

# Learning and memory: recent findings

Peter Bright and Michael D. Kopelman

Recent findings from neuroimaging, event-related potential and lesion investigations reflect a rapidly emerging view that the memory system is widely distributed throughout the cortex. It is clear that the pattern of cortical involvement during encoding and retrieval of memories is critically dependent on the nature and complexity of task demands. This has implications, both for existing models of memory function, and in the methodology of future investigations and the issues they address. No consensus has yet been reached on a number of issues, perhaps most notably the role of the hippocampus in retrieval, but advances in measurement techniques should enable some of these matters to be resolved. Further work must address the complex dynamics of the memory system, the extent to which the same regions underlie different functions, and how different regions interact and reflect common functions. *Curr Opin Neurol* 14:000–000. © 2001 Lippincott Williams & Wilkins.

Department of Experimental Psychology, University of Cambridge, Cambridge, UK

Correspondence to Peter Bright, Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK  
Tel: +44 01223 766 457; fax: +44 01223 766 452; and e-mail: pb208@cam.ac.uk

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## Abbreviations

**MRI** magnetic resonance imaging  
**REM** rapid eye movement

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## Introduction

The present review examines recent neuroimaging, event-related potential and lesion investigations of human memory and learning (mostly published since February 2000). We have avoided purely cognitive, theoretical studies, except where they have direct relevance to issues of localization. The effects of ageing on memory and learning processes are also excluded. The findings are grouped together into four broad areas of interest: working memory, episodic memory, remote memory and semantic memory. Finally, we consider other issues that do not fall easily into any of those categories.

## Working memory

The concept of working memory provides a structure by which the temporary storage of information that is necessary for performing complex cognitive tasks can be conceptualized [1]. At the centre of the model is an attentional controller, the central executive, which is served by two slave systems, one holding verbal and acoustic information, and the other holding visuo-spatial information. A further component has recently been proposed, the ‘episodic buffer’, which binds information held in working memory subsystems and long-term memory into a single, integrated representation [2•]. Under the control of the central executive, it is presented as a capacity-limited, critical stage of long-term episodic learning. Evidence for the role of the prefrontal cortex in the temporary integration of verbal and spatial information has been suggested in a functional magnetic resonance imaging (MRI) study by Prabharakan *et al.* [3].

The central executive remains the least understood component of working memory. However, recent lesion and neuroimaging studies have begun to delineate possible subcomponents. Burgess *et al.* [4] examined retrospective memory, prospective memory and planning components of a novel multitasking procedure in 60 patients with focal frontal, parietal or occipital lesions. Evidence for fractionation of the central executive was found, with deficits in delayed recall of task rules associated with left anterior cingulate involvement, and planning deficits related primarily to a right dorsolateral prefrontal involvement. Retrospective (e.g. rule learning) and prospective (e.g. plan-following) deficits were both associated with left posterior cingulate and occipital lesions.

Dissociation of different components of verbal short-term memory was demonstrated in a functional MRI study by Henson *et al.* [5<sup>\*</sup>]. Phonological recoding of visually presented items produced largely left hemisphere activations, including in Broca's area, parietal and posterior temporal regions, which is consistent with articulatory/lexical functions associated with these areas [6,7]. The left supramarginal gyrus was associated with phonological short-term storage, which is consistent with earlier lesion and imaging studies [8,9]. Serial rehearsal produced activation in the left lateral premotor cortex (BA 6), indicating its importance in memory for temporal order. An overlapping area of the left dorsolateral premotor cortex was implicated in temporal grouping, which is in accord with the presence of a timing signal critical for the serial organization of rehearsal [10].

Increasingly, a long-held emphasis on the role of the prefrontal cortex in executive functions is giving way to a more distributed perspective, with a complex pattern of posterior as well as frontal involvement. In particular, parietal regions 7 and 40 (left parietal in verbal/numeric tasks, bilateral in nonverbal tasks) are commonly highlighted; this is consistent with a ventral/dorsal pathway for object and spatial processing, respectively, in working memory (although this has been contested by Postle and D'Esposito [11]). Established tests of executive function (e.g. card sorting, Tower of London), in addition to activating frontal regions, also consistently activated basal ganglia, thalamic and cerebellar regions, which was possibly related to skill learning in such tasks [12<sup>\*</sup>,13<sup>\*</sup>].

### **Episodic memory**

A crucial role for the prefrontal cortex in the encoding and retrieval of episodic information (i.e. personally experienced incidents and events that are distinct in time and place) has been reinforced and clarified in a number of recent studies. Logan *et al.* [14] examined the neural correlates of deep (meaning-based) and shallow (phonologically based) incidental encoding of verbal material, finding dorsal inferior frontal gyrus activation (BA44–46) in both conditions. The primary difference was a stronger activation of the more inferior aspect of the inferior frontal gyrus (BA 45) in the deep encoding condition, which is in accord with other studies [15,16]. This functional dissociation within the left frontal lobe was consistent with dorsal regions serving a primarily phonological processing role and inferior/anterior aspects being more closely related to deeper, meaning-based coding of information [17].

Spatially equivalent scalp distributions of event-related potentials for cued retrieval of words that were studied under different coding conditions (shallow or deep, visual or auditory) were found by Allan *et al.* [18]. Rather

than reinstating those cortical regions that were involved in the initial encoding, the results were more consistent with a common set of retrieval operations activated irrespective of encoding conditions. Other studies [19–21] have indicated that the pattern of frontal lobe involvement during memory encoding or retrieval varies as a function of the complexity of the task.

The hemispheric encoding/retrieval asymmetry framework [22] predicts prefrontal cortex activations to be left lateralized during episodic encoding and semantic retrieval, and right lateralized during episodic retrieval. Findings consistent with the episodic/semantic retrieval distinction were reported by Hunkin *et al.* [20]. In that study, however, an increase in complexity produced right inferior frontal activations in episodic and semantic conditions, and further increases were associated with left dorsolateral activations. Bilateral medial frontal activations, which are also sensitive to complexity of retrieval, were associated more with semantic than with episodic processing. The orbitofrontal cortex has been identified as a primary region for the encoding of visual information [19], with activation of lateral frontal regions associated with increasing strategic and organizational demands.

Iidaka *et al.* [23] have argued that the consensus attributing episodic encoding to the left prefrontal cortex might have arisen more because of the nature of materials used in imaging studies (i.e. predominantly verbal stimuli) than because of genuine lateralization. Those investigators found that pattern encoding activated the prefrontal cortex bilaterally. Common to word and pattern encoding was left dorsal prefrontal and right cerebellum activation, but a wider network was involved in the latter, including parieto-occipital and premotor regions of both hemispheres. There was little evidence for right prefrontal frontal activation during word retrieval. Kirchoff *et al.* [24] found lateralized activity in the inferior prefrontal cortex and fusiform gyrus, depending on whether encoding involved pictures (right) or words (left). Evidence of left lateralization for episodic retrieval of verbal stimuli was also provided in a functional MRI study reported by Konishi *et al.* [25<sup>\*</sup>]. In that study, episodic retrieval success was associated with predominantly left lateral and medial parietal cortex, and left prefrontal activations.

An interesting examination of sex differences in activation during episodic retrieval was presented by Nyberg *et al.* [26]. A greater increase in anterior cingulate activity during retrieval relative to baseline conditions in women ( $n=17$ ) was linked to the tendency for women to outperform men, the reasoning being that this region is important in executive/attentional control. Areas of the inferior frontal gyrus showed increased activity in men

but decreased activity in women, relative to baseline values. Those authors suggested that inhibition of pathways within these regions, which is believed to play a role in semantic processing [12•,13•], may be important for efficient retrieval of episodic memories. While these interpretations are clearly tentative, the work offers an important step toward the scientific study of a reliable difference in male and female performance.

The primary functions of the hippocampal complex during retrieval remain unresolved. Iidaka *et al.* [16] suggested, as have others [27,28], that the hippocampus might be involved in relatively automatic functions, such as novelty formation. However, this view does not easily fit with other imaging studies of memory retrieval [29,30]. Kirchoff *et al.* [24] have shown that those regions sensitive to novelty effects (including medial temporal and prefrontal areas) also predict subsequent recognition performance.

In summary, it is clear that both frontal and temporal lobe involvement is important in episodic memory formation and retrieval. However, the regions that are activated may crucially depend on the nature of the task and the type of processing required [17,24,31–33]. Further work examining the interactions between frontal and medial temporal regions across different encoding and retrieval conditions should enable some of the controversies in this area of study to be resolved.

### Remote memory

It is generally accepted that early memories are relatively unaffected in organic amnesia, but that the slope of the resulting temporal gradient of memory loss can vary markedly between patient groups and between individual patients. A number of recent studies have examined the pattern of memory loss in patients with retrograde amnesia for information from different periods dating back to childhood, while others have focused on the long-term forgetting of new information over a period of minutes, days and weeks. A central issue in both forms of investigation was the role of the hippocampus in memory consolidation.

### Retrograde amnesia

Evidence for a critical role for the hippocampus in the retrieval of remote episodic memory [34] has been provided by Cipolotti *et al.* [35] and Viskontas and McAndrews [36]. In a patient with lesions largely restricted to the hippocampi (VC), Cipolotti *et al.* [35] found a severe retrograde memory loss encompassing four decades before the onset of amnesia, although their claim that the remote memory deficit was temporally ungraded was not supported by their data. A temporal gradient of episodic memory loss was observed in a

herpes encephalitis patient with medial temporal damage [37•]. However, general cortical atrophy, and clear deficits on frontal lobe/executive tests (verbal fluency, Wisconsin Card Sorting Test) may have contributed to produce this pattern of impairment.

The study of Viskontas *et al.* [36] of 25 ‘temporal lobe epilepsy’ patients with unilateral medial temporal damage (11 right, 14 left) found impairments in episodic memory performance on the Autobiographical Memory Interview [38], but no evidence of a temporal gradient, relative to healthy control individuals. Furthermore, the degree of medial temporal damage showed no association with the extent of remote memory loss. In contrast to the severe impairment in episodic memory, there was no evidence of personal-semantic memory loss, relative to control individuals, at any period (childhood, early adult, recent). Hippocampal consolidation theory [39] was argued against, because this should have rendered episodic and personal-semantic memories equally affected. Instead, the results were interpreted within a multiple trace theory framework [34,40], whereby semantic information is proposed to leave multiple traces over time (a result of repeated retrieval attempts).

### Long-term forgetting rates

Findings inconsistent with hippocampal consolidation theory were presented by Stark and Squire [41] in a functional MRI study of medial temporal activation during visual recognition testing at 3 delays (30 min, 1 day, 1 week). Targets elicited greater activation than foils in hippocampal and parahippocampal regions, but no effect of study–test interval was observed. One implication of these results is that hippocampal activity was necessary at each test period, although those authors suggested that the time span might have been of insufficient duration for observable changes to occur. Indeed, an investigation by Blake *et al.* [42] found verbal retrieval deficits after a delay of 8 weeks in left temporal lobe epilepsy patients, relative to right temporal epilepsy patients and control individuals. All participant groups performed equally well on standard tests of memory retention at 30 min. The results were taken as evidence for a preserved fast consolidation process, which is dependent on the hippocampus, but an impaired slower process of learning, which is more dependent on the neocortical areas [39].

### Summary

To date, the role of medial temporal regions in the retrieval of remote memories remains controversial, not least because of the presence of concomitant, often extensive, damage in many cases. The increased adoption of recent advances in measurement, such as MRI-based volumetric imaging, to provide

precise and detailed lesion information in memory studies [35,43–45], should improve our ability to tackle this difficult issue.

### Semantic memory

The cortical distribution in semantic dementia at various stages of the disease was recently investigated by Mummery *et al.* [46•] using voxel-based morphometry. The six patients studied showed significant left temporal pole atrophy (BA 38), with bilateral involvement in five patients. The atrophy extended to encompass the left amygdaloid complex, left middle and inferior temporal gyri, and the ventro-medial frontal cortex. Those investigators interpreted the frontal involvement as more related to ‘executive’ selection/manipulation of relevant information than to semantic retrieval *per se*, although this has been contested [47,48]. No significant atrophy was observed within the hippocampal complex or entorhinal complex, but the complex nature and distribution of medial temporal regions prevented clear judgement of this important issue. The extent of anterior temporal lobe involvement was correlated with results on the word/picture-matching component of a semantic battery [49], which is consistent with a central role for this region in semantic processing.

A comparison of spelling for orally presented words with predictable and unpredictable sound-to-spelling correspondences showed that semantic dementia patients were especially impaired on the unpredictable items, relative to normal control individuals [50]. Level of spelling success was reflected by word frequency [51], such that, over the period of observation (12–64 months), performance on all but the highest frequency words dropped significantly. However, reading skills showed a clear deterioration only on low frequency exception words. Although acknowledging cases in which no association was found between spelling/reading deficits and semantic impairments [52,53], the authors asserted that, without adequate semantic representation, only words with highly predictable spellings would continue to be spelled appropriately.

Verfaellie *et al.* [54] focused on the extent to which the cortical areas surrounding (but not including) the hippocampus might be involved in semantic learning, given the relatively preserved semantic memory observed in children with a form of amnesia resulting from damage limited to the hippocampus itself [55]. Partial support for a dissociation between episodic and semantic memory processes was presented in a 40-year-old amnesic patient (PS) with apparent purely hippocampal damage after an episode of anoxia. For words and faces of people that became publicly known after the onset of amnesia, recall was severely affected, relative to control individuals, but recognition for appropriate definitions of

the words and judgement of familiarity of faces was largely preserved. In contrast, a 71-year-old postencephalitis amnesic patient (SS) with more extensive damage, including amygdala, and entorhinal and perirhinal cortices, demonstrated severely impaired knowledge of recent vocabulary and faces, irrespective of retrieval demands. Despite rather widespread damage to other temporal regions in SS (including the temporal poles and left infer-lateral temporal cortex), the patient comparison led Verfaellie *et al.* to contend that distinct networks within the medial temporal lobe contribute to episodic and semantic learning, the latter mediated by the subhippocampal cortices.

Hodges *et al.* [56] explored a theory that residual object-specific conceptual knowledge, sustained by problem-solving skills, underlies preserved object use in semantic dementia. On a test of novel tool use [57], those investigators found equivalent scores in patients and in age-matched and education-matched control individuals (although this might have been a product of near-ceiling effects in both groups). However, the patients were severely impaired in the naming and appropriate use of common objects. These findings were interpreted in terms of a disrupted ventral (object identification) pathway, but preserved dorsal (action planning and guidance) pathway in semantic dementia.

### Other issues

Other important issues that have been recently addressed include the dissociability of components of spatial memory and topographical learning, and the role of different sleep phases in memory processing.

### Spatial memory

Recent studies of spatial memory performance [58–60] have revealed dissociations among component processes. In a patient with bilateral hippocampal damage (YR), Holdstock *et al.* [59] found evidence for a greater hippocampal involvement in allocentric than egocentric spatial long-term memory, although this position has been contested [61]. Unfortunately, the potential for strategic recall in both conditions tends to blur the distinction between presumed egocentric and allocentric frames of reference. The position is further complicated by evidence that there are a number of different egocentric frames of reference that can be differentially affected in brain damage [60].

In their study of spatial processing, Bachtold *et al.* [60] had normal, healthy individuals memorize the relative positions of six horizontally aligned figures presented to the left, right or directly in front of them. Results demonstrated hemispace effects during encoding but not recall. Specifically, persons who initially memorized the figures in the left hemispace recalled them more quickly

than did those who initially memorized them in the right hemisphere (although the inclusion of within-group baseline reaction time scores might have strengthened the findings).

### Topographical learning

Barrash *et al.* [62] studied route learning in 127 patients with focal brain damage, finding that primary risk factors for impaired topographical learning included damage in right or left medial occipital and posterior parahippocampal cortices, right hippocampus and right inferotemporal regions. Those authors suggested that the representation of appearance and spatial relationships between places is crucially dependent on posterior parahippocampal gyrus and right hippocampal integrity. There was no evidence for a 'pure' anterograde topographical impairment, because virtually all individuals showed deficits on one or more standard neuropsychological tests of memory, learning or perception.

### Sleep and memory

It is believed that slow wave sleep and rapid eye movement (REM) phases of the sleep cycle may both contribute to memory formation [63]. Maquet *et al.* [64] found that the same brain regions that were activated during execution of a serial reaction time task were found subsequently to be significantly more active during REM sleep in trained individuals than in persons who had not been trained on the task. No experience-dependent modifications were present during slow wave sleep, but those authors were unable to discard the possibility of non-REM phase contributions to memory processing. Although preliminary, these findings offer tangible evidence for the processing of memories during REM sleep.

### Conclusion

It has become increasingly apparent that memory networks are widely distributed throughout the cortex, and that apparently similar deficits can result from damage to different areas [65,66,67]. Indeed, there is now a compelling argument from imaging studies that the same cortical neurones (or group of neurones) may serve a number of different cognitive functions [13,67,68], although it is possible that this may relate more to a lack of image resolution than shared processes. There is also evidence that some of the dissociations reported in the memory literature (e.g. focal retrograde versus focal anterograde amnesia) may have arisen in the absence of proper control for possible confounding factors, such as the relative difficulty of measures and psychological issues [66,69]. However, there remains clear evidence for functional speciality within broad regions, although this may not reflect a straightforward storage and access/retrieval dichotomy.

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