PREFRONTAL AND MEDIAL TEMPORAL LOBE INTERACTIONS IN LONG-TERM MEMORY

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Cognitive neuroscience has made considerable progress in understanding the involvement of the medial temporal and frontal lobes in long-term memory. Whereas the medial temporal lobe has traditionally been associated with the encoding, storage and retrieval of long-term memories, the prefrontal cortex has been linked with cognitive control processes such as selection, engagement, monitoring and inhibition. However, there has been little attempt to understand how these regions might interact during encoding and retrieval, and little consideration of the anatomical connections between them. Recent advances in functional neuroimaging, neurophysiology, crossed-lesion neuropsychology and computational modelling highlight the importance of understanding how the medial temporal and frontal lobes interact to allow successful remembering, and provide an opportunity to explore these interactions.

FORNIX
A major input/output of the hippocampus, connecting it to prefrontal cortex and a range of subcortical structures.

The ability of humans and other animals to remember past experiences, which forms an integral part of our existence, has long fascinated philosophers and scientists. With advances in our knowledge of brain function, the study of the contributions made by different brain regions to memory has occupied a central position in cognitive neuroscience. Studies involving patients with amnesia and animals with experimental lesions have consistently identified the medial temporal lobe and the prefrontal cortex as being crucial for memory[1–7].

The medial temporal lobe comprises the hippocampus, FORNIX and amygdala, and the surrounding entorhinal, perirhinal and parahippocampal cortices (FIG. 1). Anatomically, much of the medial temporal lobe is shared between humans, non-human primates and rats, with the possible exceptions of the primate parahippocampal cortex, which is generally termed postrhinal cortex in the rat, and of the perirhinal cortex, the boundaries of which are less clear in man than in other animals[8]. The prefrontal cortex is divided into a medial and a lateral surface, with the latter consisting of ventrolateral, dorsolateral and anterior prefrontal regions, each of which might be further divisible[9].

The rodent prefrontal cortex is relatively smaller and less developed than in primates[10]. Although in different primate species the prefrontal cortex takes up a similar percentage of overall brain volume, regions such as the anterior prefrontal cortex are proportionally larger in humans, and their underlying connectivity is greater[11].

Damage to the medial temporal lobe or the prefrontal cortex commonly impairs memory in humans or animals. Perhaps because these regions are anatomically remote from one another, their roles in memory have largely been considered independently, with little investigation of how they might interact to support remembering. Although other brain regions, such as the thalamus, mamillary bodies and retrosplenial cortex, are also important for long-term memory, we focus on the roles of the medial temporal lobe and prefrontal cortex. Emerging evidence from functional neuroimaging, neurophysiology and computational modelling highlights the importance of interactions between these regions for memory function, indicating that we must understand these interactions if we are to develop a full account of how memory processes are represented in the brain.

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a Lateral view

DLPFC
APFC
VLPFC

b Medial view

DLPFC
MPFC
Fornix
Hippocampus

c Connections

Neocortical association areas

Parahippocampal cortex — Perirhinal cortex

Entorhinal cortex

Hippocampus
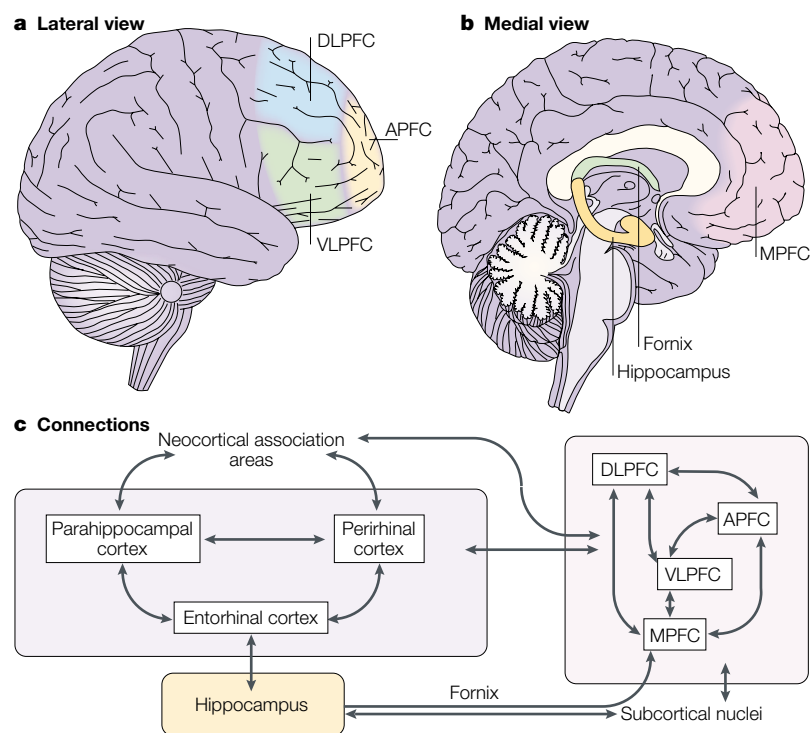
DLPFC
APFC
VLPFC
MPFC

Fornix

Subcortical nuclei

Figure 1 | **Anatomy of the medial temporal lobe and prefrontal cortex. a,b** | The prefrontal cortex (PFC) can be divided into anterior (APFC, Brodmann area (BA) 10), dorsolateral (DLPFC, BA 46 and 9), ventrolateral (VLPFC, BA 44, 45 and 47) and medial (MPFC, BA 25 and 32) regions. BAs 11, 12 and 14 are commonly referred to as orbitofrontal cortex. The medial temporal lobe comprises the hippocampus and amygdala, as well as the entorhinal, perirhinal and parahippocampal neocortical regions. The hippocampus includes fields CA1–CA3 of the hippocampus proper, the dentate gyrus and the subicular complex. **c** | Connections. There are large cortico-cortical direct reciprocal connections between the PFC and the medial temporal lobe, passing through the uncinate fascicle, anterior temporal stem and anterior corpus callosum. The orbitofrontal and dorsolateral cortices have strong reciprocal connections with the perirhinal and entorhinal cortices[125]. There are more connections from the PFC to the perirhinal cortex than vice versa[126]. Unidirectional projections exist from the CA1 field to the caudal region of MPFC[127,128]. The subicular complex and neocortical medial temporal regions have reciprocal connections with caudal MPFC[129,130]. In addition, the medial temporal lobe receives information from a range of unimodal and polymodal sensory association areas. This information predominantly enters through the perirhinal and parahippocampal cortices, which project back to these regions[131]. The PFC has reciprocal connections with sensory association cortices including temporal and parietal regions[130] and many subcortical structures[132]. Anatomical images adapted, with permission, from REF. 133 © (1996) Appleton & Lange.

FAMILIARITY-BASED MEMORY
Recognition of previously presented items based on a feeling of familiarity in the absence of recollection of the earlier study episode.

DELAYED NON-MATCHING-TO-SAMPLE
A task in which an object/item is presented and following a delay, presented again along with a new item, and the participant is required to choose the new item.
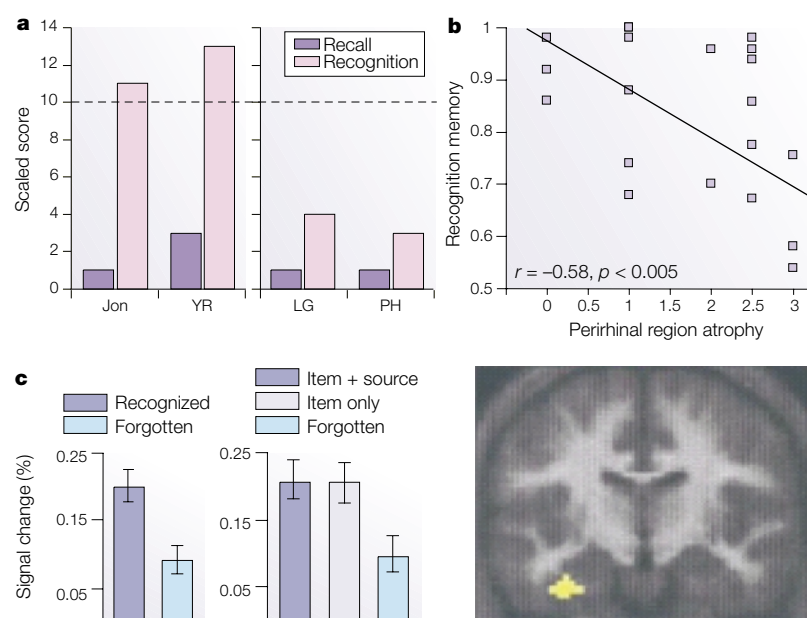
We begin by documenting what is known about the memory processes subserved by the medial temporal lobe and prefrontal cortex. We then characterize some of the functional interactions between these regions, and finally propose a unifying framework by which we can better understand how they might work together to support remembering.

Medial temporal lobe

The crucial role of regions of the medial temporal lobe for memory processing became apparent with the first reports of patient HM[1,12], who became profoundly amnesic after bilateral surgical resection of the medial temporal lobes and partial removal of hippocampal structures to relieve epilepsy. Such observations prompted researchers to use animal models to investigate memory impairments associated with lesions to specific regions of the medial temporal lobe. Some of these studies provided evidence that distinct regions in the medial temporal lobe support functionally dissociable memory systems[7], although this conclusion is disputed[13]. According to the functional dissociation view, a system involving the hippocampus (as well as the thalamus, mamillary bodies and retrosplenial cortex) supports the recollection of stored memories with their associated spatiotemporal context. Consistent with this, animals with hippocampal or fornix lesions are impaired on tests of spatial memory[14,15]. Electrophysiological studies have identified hippocampal neurons that respond when animals are in particular locations in an environment[16,17] and show lasting, experience-dependent plasticity[18], indicating that the hippocampus might provide a spatial context that allows different aspects of an episode to be linked over the long term[17].

An anatomically separate system that includes the perirhinal cortex is thought to underlie FAMILIARITY-BASED RECOGNITION of previous occurrence, as measured in animals by tests such as DELAYED NON-MATCHING-TO-SAMPLE[19–21]. Whether the hippocampus is also involved in familiarity is controversial: some studies have found no effects of hippocampal or fornix lesions on recognition[15,22,23] whereas other researchers have reported deficits[13,24]. The importance of the perirhinal cortex for familiarity-based memory is less controversial. Electrophysiological studies have found perirhinal neurons that show diminished responses to repeated stimuli[25,26], whereas few such neurons have been found in the hippocampus[27,28]. The perirhinal cortex might have a role in perceptual as well as mnemonic processing, with evidence that complex feature conjunctions might be represented in this region[29,30].

Clinical studies can also address whether recollection and familiarity are supported by anatomically separate neural systems. Although most amnesic patients are impaired on both forms of memory, some patients that have selective damage to the hippocampus or connecting structures such as the fornix show impaired recollection with relatively preserved familiarity-based memory[31–34]. Again, other researchers have reported familiarity deficits after selective hippocampal damage[35] (FIG. 2a). Selective lesions of the perirhinal cortex in humans are rare, but two patients with extensive medial temporal lobe damage that included the perirhinal cortex showed worse recognition memory than patients with selective hippocampal damage[36,37]. Furthermore, there is evidence from patients with SEMANTIC DEMENTIA that the extent of impairment of recognition memory correlates significantly more highly with the degree of atrophy of the perirhinal region than of the hippocampus[38,39] (FIG. 2b).

Another controversy centres on the involvement of the hippocampus in the consolidation and retrieval of memories from the past. One hypothesis is that the hippocampus has a time-limited role in remote memory, with the temporal neocortex becoming more important after a certain time[2,3,40], whereas others propose that the hippocampus is involved in retrieving memories from the entire lifespan[41,42]. Little is known about the effect on retrograde memory of lesions to connecting structures

Figure 2 | **Medial temporal lobe function. a** | Controversy concerning the effects of selective hippocampal damage on recollection and familiarity. The panel shows the performance of four patients with damage restricted to the hippocampal region on the Doors and People Test[134] of recall (based on recollection) and recognition (considered to be based on a combination of recollection and familiarity), expressed as combined scaled scores. A score of 10 (dashed line) represents the population mean for each patient's age group. Some patients, such as Jon[32] and YR[33], have impaired recall but preserved recognition. Other patients, such as LG and PH[35], are impaired at both recall and recognition. The reasons for this discrepancy are unclear. **b** | Comparison of recognition memory performance and atrophy affecting the region of the perirhinal cortex (assessed by measuring depth of collateral sulcus from magnetic resonance imaging (MRI) scans) in patients with semantic dementia. The panel shows a significant correlation between increasing atrophy and impaired recognition memory. Units are rated extent of atrophy (where zero is normal) and proportion correct for recognition memory, combining data from two experiments[38,39]. **c** | Results of a functional MRI experiment on encoding processes. The activation in the left perirhinal cortex during encoding predicts whether words are later recognized as familiar, not whether the source of items is recollected[52]. Panel c modified, with permission, from REF. 52 © (2003) National Academy of Sciences, USA.

such as the fornix, but the existing evidence is consistent with the idea that the hippocampus is more important in the acquisition of new information than in the retrieval of past memories[43].

Neuropsychological evidence for the importance of medial temporal lobe structures in memory has led to the use of functional neuroimaging to investigate this area. Several early studies found no memory-related activation in the medial temporal lobe, although whether this was due to task characteristics or limitations in the technology is unclear. More recently, activation in this region has been documented during both the encoding and retrieval of information[44]. Echoing the results of animal studies, hippocampal regions (primarily on the right) are activated during spatial memory and navigation tasks[45,46]. Similarly, hippocampal activation has been associated with the recollection of contextual information[47,48], and several studies have reported greater activation in the hippocampus for recollection than familiarity decisions[49–51]. There is less evidence on the role of the perirhinal cortex in familiarity-based memory, but in one study, activation during encoding in a region identified as perirhinal cortex predicted later item recognition

but not source recollection, whereas activation in hippocampal regions predicted subsequent recollection[52] (FIG. 2c). Along similar lines, a meta-analysis identified a common region of anterior medial temporal lobe, close to the perirhinal cortex, in which activation at retrieval was modulated by the relative familiarity of test items[53].

Computational network models of the medial temporal lobe have attempted to examine many of the issues surrounding the functional roles of the medial temporal lobes, predominantly focusing on the hippocampal formation and its role in memory. Marr[2] was the first to ascribe mathematical operations to regions in the medial temporal lobe, suggesting that the hippocampal formation classifies and indexes incoming information, rapidly storing it for later transfer to neocortical regions where it is reorganized during sleep. In recent models[54–56], different medial temporal lobe structures are represented by layers of neurons, with the strength of the connections between neurons corresponding to the association between components of sensory information stored in other regions of cortex. A common feature of such models is that units of sensory information are represented as patterns of neuronal activity primarily in entorhinal cortex, and during encoding this activity spreads through subregions of the hippocampus into region CA3. In CA3, strengthening of a limited number of RECURRENT COLLATERAL connections allows neurons to associate and form sparser representations of the entorhinal activation patterns which, through a process of PATTERN SEPARATION, are kept sufficiently distinctive to be stored discretely from other episodes. During retrieval, the presentation of a subset of the original information activates the hippocampus and causes the network to reinstate the original pattern of activity (by PATTERN COMPLETION), allowing recall of the stored information. Such models vary primarily in how the learning and activation rules operate.

Recently, researchers have attempted to address in their models some of the controversies that surround medial temporal lobe function. The processes involved in recollection and familiarity have been examined by modelling the familiarity component as a slow-learning, distributed neocortical network and the recollection component as a rapid-learning, associative hippocampal network[57]. Memory consolidation has also been explored, with some models positing a gradual transition from information stored in connections between hippocampus and neocortical regions to representations stored solely between connections in neocortical regions[56,58], and other models indicating that new connections between hippocampus and neocortical areas are created every time an EPISODIC MEMORY trace is retrieved[59]. On the basis of evidence that place cells in the hippocampus represent spatial layout, some models have attempted to understand how medial temporal lobe regions might support memory for the layout of the environment[60,61], and it has been indicated that connections between represented locations can be used to retrieve and reconstruct a previously experienced scene from a particular viewpoint and to associate this with non-spatial aspects of the experienced event[62].
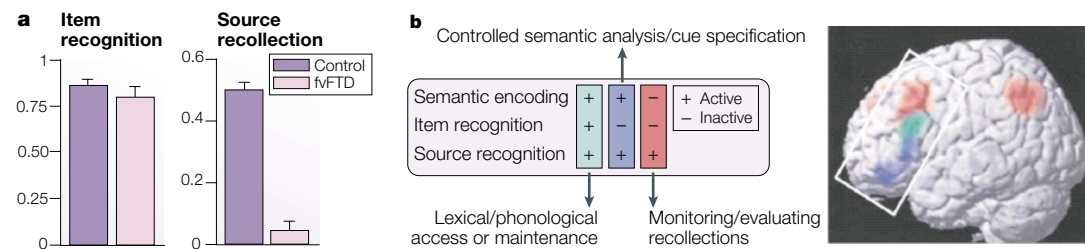
Figure 3 | **Prefrontal cortex function. a** | The performance of patients with frontal variant of frontotemporal dementia (fvFTD) on item recognition and source recollection[65]. Although patients show no impairment relative to controls at recognizing previous occurrence of stimuli, their source recollection is at chance levels. **b** | Different regions of prefrontal cortex subserve different cognitive control operations in episodic memory[84]. The left panel illustrates the logic of data interpretation, with a plus sign indicating significant activation and a minus sign indicating no significant activation. The right panel illustrates regions that show particular patterns of activation. The posterior ventrolateral prefrontal cortex (green) is activated during semantic encoding, item recognition and source recollection, and so is associated with lexical/phonological processing according to interpretation logic; the anterior ventrolateral prefrontal cortex (blue) is activated during semantic encoding and source recollection, and so is associated with semantic processing and cue specification; the dorsolateral prefrontal cortex (red) is activated during source recollection only, and so is associated with monitoring and evaluation. Panel b modified, with permission, from REF. 84 © (2002) Elsevier Science.

Prefrontal cortex

Although the importance of medial temporal lobe structures in memory has been recognized for at least half a century, the importance of frontal lobe regions has been appreciated only more recently. Deficits in memory after frontal lobe damage in humans might go unnoticed in the context of the more obvious symptoms such as disinhibition, impulsiveness and disorganization, but it is clear that frontal lobe damage can markedly impair certain aspects of memory. For example, patients with damage to lateral prefrontal cortex often show deficits in remembering contextual details such as the source or recency of remembered information[63–65] (FIG. 3a), as do those patients with predominantly temporal lobe damage who also perform poorly on tests of frontal lobe function[63–65]. Patients with frontal lobe dysfunction are particularly impaired when there is significant interference between stimuli to be recalled[66]. Another memory disorder associated with frontal lobe damage, particularly in the ventromedial prefrontal cortex, is confabulation — the production, often during autobiographical recollection, of statements or beliefs that involve unintentional, and sometimes bizarre, distortions of memory[67,68]. Confabulation is considered to be the result of impairment to memory control processes that are responsible for the specification of retrieval task parameters and the verification and monitoring of recollected information[68], processes that have been associated with ventrolateral and dorsolateral regions of prefrontal cortex, respectively (see later discussion).

In contrast to the deficits in recall that are associated with frontal lobe dysfunction, other aspects of memory are typically less affected. For example, patients with prefrontal cortex damage who perform poorly at discriminating the source of information are often relatively unimpaired at recognizing the information as having been seen before[64,65] (FIG. 3a). Such evidence has led to the view that the prefrontal cortex is crucial for recollection but less important for familiarity-based memory. However, few studies have matched recollection and familiarity tasks for difficulty, so frontal lobe patients might perform more poorly at source recollection simply because it is more difficult and requires greater cognitive resources than item recognition. Patients with lesions in orbitofrontal cortex do show deficits in reward-related familiarity-based learning[69], and functional imaging studies have identified some prefrontal regions that show greater activation for familiarity than recollection decisions[49,70].

Clinical lesions vary considerably in both location and extent, but lesion and neuronal recording methods in non-human primates and functional neuroimaging in humans can be used to localize processes more precisely. The predominant view is that distinct regions of prefrontal cortex are specialized for different cognitive functions[9,71], although it has been suggested that prefrontal regions might be commonly recruited together, adapting their function depending on the nature of the task being undertaken[72,73]. According to this latter view, the apparent regional specialization reported by primate and human studies could reflect relative rather than absolute differences[74].

Several types of regional distinction in memory processing in the prefrontal cortex have been reported. One prominent position has been that the left and right frontal cortices might be lateralized for the encoding and retrieval of memories, respectively[75,76]. More recent evidence, however, indicates that lateralization within the prefrontal cortex might depend as much on the type of material being remembered as on the memory process being undertaken[77–79]. Another key distinction has been between the memory-related processes that are supported by medial and lateral aspects of prefrontal cortex. The medial surface, in particular medial orbitofrontal cortex, has been linked with the processing of stimulus–response mappings on the basis of reward[80,81]. By contrast, the evidence indicates that lateral prefrontal cortex subserves goal-directed cognitive control functions that support the encoding of discrete memory traces, and the subsequent strategic search, retrieval and evaluation of stored representations[82].

PATTERN COMPLETION
A process by which a stored neural representation is reactivated by a cue that consists of a subset of the stored pattern.

EPISODIC MEMORY
Memory for events and episodes, which are uniquely characterized by a specific time and place.

Distinctions have been made between ventral and dorsal regions of lateral prefrontal cortex. One hypothesis is that ventrolateral and dorsolateral areas are involved in processing information about object form and object location, respectively[71], whereas an alternative view suggests that the distinction between these regions lies in the memory process being undertaken rather than the type of stimulus material[9] (FIG. 3b). The ventrolateral region is thought to be involved in the elaborative encoding of information into episodic memory[70,83], as well as in the specification of retrieval cues[84] and the maintenance of retrieved information[85,86]. This region can be further subdivided into anterior and posterior portions, which are suggested to subserve semantic and lexical/phonological control processes, respectively[84,87]. Dorsolateral prefrontal cortex is considered to be involved in the organization of material before encoding[88], as well as the verification, monitoring and evaluation of representations that have been retrieved from long-term memory and are maintained by ventrolateral frontal cortex[84,89,90]. These post-retrieval processes might additionally be supported by an area of anterior prefrontal cortex near the frontal pole, although this region might perform a higher-level function in mnemonic control such as the processing of internally-generated information[91–93].

Most computational models of prefrontal function have focused on the more general role of this region in executive functions and WORKING MEMORY[94,95]. However, one recent model has attempted to understand the role of the prefrontal cortex in strategic encoding and retrieval of long-term memories[96]. In this model, the prefrontal cortex develops mnemonic codes through reinforcement learning during repeated encoding and retrieval sessions, which are later used to aid retrieval of information from medial temporal lobe regions. This model indicates a defined manner in which the prefrontal cortex might interact with the medial temporal lobe during long-term memory processes. Evidence is accruing that such interactions might be important to an understanding of the manner in which memory processes are represented in the brain.

Interactions

With some notable exceptions, there has been little attempt to understand how the medial temporal lobe and the prefrontal cortex might work together, or to construct cognitive or neural models of their interactions. Emerging evidence indicates that the prefrontal cortex and the medial temporal lobe might form part of a distributed functional network of regions that are involved in memory, in which the relative contribution of these regions is modulated by factors such as the memory process being undertaken, the type of material being remembered, and the accessibility of the stored information in memory. Although appreciation of the separate contributions of frontal and temporal regions is useful, an understanding of the interaction between these regions might lie at the heart of a full account of memory processing in the brain.

It is important to consider what is meant by 'interaction'. One example of an interaction is the concurrent engagement of two or more brain regions in the operation of a particular task that might involve the unidirectional or reciprocal transmission of information between brain regions. Interactions can also be thought of as the action of one brain region on another to bias or change the representation being processed in the second region. This type of interaction is commonly described as either top-down or bottom-up control, depending on whether the influence derives from earlier or later stages in the processing hierarchy. Such influences might be excitatory or inhibitory in nature, and can be beneficial or essential for performance. It is likely that these types of interaction all occur in the brain in certain instances depending on the task being undertaken, but there has been little consideration of how such interactions might be modulated.

An early appreciation of the importance of frontal–temporal interactions in memory came from Warrington and Weiskrantz[97], who suggested that the profile of memory impairments that is typical of amnesia could be explained by a disconnection between frontal and temporal memory systems. As described earlier, most patients with amnesia experience difficulties with both recognition and recall of information[1,7], whereas patients with prefrontal cortex lesions might have normal recognition but impaired recall or contextual recollection[64,65]. One patient, whose lesion included the uncinate fascicle, an important route of connection between frontal and temporal areas, was particularly impaired at recalling autobiographical events from his past, but performed normally on tests of new learning[98]. This indicates that in complex, effortful retrieval situations such as recall, which typically make greater demands on processes of organization, strategic search, monitoring and verification, the interactions between prefrontal and medial temporal regions might be more important than in relatively automatic examples of remembering, such as many instances of familiarity-based recognition.

It is difficult to learn much about the dynamic nature of prefrontal–medial temporal interactions from clinical studies because one cannot systematically examine the effects of disconnecting in turn each of the relevant brain regions. Transcranial magnetic stimulation has been used to study interactions between different visual processing areas in humans[99], but the technique cannot currently be applied to deep brain regions such as the medial temporal lobe. In animals, anatomical disconnection studies have been undertaken, including the disruption of frontal–temporal interactions by making crossed unilateral lesions of the frontal lobe in one hemisphere and the temporal lobe in the other hemisphere[80,100] (FIG. 4a). The results show that interruption of communication between these regions affects many forms of conditional learning, although recent evidence indicates that different memory impairments involving, for example, conditional strategy implementation and associative learning, can be observed when different routes of interaction between temporal and prefrontal areas are disconnected, such as those mediated by the basal forebrain or by subcortical structures such as the striatum[101,102].

WORKING MEMORY
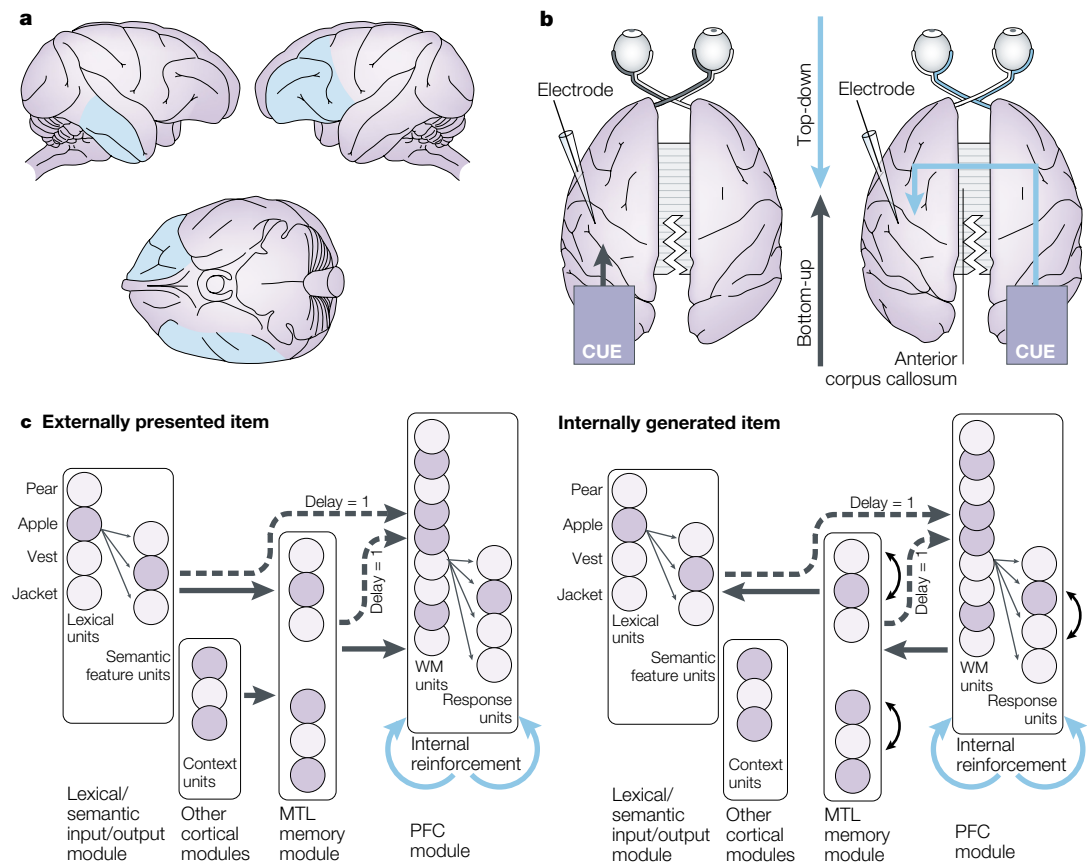Short-lasting memory associated with active maintenance and rehearsal of information.

Figure 4 | **Techniques for systematically examining prefrontal–temporal interactions. a** | Crossed-lesion neuropsychology[100]. Studies involve, for example, unilateral temporal lobe ablation in one hemisphere (shown on left) and unilateral frontal lobe ablation in another hemisphere (shown on right). **b** | Recording from single-unit electrodes after posterior disconnection of the cerebral hemispheres by transection of the posterior corpus callosum[119,121]. Left: when a cue is presented to the hemisphere ipsilateral to the recording site ('electrode'), bottom-up sensory signals are detected (black arrow). Right: when a cue is presented to the hemisphere contralateral to the recording site, sensory signals do not reach visual areas in the opposite hemisphere, but top-down signals (blue arrow) from the prefrontal cortex (PFC) activate temporal neurons, permitting successful retrieval[121]. **c** | Computational modelling of prefrontal and medial temporal interactions in memory[96]. Large blue arrows represent a modulatory reinforcement learning signal that modulates the internal and external (input and output) connections of the prefrontal module. Arrows labelled with 'delay = 1' are the pathways along which information from the previous time step are sent. Left panel: learning phase, where bottom-up activation occurs from the presentation of an external stimulus. Right panel: retrieval phase, where top-down activation from the PFC is internally generated. See also BOX 1 for a description of the technique of effective connectivity. MTL, medial temporal lobe; WM, working memory. Panel a modified, with permission, from REF. 101 © (2002) Society for Neuroscience; panel b modified, with permission, from *Nature* REF. 121 © (1999) Macmillan Magazines Ltd; panel c modified, with permission, from REF. 96 © (2003) The MIT Press.

Bilateral disconnection of another route of communication between these areas, the uncinate fascicle, has little effect on conditional learning in monkeys[103] although, as noted above, it might be important for autobiographical retrieval in humans[98]. Another connection between prefrontal and medial temporal regions, through the medial dorsal thalamus, might be particularly important for familiarity-based memory. Disruption of this link impairs recognition memory in monkeys and rats in a similar manner to lesions of perirhinal cortex[104,105]. Combined lesion studies in animals have also identified further factors that might modulate the interaction between prefrontal and hippocampal regions, such as the delay between study and test. For example, although both regions are involved in spatial memory, hippocampal involvement might be essential only when a sufficient delay is introduced[106].

Recent advances in functional neuroimaging have also provided insights into the interactions between frontal and temporal lobe regions in memory. Many studies have demonstrated co-activation of prefrontal and medial temporal regions during the performance of memory tasks. As in the lesion studies described earlier, the nature of these activations has been found to be modulated by task demands, with a consistent distinction between the networks that are engaged during the encoding of information and those that are engaged during retrieval. A number of studies have identified regions of prefrontal and medial temporal cortex in which the magnitude of activation during encoding predicts whether events will be remembered[70,83]. Activation of this network tends to be lateralized according to the type of material involved, with predominantly left frontal and medial temporal regions implicated for verbal stimuli and an analogous network
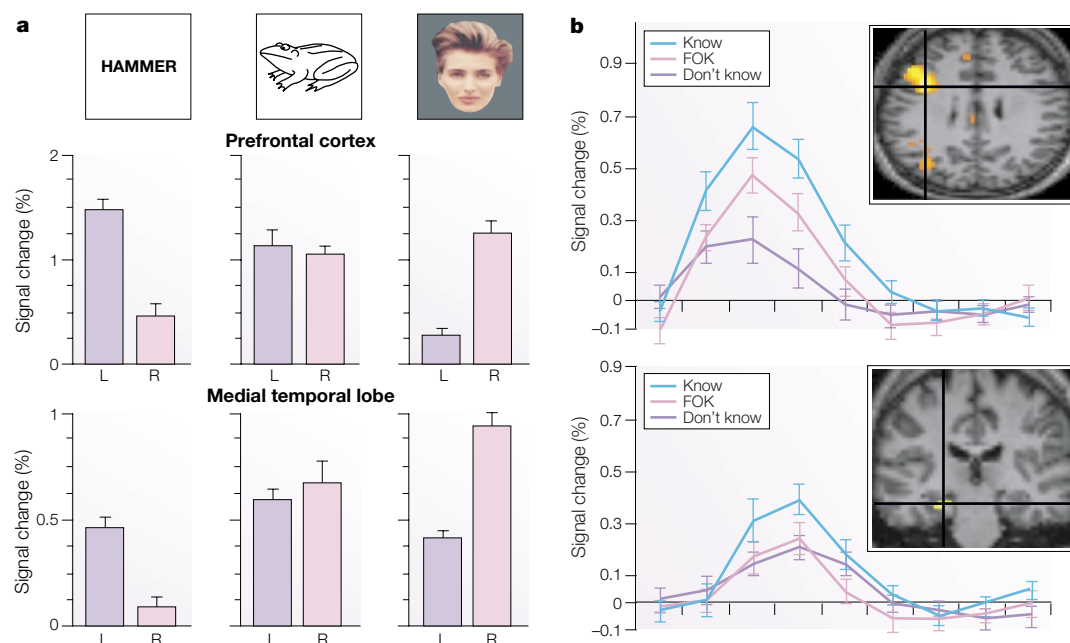
Figure 5 | **Interactions between prefrontal cortex and medial temporal lobe. a** | The prefrontal cortex–medial temporal lobe interaction during encoding is modulated by the type of material being remembered[77]. The left-hemisphere network (L) is more activated for words, there is bilateral involvement for nameable objects, and activation is predominantly in the right hemisphere (R) for unfamiliar faces. Similar material-specific lateralization is also seen during retrieval from memory[79,109]. **b** | The interaction between the prefrontal cortex and the medial temporal lobe might be more complex during retrieval[111]. The prefrontal cortex shows a graded response, reflecting instances of full retrieval of details about studied items (know), intermediate retrieval or 'feeling of knowing' (FOK), or limited retrieval of details (don't know). The medial temporal lobe differentiates between successful (know) and unsuccessful retrieval (FOK and don't know) only. Panel a modified, with permission, from REF. 77 © (1998) Elsevier Science; panel b modified, with permission, from REF. 111 © (2003) Elsevier Science.
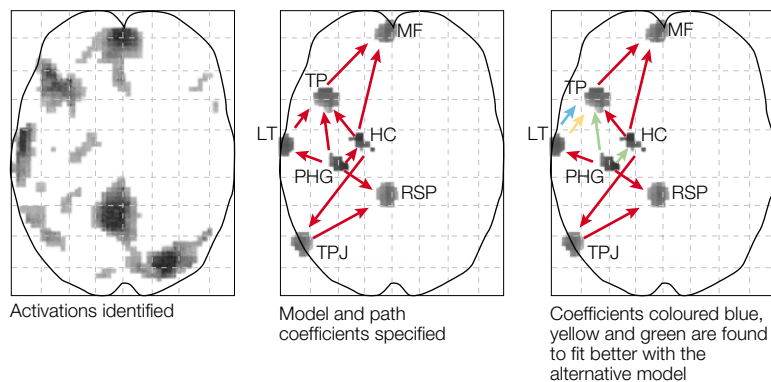
in the right hemisphere being engaged for non-verbal stimuli[77,83] (FIG. 5a). The interaction between prefrontal and medial temporal cortices is also modulated by the type of elaborative processing undertaken during encoding, with tasks that emphasize the processing of lexical/semantic and phonological attributes resulting in the recruitment of different inferior prefrontal regions to the network[107,108].

At retrieval, lateralization of the prefrontal–temporal network is again modulated by the type of material being remembered[78,79,109]. Beyond this distinction, there is evidence that the interaction between frontal and medial temporal lobe regions might vary on the basis of factors such as the orientation of attentional processes towards particular aspects of mnemonic information[51,110], the amount of cognitive effort expended during a retrieval attempt[47], and the level of success achieved in retrieving the sought-after information[49–51,111], although the evidence is inconsistent. Some studies have identified a network containing prefrontal and medial temporal regions (as well as posterior cingulate and parietal cortex) that was more strongly activated for successful than unsuccessful episodic retrieval[49,50]. Other researchers have suggested a more complicated pattern of interaction, with the prefrontal cortex exhibiting activation that reflected either the orientation of attention at retrieval[51] or the amount of information that was retrieved[111]. In the latter study, for example (FIG. 5b), a graded level of activation in prefrontal cortex reflected whether participants recalled many details about studied items, an intermediate level of

detail that was termed a 'feeling of knowing' that the items had been presented, or very few details. As with other studies, medial temporal lobe responses differentiated between successful and unsuccessful retrieval alone[111].

One difficulty with standard methods of analysing data from functional neuroimaging or single-neuron recording is that co-activation of different brain regions tells us nothing about the influence of one of the regions over the other. A promising technique for addressing this issue is the application of structural equation modelling to functional imaging data to examine the EFFECTIVE CONNECTIVITY between brain regions[112,113] (BOX 1). Such data can provide information about how the relationship between two or more regions changes under different conditions. Using this technique, interactions have been observed between prefrontal and medial temporal regions that are consistent across several domains of retrieved information, such as object identity and location[114]. Similarly, comparable interactions have been observed between prefrontal and medial temporal lobe regions during retrieval of autobiographical memories, public event information and general knowledge, although increased connectivity was found between different regions within the medial temporal lobe for autobiographical recollection compared with other memory types[115] (see BOX 1). Of importance to the debate over retrieval orientation and success is the evidence from effective connectivity studies that prefrontal–medial temporal interactions can reflect either orientation or success,

EFFECTIVE CONNECTIVITY
Multivariate analysis of activity in different regions to model the influence that regions exert over each other.

Box 1 | **Modelling effective connectivity in functional neuroimaging**

Activations identified

Model and path coefficients specified

Coefficients coloured blue, yellow and green are found to fit better with the alternative model

Structural equation modelling, also known as path analysis, is a correlational statistical method that can be used to examine the influence that brain regions in a network have on each other under a set of specific experimental conditions. These influences are referred to as effective connectivity. Different approaches are used to construct and analyse the models; one method is described below in a simplified form[113,115].

• The brain regions activated by different experimental conditions are identified.

• An anatomical model of unidirectional connections between selected regions is specified on the basis of existing knowledge.

• Path coefficients (numerical weights) are assigned to each connection. These represent the change in activation level in the target region that is associated with one standard deviation of change in the source region, with activity in all other regions kept constant.

• Two candidate models are created: one is a null model in which all path coefficients are equal for each task condition, and one is an alternative model in which the regions of interest are allowed to vary depending on the task conditions.

• The goodness-of-fit of the null model and the alternative model are compared.

Where path coefficients in the alternative model provide a better fit, the relationship between the regions can be identified as being different for the two experimental conditions. Shown are data from a study of autobiographical retrieval[115], showing regions (left) that were activated by a memory versus control condition, which were used to construct an effective connectivity model (right). The illustration shows consistent interactions (red arrows) between medial frontal (MF) and temporal lobe regions (PHG, parahippocampal gyrus; HC, hippocampus; LT, lateral temporal lobe; TP, temporal pole) as well as retrosplenial cortex (RSP) and temporoparietal junction (TPJ) for retrieval of autobiographical and other forms of memory. Within the medial temporal lobe, there was increased connectivity for autobiographical retrieval (green arrows), and for retrieval of public events (yellow arrow) and general knowledge (blue arrow). Modified, with permission, from REF. 115 © (2001) Oxford University Press.

Whereas this technique allows us to go beyond observation of activation, several important issues should be considered when interpreting data from effective connectivity studies. Several potential models might account for the data, with the one reported perhaps representing only one of a potential set. In addition, much anatomical brain connectivity is reciprocal, particularly in the neocortex, whereas unidirectional connections must be assumed for models to be robust. Alternative methods of determining the alternative model and the goodness-of-fit mean that researchers should take care when comparing data from different studies.

depending on the regions of cortex that are functionally linked[112]. The analysis of effective connectivity in functional imaging data is still in its infancy and current models are simple, including only unidirectional connections and a lack of anatomical specificity, but ongoing development[116] might realize the technique's potential to provide useful information on how brain regions interact.

Another technique that has proved informative in understanding interactions between frontal and temporal

brain regions is recording from extracellular electrodes in behaving monkeys. The prefrontal cortex has been shown to be particularly important for memory tasks that involve the associating or integration of events over time[117]. For example, during a delayed matching-to-sample task, neurons in the temporal cortex increase their response to repetition of the sample stimulus but not to distracting stimuli, whereas prefrontal neurons sustain activation across the intervening items[118], indicating that there might be a top-down influence in this region. Neuronal recordings from monkeys with posterior disconnection of the two cerebral hemispheres by transection of the posterior corpus callosum have shown, during a visual paired-associate learning task, that when a visual cue is presented to one hemisphere, single neurons in the disconnected contralateral inferior temporal lobe can be activated by a top-down signal from the prefrontal cortex, permitting successful retrieval[119] (FIG. 4b). This prefrontal neuronal signal acts in a prospective manner in associative learning, initially reflecting the sample cue and then, before presentation of a test cue, reflecting the expected target stimulus that was previously associated with the sample[120]. Moreover, when this prefrontal signal is removed by transecting the remaining anterior corpus callosum, performance on the associative memory task is severely impaired[121]. These results indicate that successful memory in these tasks is guided by top-down influences from prefrontal cortex on temporal cortex to process information that is relevant to particular behavioural demands.

Insights can also be gained through the implementation of sophisticated computational models that seek to go beyond modelling medial temporal or prefrontal cortex function in isolation. One model[96] (FIG. 4c) has been proposed in which information provided by medial temporal and other cortical regions is rapidly organized according to task requirements and combined into mnemonic codes in the prefrontal cortex through a process of reinforcement learning. These mnemonic codes can be used at retrieval by the prefrontal cortex in a top-down manner to search for and access stored information in the medial temporal lobe system, evaluating the products of retrieval on the basis of heuristic properties that vary depending on the task. The development of mnemonic codes in this model during learning is modulated continuously through monitoring of present performance relative to an intended goal state, which means that the model essentially develops retrieval strategies dynamically[96].

Although the interaction between frontal and temporal regions in memory has typically been neglected in cognitive neuroscience, it might be crucial for a full understanding of how memory processes are represented in the brain. There is a complex pattern of interactions between the prefrontal cortex and the medial temporal lobe. Although our understanding of these interactions is still at an early stage, in the next section we attempt to draw on what is known to define theoretically the manner in which some of these interactions might operate.
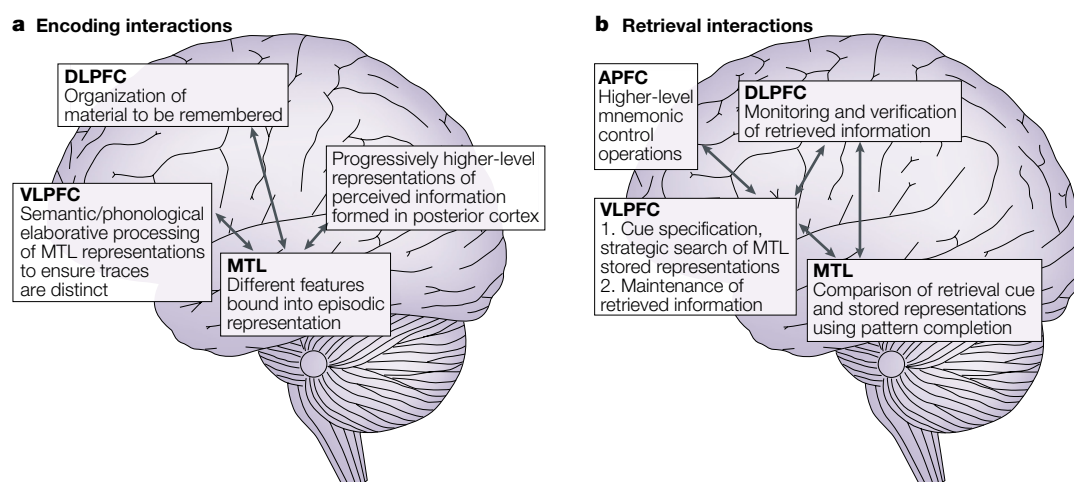
a Encoding interactions

DLPFC
Organization of
material to be remembered

VLPFC
Semantic/phonological
elaborative processing
of MTL representations
to ensure traces
are distinct

Progressively higher-level
representations of
perceived information
formed in posterior cortex

MTL
Different features
bound into episodic
representation

b Retrieval interactions

APFC
Higher-level
mnemonic
control
operations

DLPFC
Monitoring and verification
of retrieved information

VLPFC
1. Cue specification,
strategic search of MTL
stored representations
2. Maintenance of
retrieved information

MTL
Comparison of retrieval cue
and stored representations
using pattern completion

Figure 6 | **Summary of principal interactions between prefrontal cortex (PFC) and medial temporal lobe (MTL) in recollection.**
a | Encoding. Perceived information is processed in hierarchical cortical areas, resulting in progressively higher-level representations that are integrated and associated into a bound memory trace in the MTL. Top-down control of encoding is provided by the PFC, involving elaborative semantic and/or phonological processing of the MTL representation in anterior and posterior ventrolateral prefrontal cortex (VLPFC), respectively. Material is selected, manipulated and organized in the dorsolateral prefrontal cortex (DLPFC). These control processes ensure the separation of traces so as to reduce interference between them. **b** | Retrieval. On the basis of the kind of retrieval task undertaken, retrieval cues are specified and elaborated in the VLPFC, before being used to strategically search stored representations in the MTL. Using a process of pattern completion that occurs outside cognitive control, the retrieval cue is iteratively compared with stored representations until correspondence is achieved and a candidate memory identified. This memory representation is retrieved and maintained online by VLPFC while various monitoring and verification processes are undertaken in the DLPFC. The retrieved information is compared with the retrieval criteria originally specified and, if these criteria are satisfied, the memory will be available for conscious thought and/or output. Otherwise, modification of the retrieval cues might occur in VLPFC and further attempts at retrieval searches are undertaken. Less certain is the nature of the higher-level mnemonic control processes, should they be required, which seem to be supported by anterior prefrontal cortex (APFC), and the processing concerning self-relevant information, which is thought to engage medial prefrontal cortex (not shown). Anatomical images adapted, with permission, from REF. 133 © (1996) Appleton & Lange.

Proposed unifying framework

Although both prefrontal and medial temporal regions are involved in the encoding of information into memory[77,83], the interactions between these regions seem to be particularly central to the retrieval of stored information[49,50,111]. By contrast, there is evidence that the medial temporal lobe alone is responsible for the storage and indexing of memories (at least for some years after encoding in humans)[3,41]. We therefore focus here on providing an outline of how prefrontal and medial temporal regions might interact during the cognitive operations involved in encoding and retrieval (FIG. 6). This description is limited by the data available and the poorly specified nature of these processes. Nevertheless, we believe that a unifying overview might highlight avenues for future research.

For information in the external world to be encoded (transferred from a currently active representation to a long-term store), it is processed by unimodal and poly-modal cortical areas before being transmitted to the medial temporal lobe. As processing proceeds along these pathways, progressively higher-level representations of the perceived information are formed, integrating and associating different features of the to-be-remembered material into a bound representation[30,54]. At this stage, the interaction with prefrontal cortex becomes important in providing top-down control of the encoding process, guiding, modifying and elaborating the representations

in the medial temporal lobe on the basis of current goals and task demands, and ensuring that the representations are sufficiently non-overlapping to be amenable for long-term storage[70,83].

The interaction will involve differential recruitment of prefrontal regions depending on the type of top-down processing required (for example, anterior and posterior ventrolateral prefrontal cortex for semantic and phonological processing, respectively[107,108]), and its relative lateralization will depend on the verbal or non-verbal nature of the information being encoded[77,83,122]. Dorsolateral prefrontal regions might be engaged if, during processing, some selection of multiple features or organization and manipulation of the material is required[88]. So the encoding of categorized lists of items might be affected by lesions that disrupt the function or connectivity between dorsolateral prefrontal cortex and the medial temporal lobe. The interactions between prefrontal and medial temporal regions that predict different states of awareness at retrieval are unclear. For example, will activation of similar networks at encoding determine subsequent retrieval when memory is assessed using tests of recollection and familiarity, or when tasks that measure implicit rather than explicit memory are used? Furthermore, the extent to which the engagement of encoding-related brain regions will vary depending on attentional factors and differences in strategies adopted has yet to be fully elucidated.

Prefrontal–medial temporal interactions might be even more important during retrieval. Retrieval can be characterized as the process by which long-term stored information is made available for current operations or behavioural responses, typically through the directed use of a retrieval cue. Cognitive models of retrieval include separate components: the specification of a retrieval cue, the interrogation of a long-term store with that cue, the reactivation of stored information, and the monitoring or evaluation of this reactivated information[68,82]. The prefrontal cortex and medial temporal lobe interact in different ways during these stages of retrieval, with cue specification and elaboration involving ventrolateral prefrontal cortex[84], and the verbal/non-verbal nature of the material influencing the relative laterality of the interaction[78,79,109]. So, disconnection of ventrolateral prefrontal cortex and the medial temporal lobe can be expected to have a greater impact on tasks with poorly defined retrieval cues (degraded pictures, for example) than on tasks in which cues are well specified.

The elaborated retrieval cue is used to interrogate the medial temporal lobe[96], strategically searching stored representations and seeking concordance between the cue and stored information, possibly through pattern completion[55]. When one or more candidate memories have been identified, their representation will be maintained in working memory by ventrolateral prefrontal cortex[85,86] while monitoring operations, thought to be supported by dorsolateral prefrontal cortex, are engaged to compare the retrieved information with the specified retrieval criteria to allow the disambiguation of competing memories[90,123,124]. This might require source verification and rejection of the retrieved representations because of inconsistencies, in which case the retrieval cue might be modified and further retrieval search interactions undertaken. Anterior prefrontal cortex might be recruited if particularly complex retrieval operations are required, for example involving the processing of internally generated information[92,93], although the circumstances in which this region is engaged are not understood. Similarly, interactions with medial prefrontal cortex might occur during the retrieval of reward-related or self-relevant information, such as autobiographical memories[81,98,115], although the mechanisms that govern the involvement of this region are still to be explained.

One issue that is not clear is the nature of the interactions between dorsolateral prefrontal cortex and the medial temporal lobe that facilitate the monitoring of retrieved information. For example, what verification criteria are used to assess the accuracy of retrieval? Does the use of these criteria vary in a task-dependent manner and, if so, what rules govern this[96]? Perhaps more fundamentally, if functional activation in prefrontal cortex is associated with a particular behavioural response (such as an indication of an intermediate level of retrieval success or 'feeling of knowing'[111]), does that mean that the level of activation in this region reflects the outcome that retrieval was moderately successful, or could this activation represent a signal to drive further retrieval searches to recover the item? Such questions relating to the causal nature of interactions are difficult to answer with standard methods of neuroimaging analysis, but might start to be addressed using effective connectivity techniques.

Conclusions

A review of the literature points to the conclusion that interactions between prefrontal cortex and the medial temporal lobe are vital for successful memory. These regions contribute in different ways to the processes of encoding, storage and retrieval, but it is only by their combined participation, and their modulatory influence over one another, that comprehensive memory function can be sustained. During encoding, the essence of the interaction between prefrontal cortex and medial temporal lobe is to provide discrete and elaborated representations that are amenable to long-term storage. At retrieval, interactions serve to specify retrieval cues, interrogate the long-term store, and reactivate and monitor stored information. Our understanding of the nature of the interactions between these regions is still at an early stage, and so our specification of the processes involved is frustratingly imprecise. Further work is needed to characterize these processes in more detail, specifying how the interactions between prefrontal and medial temporal regions might differ during operations such as cue specification, maintenance and monitoring of retrieved information. This endeavour will require the use of analogous tasks and comparable methods across species and techniques so that convergent evidence can accumulate, providing information that cannot be derived from individual fields of study in isolation. In addition, theoretical work remains to be undertaken, bridging the gap in understanding between cognitive models and empirical observations such as changes in neural connectivity. With the contribution of studies employing the different methodologies described in this article, and interpreting their results within common, unified theoretical terms of reference, we might begin to move closer to a full account of the manner in which the prefrontal cortex and medial temporal lobe work together to support remembering.

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