

# Neural bases of learning and memory: functional neuroimaging evidence

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Positron emission tomography and functional magnetic resonance imaging studies have identified brain regions associated with different forms of memory. Working memory has been associated primarily with the bilateral prefrontal and parietal regions; semantic memory with the left prefrontal and temporal regions; episodic memory encoding with the left prefrontal and medial temporal regions; episodic memory retrieval with the right prefrontal, posterior midline and medial temporal regions; and skill learning with the motor, parietal, and subcortical regions. Recent studies have provided higher specificity, by dissociating the neural correlates of different subcomponents of complex memory tasks, and the cognitive roles of different subregions of larger brain areas. *Curr Opin Neuro* 13:415–421. © 2000 Lippincott Williams & Wilkins.

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## Abbreviations

<b>BA</b>	Brodman area
<b>ER-fMRI</b>	event-related functional magnetic resonance imaging
<b>fMRI</b>	functional magnetic resonance imaging
<b>HAROLD</b>	hemispheric asymmetry reduction in old adults
<b>HERA</b>	hemispheric encoding/retrieval asymmetry
<b>HIPER</b>	hippocampal encoding/retrieval model
<b>MTL</b>	medial temporal lobe
<b>PET</b>	positron emission tomography
<b>PFC</b>	prefrontal cortex

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## Introduction

The neural bases of learning and memory can be investigated at very different levels—from molecules to systems—and with very different methods—from genetics to functional neuroimaging. The present review focuses on the system level, with *positron emission tomography* (PET) and *functional magnetic resonance imaging* (fMRI) as the primary methods.

There are many ways of classifying memory functions, but most taxonomies distinguish between working memory, semantic memory, episodic memory, and skill learning. Working memory refers to the maintenance and manipulation of information in short-term memory; semantic memory to general knowledge of the world; episodic memory to memory for personally experienced events; and skill learning to the gradual acquisition of motor and non-motor abilities [1].

Table 1 summarizes the most typical activations for these memory functions in PET and fMRI studies until December 1998 [2\*]. Below, we discuss the patterns in Table 1, review recent (1999–2000) PET/fMRI studies with healthy young adults, and summarize some results from PET/fMRI memory studies with healthy old adults.

## Working memory

As illustrated by Table 1, working memory is typically associated with activations in the prefrontal cortex (PFC), anterior cingulate, parietal, and occipital regions (for a review, see [3]). Verbal tasks often activate the left PFC Brodmann area (BA) 44 (Broca's area), which may be involved in phonological rehearsal [4–6], and left parietal BA 40, which may be involved in phonological storage [4,5,7]. Object tasks tend to activate the temporal-occipital regions (BA 37), whereas spatial tasks tend to activate the parietal-occipital regions (BA 7 and 19). This pattern is consistent with the distinction between a ventral pathway for object processing ('what') and a dorsal pathway for spatial processing ('where') [8].

Several recent studies have focused on the distinction between two fundamental working-memory processes: the passive *maintenance* of information in short-term memory and the active *manipulation* of this information [3]. Available evidence suggests that ventrolateral PFC is associated with maintenance (as well with response selection and interference [9,10,11\*,12]), whereas dorso-

**Table 1. Typical positron emission tomography/functional magnetic resonance imaging activations during memory tests**

Process	Frontal			Midline			Parietal		Temporal			Occipital			Subcortical																		
	10	9	46	1	47	45	44	6	8	4	32	24	23	31	7	40	39	38	in	42	22	21	20	mt	37	19	18	17	bg	th	cb		
Working memory																																	
Verbal/numeric			*	*											*																	*	
Object			*	*		*	○				+				*	*									*							*	
Spatial			*	*		*									*	*										*	*	*				*	
Problem solving	*	*	*		○	*		*	*		+				*	*	*									*	*	*				*	
Semantic retrieval																																	
Categorization						○																	○										
Generation						○	○				+																						
Episodic encoding																																	
Verbal			○	○		○																			○								
Object			○	○		○	*	*			+													*	*	*	*	*	+				*
Spatial															*									*	*	*	*					*	
Episodic retrieval																																	
Verbal	*	*	*		*						+				+										*	*	*	*	*				*
Non-verbal	*	*	*		*			*							+									*	*	*	*	*					*
Retrieval success	*	*	*		*										+	○								*	*	*	*	*					*
Retrieval effort	*	*	*		○																												
Retrieval mode	*	*	*		○						+					*																	*
Context memory								*							*	*																	*
Skill learning																																	
Motor										○					*	*																*	
Non-motor															*	*											*	*					*

Symbols: ○ left lateral; ● right lateral; \* bilateral lateral; ≤ left medial; + bilateral midline;

Proportion of contrasts in each subsection: ● 40–50%; ● 51–70%; ● 71–100%. Activations were displayed as lateralized if there were at least twice as many activations in one hemisphere as in the other (bilateral activations counted for both hemispheres).

From Cabeza and Nyberg [2\*].

lateral PFC is associated with manipulation (as well as with maintenance) [see also refs 7,13,14\*]. Activity in dorsolateral PFC has been shown to vary as a function of load (i.e. number of items held in working memory), showing an increasing [15] or inverted-U [16] response. Event-related fMRI (ER-fMRI) studies, which allow separate activity measures for the encoding, retention, encoding-, retention-, and retrieval phases of working memory, have associated load-related dorsolateral PFC activity not with delay [14\*,17\*], but with the encoding phase [17\*]. Dorsolateral PFC activity has also been found to increase in conditions involving manipulation [13,14\*,17\*,18,19]. In contrast, the bilateral ventrolateral PFC has been associated with maintenance [13,17\*,19] and target tracking [20], and the left ventrolateral PFC with response selection [9,10] and interference resolution [11\*,12]. One possibility is that ventrolateral PFC processes and filters out incoming information before it is manipulated by the dorsolateral PFC (SA Bunge, JE Desmond, GH Glover, JDE Gabrieli, in preparation).

In summary, PET/fMRI data are consistent with the idea that the ventrolateral PFC is primarily involved in simple short-term memory operations whereas dorsolateral PFC is primarily involved in executive functions and monitoring [21–23]. By contrast, the hypothesis that ventrolateral PFC is associated with object working memory and dorsolateral PFC with spatial working memory has been challenged by a recent study [24], which found evidence for the

object/spatial distinction in posterior regions (i.e. temporal versus parieto-occipital) but not in PFC (for discussions, see [25,26]).

### Semantic memory retrieval

Table 1 suggests that semantic memory is primarily associated with activations in left PFC and temporal regions (for a review, see [27]). Activations in left PFC BA 45 may reflect semantic processing and those in left PFC BA 44 (i.e. Broca's area), articulatory processes during word generation [2\*]. Temporal activations in BA 21 are common for both verbal and pictorial stimuli, suggesting amodal semantic processing [2\*]. Several studies dissociated the neural correlates of different kinds of knowledge. Knowledge about animals was associated with occipital activations [28–30] and knowledge about tools with PFC activations [28,29]. Knowledge about colour was associated with colour perception regions in the fusiform gyrus, and knowledge about actions with motion perception regions in the temporo-occipital cortex [31].

Recent studies have emphasized two topics: (i) the role of left PFC in semantic memory; and (ii) dissociations between different kinds of knowledge (animals versus tools, etc.). Confirming the association between left PFC and semantic retrieval, a recent study [32] found that left PFC was more activated when subjects named the colour of objects based on their knowledge of the world (semantic memory)

rather than on a new learning event (episodic memory). Moreover, left PFC activity during semantic retrieval in bilingual individuals was not affected by the language of presentation, suggesting that it reflects access to a common semantic system [33]. However, other studies have suggested that left PFC activity may reflect top-down processing [34] or the selection of competing alternatives [see also refs 9,10]. As for dissociations between different kinds of knowledge, a recent fMRI study associated animal knowledge with the medial occipital gyrus, lateral fusiform gyrus, and superior temporal sulcus, and tool knowledge with the inferior occipital, medial fusiform, and middle temporal gyri [35,36]. In that study, activations for animals were clustered with activations for faces, and activations for tools were clustered with activations for houses. This pattern may reflect category-specific systems (e.g. biological versus non-biological) or it may mirror the organization of sensory and motor systems. For example, activations for animals and faces in the posterior superior temporal sulcus were close to regions associated with the perception of biological motion. However, semantic retrieval regions do not always overlap with perception regions. For example, the retrieval of colour information was found to engage occipital regions more lateral than those associated with colour perception [37].

### Episodic memory

As illustrated by Table 1, episodic encoding and retrieval engage PFC, medial temporal lobe (MTL), and parieto-occipital regions (for a review, see [38]). PFC activations tend to be left lateralized during encoding and right lateralized during retrieval, a pattern known as hemispheric encoding/retrieval asymmetry (HERA) [39–41]. Encoding activations in left BA 45, 44, and 9/46 have been respectively attributed to semantic processing, rote rehearsal, and working memory operations during encoding [2•]. Retrieval activity in sub-regions of the PFC has been found to increase (retrieval success [42]), decrease (retrieval effort [43]), and remain constant (retrieval mode [44]) as a function of the amount of information recovered. MTL activity during encoding tends to be left lateralized for verbal materials and bilateral for non-verbal materials [45], and has been found to predict performance in subsequent memory tests [46–49]. MTL regions may interact with material-specific regions during encoding. For example, consistent with the dorsal/ventral pathway distinction [8], parietal activations are more frequent for spatial information and occipito-temporal activations for object information [50]. MTL activations during retrieval are less frequent than during encoding, but have been strongly linked to episodic recovery [43,51,52]. Retrieval activations in the cuneus/precuneus region (e.g. BA 31, midline BA

7) have been attributed to imagery [53] and retrieval success [54], and retrieval activations in the cerebellum have been attributed to self-initiated retrieval operations [55,56].

Recent studies shed light on the functional roles of PFC regions during encoding and retrieval. For example, one study [57] associated impaired encoding during divided attention with reduced left PFC activity. Encoding-related activity in some PFC regions is affected by the type of stimuli, with left PFC more active for verbal stimuli and right PFC for pictorial stimuli [58,59]. During retrieval, a recent ER-fMRI study (R. Cabeza, S.M. Rao, A.D. Wagner, *et al.*, in preparation) found that right polar PFC was similarly activated for old and new items (retrieval mode, [60,61,62•]), bilateral dorsolateral PFC was more activated for old than for new items (retrieval success [60,63,64•,65]), and left ventrolateral PFC was more activated for new than for old items (retrieval effort [65–67]). This study thus found a within-subject dissociation between the involvement of different PFC regions in component processes of retrieval (for other within-subject dissociations, see [60,63,65,68]). It has been suggested that the right lateralization of retrieval activity described in the HERA model is primarily driven by retrieval mode activations [61], whereas left PFC activity during episodic retrieval reflects effortful semantic [69] or generation [70] operations.

Recent studies have also clarified the involvement of the MTL in encoding and retrieval [for a review, see ref. 71]. One issue has been the localization of encoding and retrieval activations within the MTL. A meta-analysis of PET data concluded that encoding activations tend to engage more anterior hippocampal regions, and retrieval activations more posterior hippocampal regions, a pattern called hippocampal encoding/retrieval (HIPER) model [72]. Although earlier fMRI results appeared inconsistent with this model [73], two recent fMRI studies provide support for HIPER [74–76]. Another issue has been the specific role of the MTL in encoding and retrieval. In the case of encoding, two recent PET studies linked hippocampal activity with the formation of associations [77,78]. In the case of retrieval, an ER-fMRI study dissociated a posterior hippocampal region, which was more activated for targets than for semantically related lures, from an anterior region, which was similarly activated for both kinds of items. The former activation may reflect the recovery of perceptual information, whereas the latter seems to reflect the recovery of semantic/associative information [69].

### Skill learning

Motor skill learning is associated with the activation of motor areas of the frontal lobes [2•], notably the

premotor and supplementary motor cortex (lateral and medial BA 6). Regions of the parietal lobes have also consistently been involved in motor skill learning, and fronto-parietal interactions have been emphasized. Furthermore, cerebellar activation has been observed in several studies. The activation pattern for non-motor skill learning is similar to that for motor skill learning [2•].

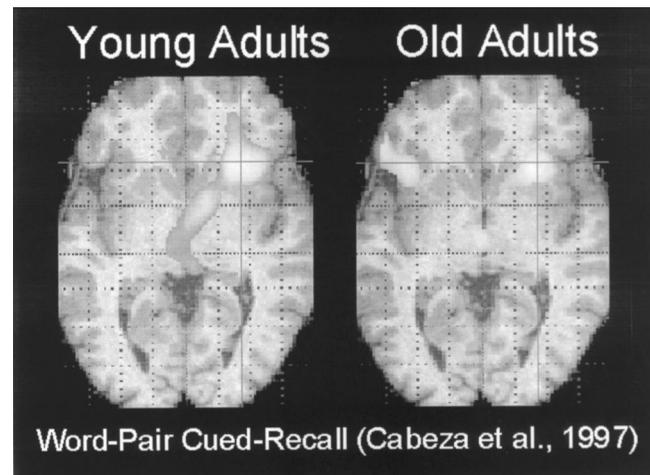
A recent fMRI study of motor skill learning examined the learning of complex finger movements in piano players and non-musicians [79]. As learning progressed, piano players showed increased activity in the contra-lateral hand area, whereas non-musicians showed a decline in primary motor cortex activation. These results suggest that practice-related changes in activity are influenced by the pre-practice experience of the subjects. A study on non-motor skill learning [80] investigated changes in brain activity during artificial grammar learning. As subjects learned grammar rules they relied less on memory for specific instances. Grammar learning was associated with an increase in left PFC activity, whereas reduced instance memory was associated with an attenuation of right PFC activity [81•].

### Functional neuroimaging of ageing and memory

Functional neuroimaging of cognitive ageing is a relatively new field, and several methodological issues are still unsolved (for a review, see [82]), such as the effect of ageing on the coupling of neural activity and fMRI measures [83]. In the memory domain, PET and fMRI studies of ageing have focused primarily on working memory and episodic memory. During working memory tasks, older adults often showed weaker PFC activations in the hemisphere primarily engaged by the young but stronger PFC activations in the contralateral hemisphere [84–86]. Age-related decreases in the dorsolateral PFC have been associated with manipulation deficits [87], and decreases in the left ventrolateral PFC with inhibition deficits [88]. The effects of ageing on working memory may also affect the MTL [85] and interactions between different regions [89].

Age-related differences in activation during episodic memory were found for both encoding and retrieval. During encoding, age-related decreases in activation were observed primarily in the left PFC [69,90,91] and MTL [91,92], and were attenuated by conditions favouring encoding, such as pictorial stimuli and semantic processing [92]. During retrieval, they were typically observed in the right PFC [60,90,93,94] but not in the MTL [93–95]. This last pattern is consistent with evidence that age-related structural and functional decline is more pronounced in the PFC than in the MTL [93].

Figure 1. Brain regions more activated during word-pair cued-recall than during reading [69].



Frontal activity was right lateralized in young adults but bilateral in old adults, a pattern consistent with a hemispheric asymmetry reduction in old adults pattern.

An observation in several studies is that lateralized patterns of brain activity tend to be less pronounced for old than for young adults. This phenomenon has been described as hemispheric asymmetry reduction in old adults (HAROLD) (R. Cabeza, in preparation). In the case of episodic memory retrieval, HAROLD summarizes evidence that PFC activity is right lateralized in young adults but bilateral in old adults. This has been observed for word-pair cued-recall (see Fig. 1 [69]), word-stem cued-recall [54], word recognition [96], and face recognition [97]. During working memory, HAROLD was found for both verbal and spatial tasks [84]. A pessimistic account of HAROLD is that the elderly have difficulty engaging specialized neural mechanisms, whereas an optimistic account is that bilateral PFC activation signals functional compensation: old adults may compensate neurocognitive deficits by recruiting both PFC for tasks in which young adults recruit only one PFC [69].

### Conclusion

It is clear from the above review that learning and memory involve large-scale networks of brain regions. The main components include: (i) PFC and parietal regions for working memory; (ii) left PFC and temporal regions for semantic memory; (iii) PFC, parietal, and MTL regions for episodic memory; and (iv) motor, PFC, parietal, and cerebellar regions for skill learning. In advanced age, activity in some of these regions decreases, and additional regions seem to come into play.

A striking feature of Table 1 is that some brain regions are associated with different forms of learning and memory.

For example, the right BA 46 is commonly engaged by working memory and episodic retrieval tasks. Also, the parietal BA 7 is usually activated by working memory, episodic memory, and skill learning tasks. A crucial question is whether these common activations reflect shared component processes. Another possibility is that the spatial resolution of available imaging techniques is not sufficient to dissociate subregions within the overlapping areas. A third possibility is that a brain region can have different functional roles depending on its interactions with other brain regions [98\*].

An important goal of future functional neuroimaging research will be not only to look for differences in the neural correlates of different cognitive processes but also for commonalities in activation patterns. The *local approach* described here and in most previous functional neuroimaging studies is to relate the role of each brain region to a process within a cognitive domain (e.g. relate to dorsolateral PFC the manipulation of working memory contents). The *global approach*, which is reflected by the columns of Table 1, is to associate the role of each brain region to a general operation that is recruited by a variety of tasks (e.g. parieto-occipital involvement in spatial working memory, spatial episodic memory, etc.). The more recent *network approach* is to interpret the role of each region (e.g. dorsolateral PFC) in relation to other regions engaged by the same task (e.g. posterior parietal or MTL regions). We believe that a full understanding of the neural basis of learning and memory, as well as cognition in general, requires the integration of these complementary approaches.

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