabilised through intracellular processes leading to the synthesis of new proteins. Failure of this cellular/synaptic consolidation process results in the loss of memory, leading to immediate forgetting (Asok et al., 2019; Dudai, 2004; Takeuchi et al., 2014). In parallel, during subsequent, off-line periods, such as sleep, hippocampal neurons spontaneously replay neural activity patterns associated with prior experiences, which in turn activate corresponding neurons across many neocortical regions. This process, so-called systems consolidation, gradually strengthens the connections between the activated neocortical neurons, leading to the establishment of neocortically based memory traces (Alvarez and Squire, 1994; McClelland et al., 1995; Squire, 1992; Teyler and DiScenna, 1986).

Research in the past 15 years accumulated evidence that the medial prefrontal cortex (mPFC) serves as a critical node in the network of the neocortically based memory traces (Frankland and Bontempi, 2005; Takehara-Nishiuchi, 2020; Tonegawa et al., 2018; Wiltgen et al., 2004). Over weeks of systems consolidation processes, synaptic structures within subregions of the mPFC are gradually modified in a manner dependent on the integrity of the hippocampus (Abate et al., 2018; Kitamura et al., 2017; Restivo et al., 2009). During the same time window, neurons in the mPFC strengthen their selectivity for memory contents (Kitamura et al., 2017; Morrissey et al., 2017; Takehara-Nishiuchi and McNaughton, 2008; Weible et al., 2012). Collectively, these observations led to a view wherein close interaction between the hippocampus and mPFC *after* memory encoding gradually stabilises a critical part of neocortically based memory traces in the mPFC.

In parallel, other studies investigated correlations of neural activity between the mPFC and hippocampus in well-trained

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animals and provided evidence for their close interaction during memory retrieval. Specifically, when animals formed multiple similar stimulus–response mappings (i.e. 'rules' or 'sets'), animals with mPFC dysfunction acquire new mappings but fail to flexibly retrieve the most appropriate mapping for the present context (e.g. Dias and Aggleton, 2000; Farovik et al., 2008; Rich and Shapiro, 2007). Moreover, the neural activity becomes transiently coupled between the mPFC and hippocampus during the retrieval of the mapping (Place et al., 2016) as well as decision-making guided by the retrieved mapping (Hyman et al., 2010; Jones and Wilson, 2005). Furthermore, the disruption of the mPFC activity diminishes the selectivity of hippocampal neurons for the mappings without affecting their selectivity for spatial locations (Guise and Shapiro, 2017; Ito et al., 2015; Navawongse and Eichenbaum, 2013). These findings led to a view that the mPFC modulates the hippocampus to recover memory representations that are most appropriate for the present context (Eichenbaum, 2017; Moscovitch, 1992; Preston and Eichenbaum, 2013; Rudy et al., 2005).

Compared to the established literature on prefrontal–hippocampal interaction during memory consolidation and retrieval, a contribution that the prefrontal cortex might make to memory encoding has thus far received limited attention (Dash et al., 2004; Jung et al., 2008; Medina et al., 2008). Since the late 1900s, several human imaging studies have shown that the prefrontal cortex is activated during the encoding phase of episodic memory tasks (Shallice et al., 1994; Tulving et al., 1994, 1996). Subsequent studies showed that the magnitude of prefrontal activation during the presentation of an item is predictive of whether the item would be subsequently remembered (Brewer et al., 1998; Kao et al., 2005; Kirchhoff et al., 2000; Wagner et al., 1998, 2016). Traditionally, prefrontal activation during the encoding phase of a task has been associated with its established role in cognitive control (Miller and Cohen, 2001; Moscovitch, 1992; Ragozzino, 2007) and working memory (Fuster, 1991; Goldman-Rakic, 1996). In this case, the prefrontal cortex is not a part of the network of brain regions storing long-term memories; instead, it facilitates the relay of new information to the memory network. A less explored possibility, however, is that the strong activation of the prefrontal cortex results in immediate changes in synaptic connectivity between local neurons, which builds a portion of the memory trace in the prefrontal cortex in parallel to other brain regions.

Through surveying behavioural, neurophysiological, and molecular studies in rodents, this opinion article seeks to evaluate the empirical support for the coordinated memory trace formation in the hippocampus and prefrontal cortex at the time of memory encoding. In the following sections, I start by outlining memory paradigms used in these rodent studies directed at neurobiological bases of episodic memories (section 'Rodent behavioural tests used to study neurobiological mechanisms of episodic memory'). The following sections summarise evidence showing that the mPFC is necessary for memory acquisition in these paradigms (section 'The integrity of the mPFC is necessary for memory formation'), and that the activation of the mPFC during training induces molecular processes leading to immediate modifications of local synapses (section 'Encoding initiates molecular processes leading to synaptic remodelling in the mPFC'). I will then discuss how the activity of neurons in the mPFC changes as rodents learn new information (section 'Neural firings in the mPFC become selective for memory contents at the time of memory encoding'), how it modulates the neural encoding of new information in the hippocampus (section 'mPFC activity modulates neural activity in the hippocampus during memory encoding'), and how its manipulation enhances memory formation (section 'Memory enhancement through artificial activation of the mPFC'). Based on these findings, in the next section 'Prefrontal–hippocampal interaction for selective memory encoding', I propose a model positing that during the encoding of new information, the mPFC may use a coding scheme different from that of the hippocampus to form a memory trace prioritising the central content over minor details of novel experiences. This model is then related to other theories regarding schema-dependent memory encoding and early tagging of cortical neurons bearing memory. The final section 'Concluding remarks' summarises the model and identifies several remaining issues that warrant future investigations.

Summary of available evidence

Rodent behavioural tests used to study neurobiological mechanisms of episodic memory

In psychology, episodic memory is defined as one type of declarative memory that relies on 'the capacity for conscious recollection about events' (Squire, 2004). It is severely impaired in amnesic patients with damages to structures in the medial temporal lobe (Scoville and Milner, 1957; Squire, 1992). Also, it includes the encoding of relationships of multiple items and events that occurred at a particular time and place (Cohen and Eichenbaum, 1993; Eichenbaum, 2017). Among these characteristics, the latter two can be incorporated into behavioural testing paradigms in rodents. These paradigms can be grouped into three types.

The first type consists of associative object recognition paradigms that exploit the natural tendency of rodents to preferentially explore novel items, such as objects and olfactory cues, over familiar ones. For example, in an 'object-in-place' recognition memory task, animals freely explore an environment containing objects (sample phase). When placed back into the same environment (test phase), they preferentially explore the objects placed in novel locations over those placed in the same location. The interval between the sample and test phases ranges from a few minutes to hours, and both phases are typically conducted on the same day. These paradigms are best suited to study neurobiological mechanisms underlying the single-shot, automatic, encoding of incidental events.

The second type includes several variants of classical conditioning paradigms in which animals associate a neutral stimulus (conditioned stimulus, CS) and an innately salient stimulus (unconditioned stimulus, US). In the standard types, such as cued fear conditioning and delay eyeblink conditioning, the CS precedes and co-terminates with the US, resulting in long-lasting memory traces in the amygdala (Johansen et al., 2011) or the cerebellum (Thompson, 2005). Notably, this simple associative learning becomes dependent on the hippocampus with small modifications of the conditioning procedures. For example, contextual fear conditioning involves the exploration of a conditioning chamber (CS), which enables subjects to form a contextual representation and to associate it with footshock (US; Maren

et al., 2013). On the other hand, in trace paradigms, a short temporal interval is interposed between the offset of a neutral stimulus (CS) and the onset of an aversive stimulus (US), making it more difficult to detect the contingency between the CS and US (Woodruff-Pak and Disterhoft, 2008). In humans, successful trace conditioning is related to the development of conscious awareness about the stimulus contingency (Clark et al., 2002), suggesting that trace paradigms engage the neural system supporting declarative memory.

The last type is spatial learning tasks, such as the Morris water maze task, plus-shaped, and radial maze tasks. In these paradigms, animals undergo repeated training sessions and gradually become capable of taking the shortest trajectory to the platform hidden underwater or a food reward placed in a specific location. These tasks can be used to test spatial reference or working memory, depending on whether the goal location is stable or varied across sessions.

It is well established that the acquisition of all these types of memories depends on the integrity of the hippocampus both in humans and rodents (Manns and Eichenbaum, 2006; Maren et al., 2013; Morris, 2001; Warburton and Brown, 2015; Woodruff-Pak and Disterhoft, 2008). Some studies, however, reported that these tasks were not impaired in subjects with permanent damage to the hippocampus (e.g. Langston and Wood, 2010; Maren et al., 1997; Richmond et al., 1999; Wiltgen et al., 2006). The apparent discrepancy may be due to multiple learning strategies that subjects can use in these paradigms. Specifically, in contextual fear conditioning, hippocampal-lesioned animals may associate footshock with a specific feature of the conditioning chamber (e.g. the colour of the wall) instead of a conjunctive representation of the conditioning context (Fanselow, 2000; Rudy and O'Reilly, 1999). In associative recognition memory paradigms, they may express recognition memory by relying on the sense of familiarity rather than recollection (Fortin et al., 2004). The following sections outline the studies that examined how memory formation in these paradigms is affected by manipulations applied to the mPFC during training.

The integrity of the mPFC is necessary for memory formation

In rodents, the mPFC consists of several subregions – including prelimbic, infralimbic, and anterior cingulate cortices – which corresponds to Brodmann area 32, 25, and 24, respectively (Laubach et al., 2018; Uylings et al., 2003). Among many studies testing the impact of prefrontal dysfunction in various behavioural paradigms, the following papers disrupted some of mPFC subregions before the training phase in a hippocampus-dependent memory task. Specifically, the pre-task lesion of the mPFC impaired memory formation in object-in-place associative recognition memory task (Barker et al., 2007), temporal order recognition memory task (Barker et al., 2007), temporal sequence memory task (Devito and Eichenbaum, 2011), trace fear conditioning (Han et al., 2003), and trace eyeblink conditioning (Kronforst-Collins and Disterhoft, 1998; McLaughlin et al., 2002; Weible et al., 2000). In the Morris water maze task, the large lesion covering both rostral and caudal parts of the mPFC impairs learning (Kolb et al., 1982), while the lesion affecting only the rostral part had no effect (De Bruin et al., 1994; Granon and Poucet, 1995).

Memory impairments induced by permanent lesions before training cannot differentiate whether the mPFC is necessary for memory encoding or retrieval. To overcome this limitation, subsequent studies used pharmacological, chemogenetic, or optogenetic manipulations to reversibly disrupt the activity of the mPFC during only the training phase of the task. In the object-in-place associative recognition memory task, recognition memory was impaired by the pharmacological blockade of N-methyl-D-aspartate (NMDA) receptors in the prelimbic region during the sample, but not test, phase (Barker and Warburton, 2008). Similarly, chemogenetic inactivation of the prelimbic cortex before the sample phase impairs social odour recognition memory, whereas inhibition of the mPFC before the test phase had no effect (Robinson et al., 2019). In contextual fear conditioning, memory acquisition is impaired by the pharmacological blockade of the GluN2B subunit of NMDA receptors (Einarsson and Nader, 2012; Zhao et al., 2005) as well as optogenetic inhibition of excitatory neurons (Bero et al., 2014) in the caudal anterior cingulate cortex. In parallel, the pharmacological inactivation or blockade of NMDA receptors in the prelimbic region impairs memory acquisition in trace eyeblink (Takehara-Nishiuchi et al., 2005) and trace fear (Gilmartin and Helmstetter, 2010) conditioning. Collectively, these findings suggest that the integrity of the mPFC during the training is necessary for the formation of various forms of hippocampus-dependent memories.

Encoding initiates molecular processes leading to synaptic remodelling in the mPFC

The mPFC has been implicated in diverse processes, such as cognitive control and working memory (Preston and Eichenbaum, 2013; Rudy et al., 2005), which act to instruct and facilitate the encoding of new information in other brain regions. This suggests that mPFC activity during novel experiences might simply reflect the online modulatory process, rather than a hallmark for the local formation of a memory trace. A key point that discerns between the two possibilities is whether the activation of mPFC neurons during learning initiates cellular/synaptic consolidation processes that stabilise modified synaptic connections between local neurons. Consistent with this view, genome-wide RNA sequencing of the caudal anterior cingulate cortex uncovered that within 1 h after contextual fear conditioning, 342 genes (121 upregulated, 221 downregulated) are differentially expressed between conditioned and control mice (Bero et al., 2014). Most of the upregulated genes are implicated in various biological processes that promote synaptic plasticity, whereas the downregulated genes are associated with processes that suppress synaptic plasticity. Also, cingulate neurons in conditioned mice exhibited expansions of the active zone, postsynaptic density, and increased numbers of docked synaptic vesicles. In keeping with these structural changes, the frequency, but not amplitude, of miniature excitatory postsynaptic current (mEPSC) was also increased at excitatory synapses.

These observations extended earlier findings showing the activation of a specific plasticity-related protein during and immediately after learning. In trace fear conditioning, the phosphorylation of the extracellular signal-regulated kinase (ERK) becomes elevated in the prelimbic region shortly after the conditioning, and the pharmacological inhibition of ERK activity

before or immediately after conditioning impairs memory retention 48 and 72 h later (Runyan et al., 2004). Similarly, shortly after trace fear conditioning, the amount of polyubiquitinated proteins (that are to be degraded by the ubiquitin–proteasome system) is increased in the prelimbic region, and local pharmacological inhibition of these proteasomes immediately after the conditioning impairs subsequent retention (Reis et al., 2013). Similar findings are also reported in studies using manipulations targeting protein synthesis in general. In the inhibitory avoidance task, protein synthesis inhibition in the prelimbic cortex starting before, but not 6 h after, training impairs the retention of passive avoidance responses on the next day (Gonzalez et al., 2013).

Notably, several studies reported that manipulations of ERK or cAMP response element-binding protein (CREB) in the mPFC do not impair memory acquisition or memory retention within a few hours after learning (Barker et al., 2020; Leon et al., 2010). Considering that these proteins are necessary for cellular consolidation, but not encoding (Bozon et al., 2003), the lack of behavioural effects is due to the molecular process, but not the region that was manipulated. Thus, these findings do not refute the involvement of the mPFC in memory encoding. Collectively, accumulating evidence suggests that novel experiences initiate molecular signalling that leads to rapid modifications of synaptic connectivity between neurons in the mPFC, and that this process is necessary for the retention of memory at later time points.

Neural firings in the mPFC become selective for memory contents at the time of memory encoding

In parallel to the manipulation studies reviewed above, other studies monitored neural activity in the mPFC as rats acquired new information. Early electrophysiological recordings during trace paradigms showed that neurons in the prelimbic region develop firing responses to a neutral stimulus predictive of an aversive shock (Baeg et al., 2001; Gilmartin and McEchron, 2005; Hattori et al., 2014). In parallel, as rats learned to alternate between visiting two spatial locations on a figure-eight-shaped maze for a reward, a subset of prelimbic neurons increases their likelihood for synchronous firing, a physiological sign indicating the increased functional connectivity among local neurons (Baeg et al., 2007).

Although supportive, a limitation of these studies is that the change in neural activity was detected across days. This makes it challenging to decipher whether the neural selectivity was acquired at the time of encoding or during consolidation processes after each conditioning session. Several recent studies, therefore, used a simple form of the spatial learning task and tracked changes in neuronal firing patterns as animals acquired new information within a day. When rats learn rules in a spatial alteration task with a W-shaped maze, both hippocampal and mPFC neurons develop selective firing patterns for a specific location within ~15 min (Shin et al., 2019). Moreover, when the hippocampus shows high-frequency oscillations, called ripples, hippocampal and mPFC neurons fire sequentially in the same temporal order as they fired during running. Importantly, this 'coherent' reply of neural firing sequences is more frequently detected for the trajectory that the rats took than those that rats had never taken, alluding to the relevance of this coordinated activity for the encoding of new experiences. Similarly, when rats learned to visit a left or right arm on a Y maze to collect a food reward, coherence of theta oscillations in the hippocampus and mPFC becomes elevated at the choice point as the rats become capable of consistently choosing the correct arm (Benchenane et al., 2010). Collectively, the evidence is growing for the rapid development of neural selectivity for newly acquired information in the mPFC and its coordination with ongoing neural activity in the hippocampus.

mPFC activity modulates neural activity in the hippocampus during memory encoding

Some of the studies mentioned above provide correlational findings for the notion that the mPFC and hippocampus work in concert during the encoding of new memories. Other studies tested the necessity of the interaction by manipulating the anatomical pathways between the hippocampus and mPFC. The two regions are connected by unidirectional, monosynaptic projections from the ventral hippocampus to the mPFC (Jay and Witter, 1991) as well as two multi-synaptic pathways via a single intermediary region. One of these pathways includes the thalamic nucleus reuniens (Vertes et al., 2007), and the other contains the perirhinal (PER) and lateral entorhinal cortex (LEC; Burwell and Amaral, 1998; Witter et al., 2000). Several studies disrupted some of these pathways with 'asymmetric' manipulation techniques in which the manipulation is applied unilaterally to each of the two brain regions but in opposite hemispheres. Specifically, rats fail to form various types of associative recognition memory when the mPFC is disconnected from the dorsal hippocampus (Barker and Warburton, 2015; De Souza Silva et al., 2016), LEC (Chao et al., 2016), and PER (Hannesson et al., 2004). In parallel, optogenetic silencing of monosynaptic projections from the ventral hippocampus to the prelimbic region during training impaired the formation of contextual fear memory (Twining et al., 2020).

In parallel, other studies have examined the impact of altered mPFC activity on hippocampal neural activity during novel experiences. Bero et al. (2014) showed that optogenetic inhibition of the caudal anterior cingulate cortex during contextual fear conditioning reduces the expression of an activity-regulated gene in the hippocampus and LEC, which in turn impairs memory formation. However, electrophysiological studies demonstrated that damage to the mPFC does not affect the selectivity of hippocampal neurons for a specific location within an environment. The mPFC dysfunction, however, destabilises the selectivity across two separate exposures to the same environment (Kyd and Bilkey, 2003) and the same environment with slightly modified sensory features (Kyd and Bilkey, 2005). Collectively, these findings suggest that dysfunction of the mPFC has a profound impact on the activity of hippocampal neurons during memory encoding and that disruption of their close interaction impairs the encoding of new information.

Memory enhancement through artificial activation of the mPFC

The above-reviewed literature collectively suggests that the mPFC modulates the activity of the hippocampus during memory

encoding. These observations predict that by manipulating the mPFC's activity, it may be possible to tap into endogenous encoding mechanisms in the hippocampus, thereby facilitating memory encoding. Consistent with this view, associative recognition memory is enhanced when excitatory neurons in the prelimbic region are activated either by optogenetic excitation or pharmacological augmentation of glutamatergic transmission (Benn et al., 2016). The same manipulations did not enhance recognition of the novel object, suggesting that the memory-enhancing effect is specific to the hippocampus-dependent form of recognition memory.

In trace eyeblink conditioning, chemogenetic activation of excitatory neurons in the prelimbic region enables rats to associate a neutral stimulus and eyelid shock over an extended temporal interval that is prohibitively long for untreated rats to learn (Volle et al., 2016). Moreover, in a differential learning paradigm, in which the only one of the two neutral stimuli is paired with eyelid shock, the same manipulation facilitates the formation of differential association without erroneously increasing behavioural responses to the other neutral stimulus (Jarovi et al., 2018). In both studies, the chemogenetic manipulation specifically augmented the duration of oscillatory activity evoked by the shock-predictive stimulus, but not the non-predictive stimulus. This finding suggests that the mPFC network is differentially activated by sensory events depending on their learned biological significance and that the enhancement of this exact computation facilitates the encoding of those relevant events. Collectively, these recent studies using gain-of-function approaches suggest that stronger activation of the mPFC results in the better encoding of new information.

Prefrontal–hippocampal interaction for selective memory encoding

The above-mentioned studies put forward evidence for the close interaction between the mPFC and hippocampus during memory encoding. They thus raise a crucial question as to what kind of unique contribution the mPFC makes to the encoding of new information. Here, I propose that the mPFC uses a different coding scheme from that of the hippocampus to capture new information, thereby forming a complementary memory trace that prioritises the central content over minor details of novel experiences.

The core concept behind this model originates from the fact that our brains do not record every single event that we encounter. Instead, we selectively form strong memories for salient information with emotional, motivational, and personal values while immediately forget most other incidental details. It is well established that emotionally arousing experiences that include rewards and threats are encoded more strongly than neutral experiences owing to the modulatory signals originating from the locus coeruleus (Sara, 2009) and amygdala (McGaugh, 2004). In parallel to these bottom-up modulatory processes, some have proposed that the commonality between new information and previously learned information also signals saliency, which in turn changes the speed of memory encoding and consolidation (Duszkiewicz et al., 2019; Morton et al., 2017; Wang and Morris, 2010). This idea inherently assumes that the brain does not interpret ongoing experiences merely by analysing incoming information as it perceived. Instead, it actively seeks a proactive link between incoming features and existing familiar information based on their perceptual and relational commonality.

The existing theories define 'commonality' as the resemblance between ongoing events and past experiences that took place hours, days, or months ago. The sense of commonality, however, may also arise while animals continuously collect new information within a single experience. Specifically, during our daily experiences, we repeatedly perceive the same sensory information and engage in the same behaviour in a variable spatial and temporal sequence (Figure 1). Similarly, training in an experimental setting also consists of multiple repetitions of incoming inputs and behaviour. For example, during the sampling phase of the associative object recognition task, animals typically investigate objects multiple times. In classical conditioning and spatial learning paradigms, animals repeatedly undergo the same sensory inputs across multiple trials and laps. Across these repetitions, incoming inputs may appear differently from previous inputs due to perceptual variation and moment-to-moment changes in external and internal states. If sensory inputs during each of these repetitions are treated as novel inputs, they are encoded separately and stamped with the temporal and spatial contexts at that moment. In contrast, if the commonality of incoming inputs to previous inputs is detected, they will be integrated into a single representation of the inputs. I propose that these two different coding schemes are implemented in the hippocampus and mPFC, respectively (Figure 1). The hippocampus accurately encodes moment-to-moment changes in incoming inputs with a spatial and temporal context. In contrast, the mPFC continuously checks whether an incoming input is related to the inputs perceived a moment ago and integrates the related inputs over time. These processes of pattern recognition and integration enable the mPFC to capture the central content of the experience. The resultant traces in the mPFC may also serve as a top-down modulatory signal that highlights the essential, relevant features within detailed, context-rich representations in the hippocampus.

One may notice the similarity between this framework and the proposed role of the mPFC in the schematisation of memories during systems consolidation. When memories of experiences are consolidated, commonalities across multiple experiences are extracted, leading to the generation of an internal model of the world, in other words, prior knowledge or schema (McClelland, 2013; McClelland et al., 1995; Marr, 1971; Sekeres et al., 2018; Winocur et al., 2010). When newly acquired information is similar to and compatible with prior knowledge, the information could be incorporated into prior knowledge, rather than being stored as a brand new memory trace, thus resulting in faster learning (Tse et al., 2007; Van Kesteren et al., 2012; Wang and Morris, 2010). During this fast track memory encoding, the mPFC becomes strongly activated, and the inhibition of the mPFC abolishes this fast learning (Tse et al., 2011; Wang et al., 2012). The presently proposed model is compatible with these memory assimilation processes by extending the mPFC's role in pattern recognition and integration to real-time operations during novel experiences. It, however, includes two unique features. First, the mPFC tracks commonality between incoming inputs by integrating them over the time scale of seconds to minutes in real time. And this process occurs regardless of whether the inputs are congruent to prior knowledge or not. Second, the activity of the mPFC during encoding not only forms a part of the memory trace locally but also helps

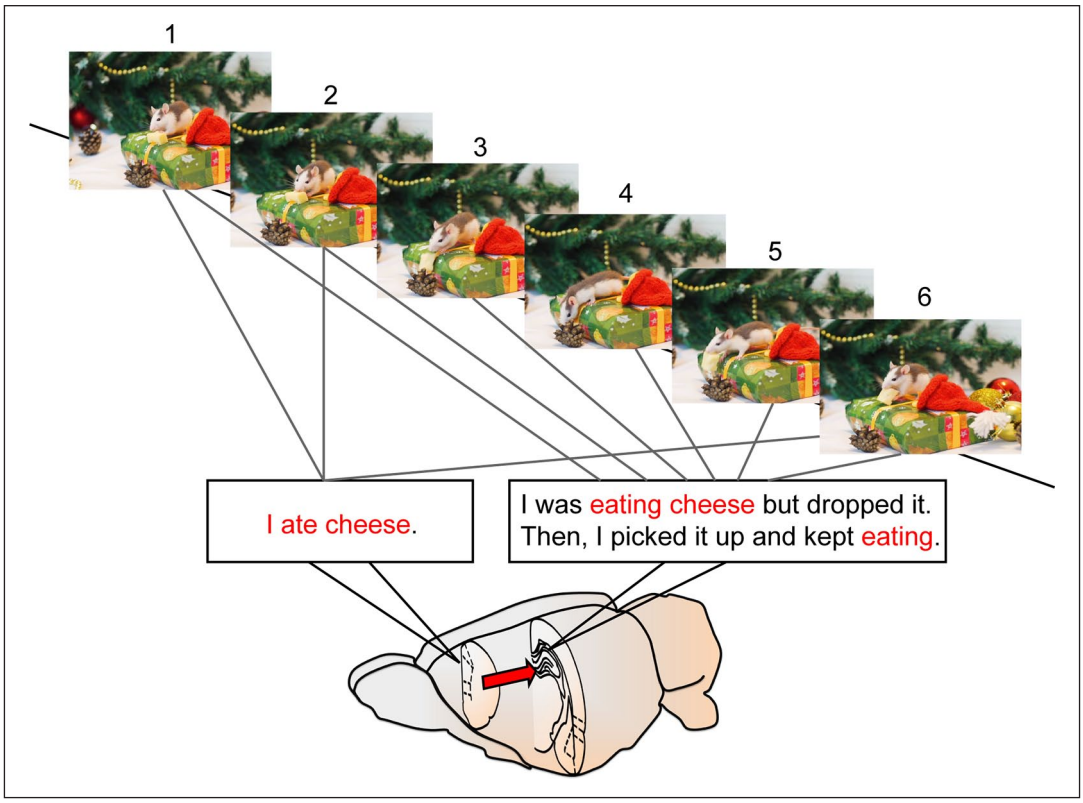

Figure 1. Complementary memory traces of novel experiences in the hippocampus and medial prefrontal cortex. A single experience consists of multiple repetitions of the same sensory information and behaviour in a variable spatial and temporal sequence. The hippocampus captures every single input and behaviour separately with the spatial and temporal context at the moment, leading to detailed, context-rich representations of the experience. In contrast, the medial prefrontal cortex (mPFC) sorts incoming inputs based on commonality and integrates them across time, leading to simple representations focusing on the essential content of the experience.

hippocampal neurons to encode behaviourally relevant content more strongly than minor details. Of note, the second point sharply contrasts with a view that schema-induced activation of the mPFC inhibits encoding processes in the hippocampus, preventing the formation of redundant memory traces (Van Kesteren et al., 2012). Human imaging studies thus far have provided mixed evidence for the proposed inhibition with some supportive findings (Van Kesteren et al., 2010, 2013) and other contradictory ones (Bein et al., 2014; Liu et al., 2017). Furthermore, a rat study showed that although the presence of schema shortens the time required for memories to become independent from the hippocampus, the hippocampal is still necessary for the formation of the new memory (Tse et al., 2007).

The proposed parallel formation of memory traces in the mPFC and hippocampus also provides a circuit basis for the hippocampal–neocortical dialogue during systems memory consolidation. Theories posit that neurons in the hippocampus form an index/pointer of neocortical neurons activated during each experience (Teyler and DiScenna, 1986; Teyler and Rudy, 2007). When the stored hippocampal memory index is reactivated, it then reactivates the corresponding neocortical areas, which strengthens the connections between the activated neocortical neurons, leading to the establishment of neocortically based memory traces. Critically, to ensure the progressive hippocampal-driven rewiring of neocortical networks, the activated neocortical neurons must be linked to the corresponding hippocampal neurons at the time of memory encoding. The first evidence for such 'tagging' processes was found in the orbitofrontal cortex during the social transmission food preference task (Lesburguères et al., 2011) and later in the prelimbic region in contextual fear conditioning (Kitamura et al., 2017). Notably, both studies showed that inhibition of these tagged neurons impairs memory retention at a remote, but not recent, time point, which is reminiscent of some earlier lesion studies reporting more profound impairments in the retention of old than new memories (e.g. Frankland et al., 2004; Maviel et al., 2004; Takehara et al., 2003). These findings lead to a view that memory-bearing neurons in the mPFC are not mature enough to maintain memory contents immediately after memory encoding (Tonegawa et al., 2018). Alternatively, the presently proposed model argues that these tagged neurons are already a part of the memory trace even at the recent time point, but their dysfunction may be compensated by the parallel trace in the hippocampus. As such, manipulations to these tagged neurons impair memory retention only after the hippocampal traces become inaccessible.

Concluding remarks

The model proposed in the previous section expands the role of the mPFC in pattern recognition and integration to real-time processes during experiences to enable the selective, and perhaps more intelligent encoding of new memories. During a novel experience, the mPFC may continuously monitor the proactive link

between incoming inputs and inputs perceived a moment ago, which allows for integrating the related inputs over time. This online process enables the mPFC network to capture, in real time, the essential content of an experience, which may also serve as a relevancy signal that enhances the contrast between relevant and incidental contents in hippocampal memory traces. The close mPFC–hippocampal interaction during encoding also ensures that newly formed traces in the mPFC and hippocampus are linked with one another, thereby facilitating the subsequent, progressive rewiring of memory networks during systems consolidation.

To further solidify evidence for this hypothesis, several key remaining questions need to be addressed in future studies. First, it is critical to investigate the real-time dynamics of prefrontal neural activity during novel experiences, by testing moment-to-moment changes in the selectivity of mPFC neurons for ongoing events as they unfold. Empirical evidence for this point is quite thin because most past studies recorded neural activity from the mPFC while well-trained animals retrieve memories.

Second, further investigations are necessary to decipher the detailed nature of the mPFC's modulation over encoding processes in the hippocampus. Although the studies in section 'mPFC activity modulates neural activity in the hippocampus during memory encoding' provide some evidence, it remains unknown exactly how the mPFC influences the neural activity of hippocampal neurons as animals learn new information. The presently proposed model predicts that the inhibition of the mPFC activity would only affect the development of properties selective for the central content of an experience, such as clustering of place fields near reward locations (Dupret et al., 2010; Mamad et al., 2017) and rate remapping depending on non-spatial information relevant for the task performance (Allen et al., 2012).

Finally, circuit mechanisms supporting the proposed mPFC–hippocampal interaction during encoding remain unknown. Several recent studies showed that during retrieval, the mPFC modulates the activity of hippocampal neurons through the nucleus reuniens (Hallock et al., 2016; Ito et al., 2015) and the PER cortex (Jayachandran et al., 2019). Detailed examination of correlations between neuronal firings and oscillatory activity will uncover the timing and directionality of inter-region interactions underlying the encoding of new information. In parallel, the necessity of these pathways also needs to be investigated with pathway-specific chemo- and optogenetic approaches.

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