THE COGNITIVE NEUROSCIENCE OF REMEMBERING

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Remembering draws on a diverse array of cognitive processes to construct a representation that is experienced as a copy of the original past. The results of brain-imaging, neuropsychological and physiological studies indicate that distinct neocortical regions might interact with medial temporal lobe structures to reinstate a memory. Frontal regions mediate the strategic retrieval attempt and monitor its outcome, with dissociated frontal regions making functionally separate contributions to retrieval. Parietal and frontal regions might supply a signal that information is old during the process of retrieval, allowing us to perceive that reconstructed representations are memories, rather than the products of new stimuli in the environment. Domain-specific cortical regions are reactivated during vivid remembering and contribute to the contents of a memory. Here, we describe how these regions interact to orchestrate an act of remembering.

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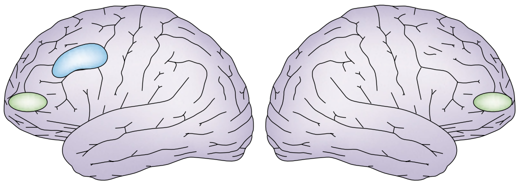
Remembering the location of a parked car or reminiscing about a recently attended symphony event are both perceptions of the past that often include rich sensory and contextual details of the original episode. For much of the past century, remembering was considered taboo for scientific exploration because of unease about exploring subjective phenomena. Progress in cognitive psychology, neuropsychology and, more recently, brain-imaging research, has provided experimental tools for the objective investigation of remembering, and provided a means to link cognitive-level description with underlying neural processes. Recent findings indicate that acts of remembering separate into component processes that are subserved by dissociable brain regions. In this review, we consider evidence for these separate neural components and how they might combine to orchestrate an act of remembering. Our discussion is framed in terms of the strategic aspects of attempting to remember and the products of a memory attempt (for more expansive models of retrieval, see REFS 1–9).

Retrieval attempt

A familiar face or scene might spontaneously trigger a memory, but most acts of remembering begin with a goal-directed attempt to remember. How does the brain support the processes associated with retrieval attempts? Clues have come from studies of patients with brain lesions. Patients with frontal cortical lesions often show retrieval difficulties, in particular when the specific context (or source) of an episode must be remembered or when minimal cues are provided to aid retrieval[7,10–17]. Gershberg and Shimamaura[10], for example, asked patients with frontal lesions repeatedly to study and recall lists of words or pictures, and found that the patients were significantly impaired at free recall. Moreover, examination of the individual ordering of the recalled items indicated that frontal patients were not using subjective organizational strategies. That is, whereas healthy control subjects had a tendency to consistently group certain words together across retrieval trials (for example, 'spoon' and 'plate'), frontal patients did so to a lesser degree, in essence recalling the words in a more random fashion.

Another clue from neuropsychogical studies is from patients who confabulate during remembering by falsely recalling details of a memory (what Moscovitch[7] calls "honest lying"). For example, during an interview, one patient with widespread frontal damage[7] was asked how long he had been married. He answered: "About four months." Then asked how



Frontal region property	Posterior: BA 44/6	Anterior: BA 10
Selective to remembering	No	Somewhat
Material dependent	Yes	No
Tracks amount of effort	Yes	No
Tracks retrieval success	No	Sometimes
Temporal profile	Early	Late
Sensitive to task	Somewhat	Very

Figure 1 | **Multiple, functionally distinct frontal regions are active during retrieval attempt and monitoring.** The top figure shows two broad regions of frontal cortex that are associated with retrieval attempt during a prototypical verbal retrieval task, with colour representing distinct functional properties, as outlined in the table below. Further functional subdivisions of left frontal cortex have been made that are not represented in the figure, including a prominent distinction between more dorsal–posterior regions near Brodmann area (BA) 44/6 and more ventral–anterior regions near BA 45/47 (REFS 23,179,180).

many children he had, he responded, "Four … Not bad for four months", and later, "They're adopted." All four children were his own, and he had been actively involved in their lives for the previous 30 years. On standard tests of memory, another patient suffering right frontal damage repeatedly endorsed new items incorrectly as having been studied earlier[18,19]. This behavioural pattern is opposite to that typically observed in memory loss, in which studied items are usually forgotten, and indicates difficulties in implementing an appropriate retrieval strategy. From these findings, it is possible to speculate that frontal cortex makes a contribution to retrieval that includes implementation and monitoring during the retrieval attempt.

HAEMODYNAMIC BRAIN-IMAGING STUDIES of memory retrieval using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have almost ubiquitously shown activated regions in frontal cortex, confirming suggestions of their participation from neuropsychological studies. Other regions of cortex have also been prominently activated but, for our purposes, frontal regions are highlighted. A prototypical series of studies was carried out by Buckner *et al.*[20] and Squire *et al.*[21] using cued recall (see also REF. 22). Before imaging, subjects studied words such as 'couple', 'string' and 'abstain'. During imaging, the beginnings of the words were presented ('cou', 'str' and 'abs') and the subjects were instructed to recall the study words that completed the stems. Activity changes occurred during recall in multiple frontal regions, including posterior left frontal cortex, extending into dorsolateral prefrontal cortex and anterior frontal-polar cortex, near BRODMANN AREA (BA) 10. Anterior frontal-polar activation also showed selectivity — it was present during the recall task but absent during additional conditions that required word completion without remembering.

The basic finding of frontal activation has been generalized to retrieval of sounds, pictures and faces, and during MEMORY TESTS of cued recall, free recall and simple recognition[23–30,182] (for reviews, see REFS 31–36). A considerable challenge has been to specify the processing contributions of these frontal regions to remembering. Some broad principles have emerged, including the finding that multiple, distinct regions of frontal cortex show functional dissociation during remembering[31] (FIG. 1).

In particular, posterior regions of frontal cortex near left-lateralized BA 44/6, and more ventrally near BA 45/47, have a general role in elaborating on verbal information that includes, but extends beyond, tasks involving remembering, as described for the cued recall task above. Demb and colleagues[37] found activation of these frontal regions during a task in which subjects classified words as representing either abstract ('freedom') or concrete ('anvil') entities. Tasks involving elaborate word generation, word classification, verbal working memory and intentional memorization of verbal material all activate these regions[38–42]. Remembering, in many contexts, seems to tap into these processes. In a similar manner, posterior right-lateralized regions of frontal cortex become preferentially activated during retrieval of non-verbal information[43–45].

Posterior frontal participation during remembering tracks the amount of cognitive effort exerted during a retrieval attempt. As an act of remembering is made more difficult by reducing the strength of the original study episode, posterior frontal regions are required to a greater extent[22,46,47]. In one study[46], subjects studied words under conditions of either highly effective or minimal encoding that promoted high and low levels of retrieval, respectively. Activity in left-lateralized posterior frontal cortex was strongest when subjects attempted to retrieve those words studied under minimal encoding conditions, tracking the amount of time (effort) that the retrieval trials required. Posterior frontal regions are also activated independently of whether or not remembering is successful[48,49]. We can tentatively conclude that posterior frontal regions provide general processing resources for the strategic elaboration required during a retrieval attempt. This role is similar to what has often been termed 'working memory' or, in this context, 'working with memory' (for a discussion of this issue, see REF. 50). To the degree that a retrieval attempt is engaged, these posterior frontal regions will be recruited. As the retrieval attempt becomes more difficult, they will be recruited more extensively.

Anterior frontal-polar cortex (near BA 10, often right-lateralized) is also reliably activated during a retrieval attempt, but its role differs from that of posterior frontal cortex in several ways (FIG. 1). Relative to posterior frontal cortex, frontal-polar cortex is more selective for tasks that tap remembering, and is not always active during elaborate verbal or non-verbal processing tasks[51] (see also REFS 52,53). Moreover, frontal-polar cortex does not show increased activity as individual retrieval attempts become more effortful[46] (but see REF. 21), but

HAEMODYNAMIC IMAGING METHODS
Techniques used to measure neural activity by monitoring changes in regional blood flow. Positron emission tomography (PET) measures blood flow directly. Functional magnetic resonance imaging (fMRI) measures oxygen concentration in the blood that relates to blood flow. PET and fMRI have good spatial resolution but relatively poor temporal resolution.

BRODMANN AREAS
(BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions based on cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains subdivisions, including BA 44, BA 45, BA 47 and others). Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

MEMORY TESTS
Formats used to test explicit retrieval in the laboratory vary in relation to how much information is provided to aid retrieval. In free recall, items are recalled in an open fashion ("Recall the words from the list."). In cued-recall, item-by-item aids are given as cues ("Recall the word that began with cou."). In recognition, the full item is given and the test is to decide whether the item was studied ("Was the word ketchup presented earlier?").

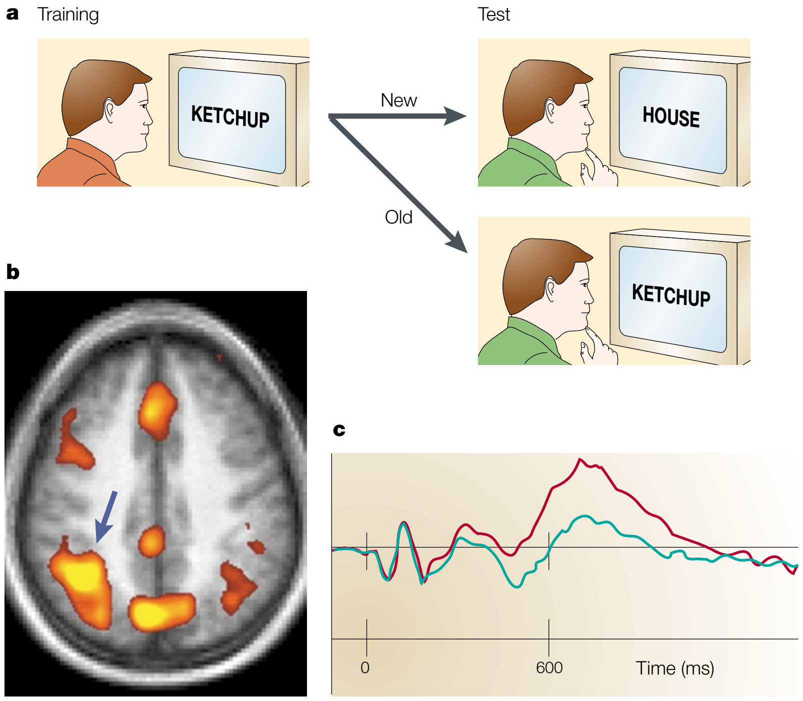


Figure 2 | **Parietal cortex is associated with retrieval success. a** | The basic experimental paradigm used to study retrieval success. Subjects are asked to recognize previously studied old and new words. Those items correctly remembered as old are directly compared with rejected new items to determine correlates of retrieval success. **b** | Functional magnetic resonance imaging (fMRI) data from REF. 49 show differential activation associated with success over multiple brain regions, prominently including left parietal cortex (arrow). **c** | Event-related potential (ERP) studies have identified a related effect, showing a rapid positive waveform that develops over left parietal sites during remembered old items (red) as compared with new items (green). Reprinted with permission from REF. 3 © 2000 Elsevier Science. The correspondence between the fMRI and ERP findings is intriguing, but should be entertained cautiously as their properties differ in certain regards (for example, contrast REF. 76 with REF. 181).

could be modulated by the subject's expectations[54]. Activity in frontal-polar cortex generalizes across retrieval of verbal and non-verbal information, tending to be right-lateralized even for verbal material[31,34,43]. Finally, frontal-polar cortex shows atypically long responses in EVENT-RELATED FMRI studies[48,55,56] that might have correlates in brain electrical activity as measured by ELECTROENCEPHALOGRAPHY (EEG)[57,58].

These counterintuitive properties have stumped any simple interpretation. One possibility is that frontal-polar cortex provides ongoing monitoring during the attempt to retrieve[29,55,57,59]. Alternatively, anterior frontal-polar cortex might contribute to the high-level monitoring required when a task demands multiple sub-goal processes. That is, certain kinds of task require dynamic navigation between multiple goals[52]. Remembering might inherently rely on this form of processing, with the rememberer continuously navigating between information provided by cues present in the environment and representations constructed from memory (see also REFS 7,60).

In summary, the above results indicate that frontal regions participate in strategic aspects of retrieval attempt with specific, dissociated regions making distinct contributions.

EVENT-RELATED FMRI
A variant of functional magnetic resonance imaging (fMRI) methods that allows neural correlates of individual trials or classes of trials to be isolated and compared.

ELECTROENCEPHALOGRAPHY
(EEG). A technique used to measure neural activity by monitoring electrical signals from the brain that reach the scalp. EEG has good temporal resolution but relatively poor spatial resolution.

Retrieval success

The goal of a retrieval attempt is to reconstruct a perception of the past. If we assume that the structures discussed above relate in some way to strategic aspects of a retrieval attempt, other brain regions probably support information about whether retrieval has been successful and the episode-specific contents of a memory.

Structures in the medial temporal lobes have been repeatedly implicated in retrieving recently learned facts and events[61–63]. In some studies, if a lesion is limited to the hippocampus, the ability to remember episodes seems to be selectively impaired, with a preserved ability to retrieve general facts[64]. Brain-imaging studies have intermittently shown hippocampal activation during retrieval (for reviews see REFS 36,65–67), and have correlated hippocampal activation with the level of retrieval success[68]. Recently, a study by Eldridge *et al.*[69] has indicated selective activation of the hippocampus when subjects report a distinct memory for an earlier episode, as opposed to having a vague sense of familiarity (but see REFS 28,70). On the basis of these kinds of observation and animal studies of hippocampal lesions, several models of retrieval have proposed that structures in the medial temporal lobes rapidly bind neural representations associated with an experience to each other during memory formation, and then, for a period of time following acquisition, function to reinstate those representations during retrieval[71–74]. Because a detailed account of hippocampal participation in retrieval has recently been published[71], we focus this review on regions outside the medial temporal lobes.

One open question has been whether there are neural changes in neocortex that signal successful retrieval of mnemonic information. During an act of remembering, we are usually aware that items being recalled are from the past and do not arise solely from our immediate surroundings or *de novo* from our imagination. In experimental settings, such neural changes might provide information that is useful for deciding whether a presented item is old or new on a recognition test. Habib and Lepage[75] explored neocortical changes associated with retrieval success in a meta-analysis of PET data from five studies. Across all included studies, measurements were made during blocks of old items, as compared with new items. Items were presented visually or aurally, and were either words or pictures. Results showed a network of brain areas, including left parietal cortex, medial parietal cortex (near cuneus) and left anterior frontal cortex, near the frontal-polar region discussed above, that responded more to the blocks of old items.

Event-related fMRI studies have extended these observations by allowing individual items correctly identified as old (hits) to be compared with items correctly identified as new. This comparison directly targets processes associated with retrieval success. Several fMRI studies[28,49,55,76,77] have identified the same basic network as reported by Habib and Lepage[75], and particularly highlighted the role of left parietal cortex (FIG. 2). Moreover, activity in this network has been shown to predict, on average, whether a subject will correctly identify an old item on a recognition test[78], and is sometimes present for old items, even when a recognition decision is not required[76,79]. Event-related potential (ERP) studies comparing remembered old items with new items have shown a relatively fast (onset ~400 ms) positive waveform over left parietal cortex that is present for remembered items and might parallel certain properties of the fMRI findings[80] (for review, see REF. 58) (FIG.2). Across these studies, words, pictures and sounds have been used as stimuli, implying that the network participates generally in retrieval success. So, its participation in retrieval is either not dependent on the episode-specific contents of a memory, or signals the retrieval of abstract forms of information that generalize across numerous retrieval contexts.

These collective findings indicate a relatively fast signal in left parietal and associated cortex that correlates with retrieval success. One speculation is that activity in these cortical regions informs a person that something is from the past. It will be important to determine, in future studies, whether these cortical correlates of retrieval success are dependent on intact medial temporal structures and how findings integrate across methods. For example, an open question surrounds whether lesions affecting these left parietal regions that are associated with retrieval success lead to changes in memory function.

Retrieval content

The identification of cortical regions that provide a general signal associated with retrieval success raises the separate question of how the brain represents the episode-specific contents of a memory. Recollective experience can include, for example, the face of a recently introduced person, the sound of his or her voice, and the topic of the conversation. Recent theories have indicated that regions controlling the strategic aspects of retrieval, such as those discussed earlier, are distinct from those that represent the remembered information[81–84] (see also REF. 85), but the general concept of top–down control is not new[1]. There is considerable evidence from a variety of experimental approaches that certain regions of the brain that process incoming (bottom–up) perceptual information are also involved in representing that information during remembering[84,86–96]. We refer to this process as 'reactivation', similar to what William James[1] called 're-excitation', as information associated during memory formation is reactivated during retrieval (see also REF. 97). The notion of reactivation also shares similarities with the more recent cognitive theoretical framework of transfer-appropriate processing, which postulates that memory performance is influenced by the overlap between the specific processes engaged during memory formation and retrieval[98–100].

Early evidence that sensory regions are associated with memory retrieval was obtained by Wilder Penfield and Phanor Perot[101]. Penfield electrically stimulated regions of exposed cortex in awake human patients undergoing surgery for epilepsy, and found that stimulation of regions of occipital and temporal cortex would sometimes elicit memories (as verified by the patient or by witness), and that the sensory modality of the memories varied depending on the region of cortex stimulated. Regions of superior and middle temporal lobes were associated with auditory memories ("I hear singing … Yes, it is *White Christmas*") whereas regions of more posterior temporal and occipital lobes were associated with visual memories ("… I saw someone coming toward me as if he were going to hit me"). Although certain aspects of these early studies have been re-examined[102,103], they provided initial evidence for the idea that cortical regions associated with sensory processing are also associated with memory processes.

Crucial insights into brain regions supporting memory representation have come from studies of mental imagery. In a typical imagery study, subjects are asked to imagine what an object or place looks like from their general knowledge (for example, "Picture an elephant in your mind" or "Picture the letters in the word HOUSE"). In other studies, participants are asked to construct images based on specific, recently learned stimuli, paralleling in many ways an act of remembering. For these reasons, findings from studies putatively targeting imagery relate closely to those exploring remembering of content-specific information. Furthermore, behavioural analyses of imagery tasks have long indicated similarities between imagery-based retrieval and stimulus-based perception[104–106] (see also REF. 87).

Assessments of visual mental imagery ability in patients with damage to visual cortex support the possibility that brain regions involved in perception are also used during imagery and remembering[107–111]. Patients with deficits in perceiving certain stimulus properties, such as colour, form or spatial location, can also have deficits in their ability to imagine that information when given verbal instructions[108,110,111]. These differing stimulus properties are probably represented in different regions of visual cortex. For instance, Farah *et al.*[109] showed that bilateral damage to temporal–occipital cortex resulted in decreased ability to imagine specific object features such as colour and size, but preserved imagery for spatial features such as mental rotation and scanning. These two components of visual information are processed in separate (but highly interconnected) visual processing streams, with visual object information processed primarily in ventral occipital and temporal cortex, and spatial information processed primarily in dorsal occipital and parietal cortex[112,113].

However, the extent to which sensory regions subserve both perceptual and retrieval processes is not entirely clear from the neuropsychology literature. Several individuals with brain damage have been described, who show impaired visual mental imagery, but relatively preserved stimulus-based perceptual processing[114]. The opposite dissociation has also been observed. Bartolomeo *et al.*[115] describe a woman with bilateral temporal–occipital lesions presenting a variety of visual processing impairments, including agnosia (the inability to recognize objects) and prosopagnosia (the inability to recognize faces), but who could imagine both objects and faces. This patient, remarkably, could draw objects from memory, but failed to perceive their identity when presented with them at a later time

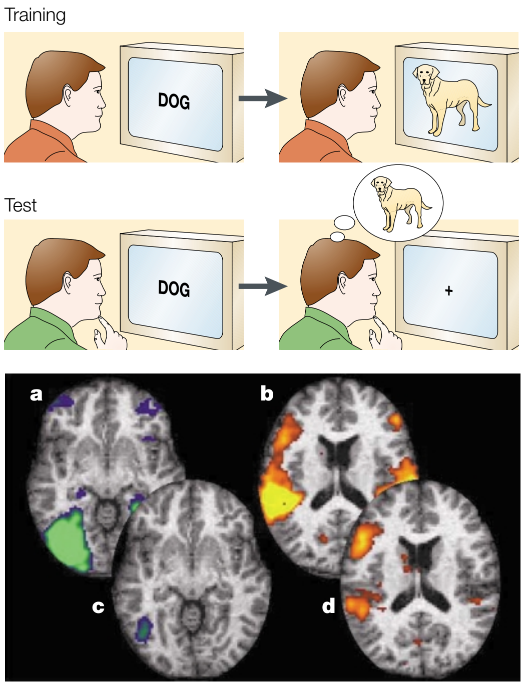


Figure 3 | **Subsets of regions activated during perception are reactivated during vivid remembering.** A paradigm used to explore modality-specific reactivation. Subjects study words paired with either sounds or pictures (example shows a picture trial). At test, subjects are asked to remember whether the words had been previously associated with pictures or sounds,encouraging retrieval of vivid, modality-specific memories. Brain images based on functional magnetic resonance imaging (fMRI) show regions of the brain active during perception of pictures (**a**) and sounds (**b**), and subsequently during retrieval of the same pictures (**c**) and sounds (**d**) from memory. Perception resulted in increased activity in visual cortex (from calcarine to fusiform gyrus) for pictures, and from auditory cortex (near Heschl's gyrus to middle temporal gyrus) for sounds. Retrieval of pictures from memory was associated with reactivation of visual cortex near fusiform gyrus, whereas retrieval of sounds was associated with bilateral superior temporal gyrus near secondary auditory regions. These results indicate that certain regions of sensory cortex associated with perception are differentially reactivated during retrieval of that information. Reproduced with permission from REF. 95 © 2000 National Academy of Sciences, USA.

(see also REFS 115–118). These findings indicate that perceptual and retrieval systems do not completely overlap, but do not address the extent to which they might share certain levels of neural representation.

EEG studies of retrieval tasks also support a reactivation hypothesis[86,119–121]. These studies indicate that neural activity in posterior regions of the brain increases when people remember detailed perceptual information. For example, Rösler *et al.*[121] asked subjects to learn associations between pictures and spatial locations, pictures and colours, and pairs of words. Subsequent EEG recordings during memory tests showed maximal responses over left frontal regions during word retrieval, parietal regions during spatial location retrieval, and occipital and temporal regions during colour retrieval. These results indicate that different regions were reactivated depending on the type of information retrieved.

Strong evidence for reactivation of sensory-specific cortex during retrieval comes from studies using PET and fMRI. Many studies in which subjects retrieve visual information result in activity increases in occipital and temporal cortex[88,95,122–136], whereas retrieval of auditory information results in increased activity in superior and middle temporal cortex[91,95,96,137,138] (see also REF. 139). Wheeler *et al.*[95] asked subjects to study a set of picture and sound items extensively over several days, then tested them on a SOURCE MEMORY TASK in which the subjects were told to vividly recall the items and indicate whether they had been studied as pictures or sounds. A subset of cortical regions that were selectively activated during perception of pictures and sounds were also reactivated during retrieval of the same forms of information (FIG. 3). A left-lateralized region along the fusiform gyrus was associated with both perception and retrieval of picture information, whereas bilateral superior temporal regions were associated with both perception and retrieval of sounds. A recent PET study showed that reactivation might extend to the motor system[140]. Subjects remembered study episodes in which physical actions were performed. During retrieval of these action-associated events, activation increased in regions of the motor system. In addition, many of these studies report involvement of frontal and/or parietal regions during retrieval, lending support to the idea that the regions involved in retrieval attempt interact with sensory and motor regions that are reactivated depending on specific memory content.

Evidence for cortical representation of retrieval content comes from SINGLE-UNIT RECORDINGS during paired-associate retrieval tasks in monkeys[90,94,141,142] and imagery recall tasks in humans[89]. During paired-associate recall, one stimulus is arbitrarily made to predict another. Because single-unit responses in certain visual areas can be highly selective for specific visual stimuli, single-unit recordings can be characterized in terms of their responsiveness to presented stimuli versus those absent but associated through learning. Sakai and Miyashita[94] (see also REF. 90) tested PAIRED-ASSOCIATE RECALL, and found 'pair-recall' neurons in inferior temporal cortex, the activity of which increased in the absence of their optimal stimuli if cues were presented that had been associated with their optimal stimuli during learning (FIG. 4). Although not all studies have found such effects[143,144], these results indicate a mechanism, at the level of individual cell ensembles, that might contribute to the representation of specific visual context during remembering.

How specific is controlled reactivation during remembering? Human fMRI studies are particularly appropriate for this question, because they can simultaneously survey indirect correlates of neuronal activity across multiple, distributed cortical regions in a sensory modality. Several recent fMRI studies in humans indicate a relatively high degree of specificity during reactivation. Ishai and colleagues[127] identified separate regions of ventral visual cortex showing category-preferential fMRI activity increases in response to faces, houses and chairs during perception. Recall on the basis of imagining these objects produced significant increases

SOURCE MEMORY TEST
A form of explicit retrieval test in which a specific attribute of the study episode is queried ("Was the dog studied as a sound or picture?").

SINGLE-UNIT RECORDING
A method used to measure the activity of individual neurons in awake, behaving animals. This method has excellent spatial and temporal resolution, but can only survey activity over small numbers of neurons.

PAIRED-ASSOCIATE RECALL
A form of retrieval test in which item pairs are studied ("dog–cat"). At test, one member of the pair is given to cue retrieval of the other ("dog").

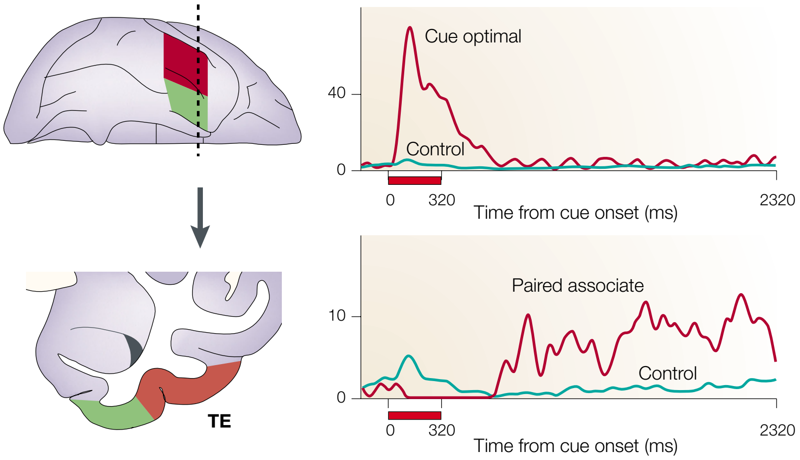


Figure 4 | **Paired-associate recall tasks in monkeys might indicate single-unit correlates of reactivation.** The left panel shows diagrams of the ventral surface of the monkey brain showing area TE of the temporal lobe, in which recordings were made (red). On the right are recordings from a neuron that responds preferentially to a specific stimulus. The bottom graph shows the response in this neuron when a non-optimal stimulus is presented that had been paired, during learning, with the cue-optimal stimulus. The neuron's activity does not show an initial response to the non-optimal cue, but does show a slowly developing response to the retrieved stimulus that might reflect a neuronal correlate of reactivation for the paired-associate. Adapted with permission from REF. 90 © 2001 American Association for the Advancement of Science.

in activity across these regions. Importantly, the regions most associated with perception of one category were also most associated with imagery from that category (FIG. 5). In another study, O'Craven and Kanwisher[134] found a similar dissociation using faces and buildings. Recalling the images of famous faces (cued by their names) reactivated a portion of fusiform gyrus that was preferentially associated with perceiving faces, whereas recalling familiar buildings reactivated a portion of the medial temporal lobes, the parahippocampal gyrus, that was associated with perceiving those same buildings. On a trial-by-trial basis, activity in fusiform and parahippocampal gyri could often predict whether the subject was imagining a face or a building. Kreiman *et al.*[89] showed similar predictability for the specific visual content of a memory based on recordings from individual neurons in humans undergoing brain surgery.

The extent to which retrieval signals traverse the visual system during remembering, from later to earlier processing areas, is also a topic of debate. Results from several studies have indicated that reactivation effects can reach as far back as calcarine cortex, at or near primary visual cortex (the earliest processing stage in the cortical visual system)[123,128,130,131,135,145,146]. One fMRI study, in which subjects imagined the appearance of visual objects they might encounter while walking though their hometowns, even indicated reactivation of the thalamic region supplying inputs to primary visual cortex (the lateral geniculate nucleus) during visual recall[123]. On the other side of the debate, many studies indicate that retrieval of detailed visual[30,88,95,124,125,127,132,133] and auditory[91,95,96,137] information can take place without robust activity in early sensory cortex. Experimental methodology (for example, choice of control task), task demands (for example, detail of the retrieved information) and differences in individual abilities might account for the discrepant results[123,128,147].

Roland and Gulyás[92], and Hebb[148], have suggested that it is sometimes unnecessary to recruit early sensory regions to recall information represented at later stages of the sensory processing hierarchy. That is, to remember what a dog looks like, it might be sufficient for retrieval processes to reactivate late visual regions in which neuronal activity codes the object representations of the dog, and not earlier regions in which activity codes more primitive visual attributes. This hypothesis is appealing, because it suggests efficiency in the systems subserving retrieval content. Reactivation processes cascade backwards through sensory processing areas as is required to represent the level of sensory detail in a memory, much as qualitatively different regions can be preferentially recruited as indicated by the studies discussed earlier[127,134] (but see REFS 128,149). It is also possible that increases in activity in visual and auditory cortex during retrieval tasks are modulated, to some degree, by attentional shifts in baseline neural activity[122,150–156] that interact with processes associated with the retrieval of specific stimuli.

Research into the neural mechanisms underlying retrieval content faces a final, difficult challenge. Memory content extends beyond simple sensory details of an original episode to include abstracted forms of representation, such as verbally mediated thoughts, emotional content and even a sense of the personal perspective of the rememberer. Prominent theories have noted that these abstract forms of representation are central to the experience of remembering[1,4]. Unfortunately, we are largely unaware of their neural bases (but see REFS 35,157–159). Nonetheless, the basic principles learned from the above discussions of how sensory details are remembered might extend to other forms of information. That is, sensory systems present the most approachable targets for initial exploration of retrieval content, because their properties are relatively well understood. However, their contributions to remembering probably represent only a fraction of the overall distributed network reactivated during retrieval. Frontal and temporal regions might reactivate to support the verbal and verbally mediated semantic contents of memories, the amygdala might participate in the emotional content[160], and so on. Collectively, these widely distributed representations reactivated during remembering might convey the vividness and richness that is experienced.

Integration during remembering

From the perspective of the rememberer, processes associated with retrieval attempt and their various products are probably experienced as one integrated memory[4]. The discussions above focus on manipulations that pull apart component processes of remembering, and provide us with some insight into their distinct properties. A remaining challenge is to understand how the component parts orchestrate an entire act of remembering. It seems likely that the separate processes discussed earlier, and their neural mechanisms, act interdependently during retrieval. In this regard, a

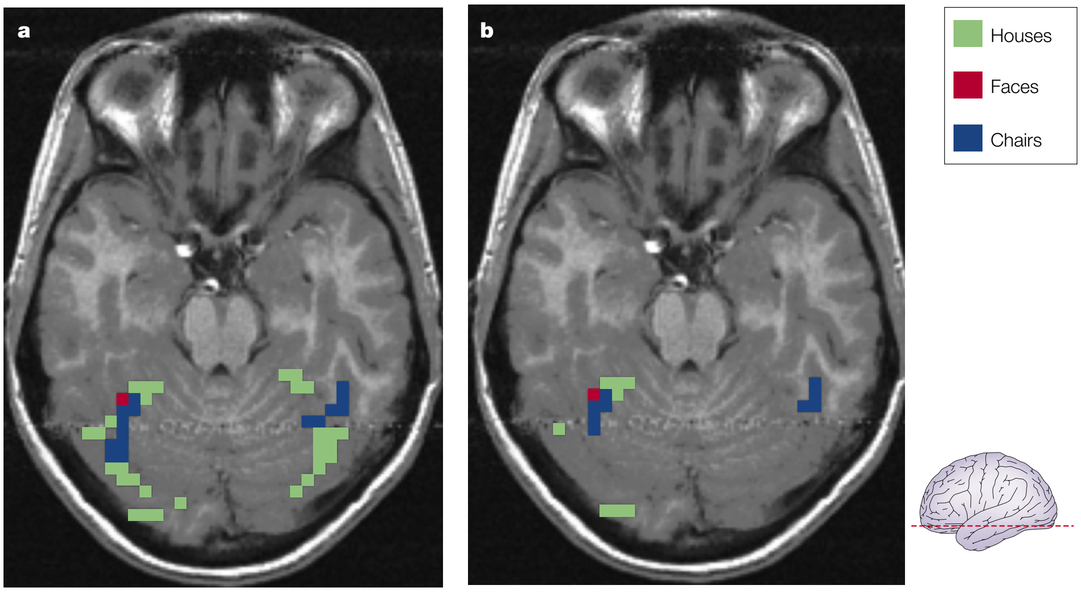


Figure 5 | **Regions of visual cortex that respond preferentially to different kinds of objects during perception show similar preference during imagery of those objects. a** | Bilateral regions of ventral temporal cortex show modulation of activity during perception of houses, faces and chairs. Within this general region, certain regions show preferential responses for the different object classes. Perception of houses is differentially associated with increased activity in medial fusiform gyrus (green), faces with lateral fusiform gyrus (red) and chairs with inferior temporal gyrus (blue). **b** | Modulation of activity during visual imagery of houses (green), faces (red) and chairs (blue) is associated with regions preferentially activated during perception of each stimulus form. Such specificity during imagery indicates that regions specialized for processing certain types of information during perception might also, to some extent, be involved in reconstructing that information during retrieval. Reproduced with permission from REF. 127 © 2000 Elsevier Science.

tentative model can be constructed on the basis of available data that describes how an act of remembering might proceed.

During successful remembering, top–down modulation from frontal cortex probably interacts with posterior neural representations of environmental cues to trigger reactivation of the cortical networks that represent a memory. The medial temporal lobe probably is required for certain forms of reactivation, perhaps through its parallel role in the rapid initial binding of information into new cortical networks. As information reflecting mnemonic representations is realized, cortical networks involving parietal and frontal regions contribute to a general signal indicating that information is old. Concurrently, reactivation of the domain-specific contents of a memory draw on later stages of sensory processing that also encode such information during sensory and imagery processing. For example, visual regions in inferior temporal cortex will be reactivated to support the visual contents of the memory. Other regions, as yet poorly understood, support abstract and verbal forms of retrieval content. It is also likely that frontal cortex participates in the ongoing evaluation of the emerging products of the retrieval attempt, and that the above processes are extended, depending on the successes and goals of the retrieval event. The operations of these interactive processes are phenomenologically experienced as remembering.

The above model is incomplete and unlikely to be correct in all details, but nonetheless illustrates how the neural basis of remembering could arise, given the available data. Extending this tentative model, it is also possible to speculate on how certain closely related cognitive experiences could differ from remembering.

An important distinction in cognitive theories of memory retrieval is between remembering and knowing[161,162], or the related distinction between RECOLLECTION AND FAMILIARITY[163,164] (see also REF. 5). Decisions about whether something is old or new are not always supported by a fully developed recollective experience. Behaviourally, the distinction is often tested in the 'remember–know' procedure, in which subjects are given the opportunity to indicate whether a correctly identified old item is simply known to be old, or whether specific details associated with the item's original presentation can be remembered[162]. In memory tests, items are often correctly identified as being old because of a vague sense of familiarity. This cognitive distinction might capture the degree to which retrieval content has been achieved during the process of retrieval — a distinction that yields qualitatively different retrieval experiences. In situations in which parietal and frontal regions signal that a perception is from the past, concurrent with reactivation of sensory-specific and other cortex associated with retrieval content, the experience will be recollection. When brain regions signal that a perception is from the past with minimal reactivation of cortex supporting retrieval content, the experience will be devoid of the richness of a fully formed memory and experienced as familiarity.

RECOLLECTION AND FAMILIARITY
Theoretical memory processes that are believed to contribute to explicit retrieval. Familiarity refers to the general sense that something is familiar (old). Recollection refers to retrieval of specific details and the context associated with an earlier episode.

Conclusions and future directions

Cognitive neuroscientific exploration into remembering is just beginning, and goes forward with an array of methods that can link neural systems to the cognitive phenomenon associated with remembering. We have provided a summary of recent findings that seem to indicate: first, specific dissociable regions of frontal cortex are involved in strategic aspects of retrieval attempt and monitoring; second, parietal and frontal regions provide a general signal of retrieval success, perhaps indicating that information is old; and last, regions within sensory cortex reactivate to provide memory content during remembering. The picture is still rather murky and the data are incomplete.

Several large gaps in understanding remain. One important future direction for research is to target how the neocortical processes described above interact with medial temporal regions that are associated with memory formation and retrieval. For example, to what degree do neocortical correlates of retrieval success depend on the integrity of the medial temporal lobe? If they do, how do medial temporal structures enable these neocortical signals to be associated with retrieval success? Answers to these questions might be clinically useful. Alzheimer's disease can be predicted on the basis of structural changes within the medial temporal lobe[165,166], and many believe that functional changes precede the gross structural changes by several years. One strategy to detect the earliest stages of dementia has been to measure medial temporal activity during memory processes using brain-imaging methods[167]. However, structures within the medial temporal lobe are relatively small and have been a difficult challenge for imaging. If specific neocortical correlates of remembering depend on the integrity of medial temporal lobe function, these correlates might provide powerful markers for medial temporal lobe function, and their measurement might predict the progression of dementia.

Significant future progress is also likely to increase the sophistication of the link between neural correlates and cognitive theories of remembering. Two distinct gaps can be identified in this area. First, ideas about the component cognitive processes involved in remembering have advanced beyond simple distinctions between retrieval attempt and retrieval content[1–9], and the methods that can distinguish between these more detailed processes are just now being developed. In this regard, we can expect to see significant progress as new methods are adopted. For example, many theories of remembering propose that adopting a preparatory cognitive state serves as a foundation for individual recollective experiences — what has often been termed 'retrieval mode'[4]. Retrieval mode might operate in the context of remembering past episodes in a manner similar to how selective attention modulates perception of externally presented stimuli. Slow-wave EEG recordings[57] and mixed-model event-related fMRI designs[168] provide new tools that can separate the neural correlates of ongoing mode-related processes from transient neural changes associated with individual retrieval events. As another example, it is widely believed that acts of remembering unfold over time, with dynamic temporal interactions between brain regions having a central role. Glimpses into the temporal orchestration of retrieval processes have come from studies using EEG[80,169,170] and single-unit recordings across multiple brain regions[90]. In addition, network analysis of brain-imaging data has indicated interactions between regions during remembering[136,171,172]. Methods that combine techniques, such as methods based on electrical activity (magnetoencephalography and EEG) and haemodynamic methods (fMRI and PET)[173–175], provide considerable potential for widespread characterization of the dynamic processes associated with remembering. A recent study has shown that it is possible simultaneously to record single-unit activity and fMRI responses in monkeys, providing another powerful tool for combining methods with different spatial and temporal properties[176].

Second, theories of remembering have often been explored in relative isolation from other fields of cognitive neuroscience. To fully understand the contribution of a brain region or set of brain regions to remembering, it will be important to integrate studies across subject areas. An obvious example relates to retrieval content. Numerous studies have explored imagery and perception. It would seem parsimonious that the role of a brain region in more than one kind of task derives from a common process that is utilized across tasks. That is, understanding a brain region's role in visual perception might clarify its contribution to remembering. A similar idea applies to those brain regions discussed in terms of strategic aspects of retrieval. Contributions of frontal cortex are not selective to remembering[38,42,43,177,178]. By fully understanding how frontal regions guide executive control processes across multiple kinds of task, such as those classically defined as working memory tasks, we will gain insight into their fundamental processing contributions and how these processes control remembering.

Links

DATABASE LINKS Alzheimer's disease

MIT ENCYCLOPEDIA OF COGNITIVE SCIENCES Positron emission tomography | Magnetic resonance imaging | Wilder Penfield | Imagery

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