Ageing: age-related changes in episodic and working memory

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1. Introduction

Ageing is associated with ongoing deterioration of not only the anatomy and physiology of our brain, but our cognitive abilities as well. As our brain shrinks and its functions decline, cognitive processes become slower and start to fail. Deficits in memory function are among the most-heard complaints in older adults, and cognitive research generally agrees with these self-observations. Modest difficulties in learning and memory can be found, to some extent, in all older adults. Understanding age-associated deficits in memory is important for two reasons. First, in view of the growing number of older adults in today’s society, cognitive ageing is increasingly becoming a problem in general health care, and effective therapeutic intervention methods can only be developed on the basis of knowledge obtained through fundamental research. Second, there is a subgroup of elderly whose memory impairments are more severe, preventing normal functioning in their environment. In these persons, such memory impairments can be the earliest manifestation of pathological age-related conditions such as Alzheimer’s dementia (AD). Particularly in the early stages of this disease, the differentiation from normal, age-related memory impairments is very difficult. Thus, it is important to outline which memory impairments can be regarded as a correlate of normal ageing and which are associated with age-related pathology.

The two forms of memory that are most affected by age are working memory and episodic memory. Working memory (WM) refers to the short-term memory maintenance and simultaneous manipulation of information. Clinical and functional neuroimaging evidence indicates that WM is particularly dependent on the functions of the prefrontal cortex (PFC) and the parietal cortex. Episodic memory (EM) refers to the encoding and retrieval of personally experienced events. Clinical studies have shown that EM is primarily dependent on the integrity of the medial temporal lobe (MTL) memory system. However, functional neuroimaging studies have also emphasized the contributions of PFC to EM processes.

Due to increased access to functional brain imaging techniques such as FMRI, ageing research has now started to focus on the relation between age-related changes in memory and changes in brain function. FMRI provides the ideal method to investigate patterns of
neurocognitive decline because changes in brain activity can be directly linked to the effects of ageing on behavioural measures, providing a bridge between cerebral ageing and cognitive ageing. One popular neurocognitive view is that the decline in memory associated with healthy ageing results from a selective decline in frontal regions, whereas degradation of other brain regions, such as the MTL, is a hallmark of pathological age-related conditions\textsuperscript{7-9}. In this chapter, we examine this idea by reviewing findings from fMRI studies of healthy ageing and memory with a focus on age-related changes in prefrontal cortex (PFC) and MTL regions. In our review, we also include studies that used an alternative brain imaging technique based on cerebral blood flow, namely positron emission tomography (PET). Although the field has generally shifted toward the use of fMRI, because of its high temporal and spatial resolution and its non-invasive character, the early landmark studies of ageing and memory have primarily used PET.

In relation to these findings, we will also address two major cognitive accounts of age-related memory decline, the resource deficit theory\textsuperscript{10} and the associative deficit theory\textsuperscript{11}. The resource deficit theory of cognitive ageing posits that ageing reduces the availability of certain cognitive resources such as attention. In turn, older adults perform poorer on cognitive tasks with increased cognitive load, requiring greater self-initiated processing. The associative deficit theory posits that age-related deficits in binding underlie age-related memory decline. Binding or co-joining two pieces of information into one cohesive unit is a cognitive process that underlies many basic cognitive functions — and can require significant cognitive resources to execute\textsuperscript{11}.

The chapter has four main parts. In the first part, we begin with a brief overview of behavioural evidence indicating how WM and EM functions change as we age, and also discuss the brain changes that accompany the ageing process. In the second part, we take an in-depth look at functional neuroimaging studies of WM and EM that revealed age-related changes in MTL and/or PFC regions. In the third part, we discuss different interpretations of age-related memory decline that have emerged from these findings and how they relate to the resource and associative deficit theories of ageing. We also discuss the possible implications for clinical applications of fMRI aimed at an earlier diagnosis of age-related pathological conditions. Finally, we discuss some current issues and future directions.

2. **Age-related changes in brain and behaviour**

2.1 **Behavioural changes**

2.1.1 **Working memory**

WM is considered to operate as a mental blackboard for computations that subserve higher-level processing such as language, problem solving, and reasoning\textsuperscript{12,13}. Within WM, a dissociation has been proposed between two different maintenance systems, a subvocal rehearsal system for verbal and phonological information (phonological loop), and a visuospatial storage system (visuospatial sketchpad). These two systems are under the control of a central processing unit, termed the central executive\textsuperscript{13}.

In general, behavioural studies have indicated that age differences in WM become larger with increasing task difficulty, presumably because of a greater reliance on executive processes.
processes. Increases in complexity include additional processing of information held in working memory\textsuperscript{14,15}, manipulations of divided attention\textsuperscript{16,17}, and proactive interference\textsuperscript{18}. For instance, a consistent finding is that simple maintenance abilities are relatively spared in older adults, while performance is affected disproportionally when WM tasks require additional processing of information\textsuperscript{19,20}. Dobbs and Rule\textsuperscript{14} compared performance on several WM tasks that differed in their maintenance and processing requirements in five groups ranging in age between 30 and 70+ years. They reported little differences on simple forward and backward digit span tasks, but substantial age deficits on an auditory version of the N-back task, which required maintenance of target information and simultaneous processing of new information. Salthouse and colleagues\textsuperscript{21} also performed a large-scale WM experiment involving 120 males ranging in age from 20 to 79 years. Age differences in performance between younger and older adults increased with both task complexity and increased demands on processing resources. Similarly, Wiegersma and Meertse\textsuperscript{14} found no age-related deficits on WM tasks involving simple reproduction of sequenced items, but age-related decline in performance when the tasks required subjective re-ordering of the sequenced items.

Older adults are also more susceptible to divided attention manipulations during WM performance than are younger adults\textsuperscript{19,20}. For example, in a study by West\textsuperscript{16}, young and older adults performed a version of the N-back task both with and without distracters. He found that older adults were much more impaired by distraction. Similar results were obtained in an event-related brain potential study by Chao and Knight\textsuperscript{17}. They compared young and older adults on an auditory WM task, which required the short-term maintenance of a single tone both with and without distracting tones. They found that older adults showed larger auditory evoked responses to the distracters, and also showed greater interference from these distracters, resulting in poorer performance in older than in younger adults.

Finally, older adults are also more susceptible to effects of proactive interference (PI) in WM tasks\textsuperscript{18}. Bowles and Salthouse (2003) found that, on two separate WM tasks, older adults demonstrated increased difficulty across the second half of trials. Results were interpreted as reflecting greater susceptibility in ageing to PI, and that this type of interference contributes significantly to age-related decline in WM. Furthermore, when interference is removed from WM span tasks, older adults demonstrate improvements in overall span scores\textsuperscript{22} and improved recall in cognitive tasks (e.g. prose recall)\textsuperscript{23}.

Although behavioural evidence suggests that age deficits in WM are most pronounced on tasks that put a greater demand on executive processes, the possibility of age-related deficits in ‘simple’ WM tasks should not be ignored. It has been suggested that deficits in maintenance tasks of WM may just be undetectable at the behavioural level\textsuperscript{20,24}. Reuter–Lorenz proposes that rote maintenance and involved processing operations decline with age, but an increased reliance on executive processes can mask declines in the former in older adults. As a result, older adults are left with less executive resources to meet increased task demands. Furthermore, this increase in activation necessary for maintenance and storage operations acts as a compensatory mechanism, reducing age-related behavioural differences on ‘simple’ WM tasks (see below).
2.1.2 Episodic memory

Age-related deficits in EM may reflect difficulties in the incorporation of new information into the episodic memory store, or episodic encoding (EE), and/or in recovery of stored information, or episodic retrieval (ER). Behavioural work has tried to separate the contributions of deficits in EE and ER to age-related EM decline by applying separate manipulations to each phase. Behavioural studies have indicated that age-related decline in EM is associated with deficits in both EE and ER phases. Like studies of WM, age deficits generally become greater when there is more demand on executive functions or little environmental support. We discuss some findings on EE and ER in the following sections.

Episodic encoding  It has been proposed that age-related decline in EM is associated primarily with problems during the encoding phase of EM tasks. This idea is based on the finding that interference during EE compared to ER results in disproportionate age differences in memory. For instance, in a study by Park et al., young and older adults studied categorized words while performing a number-monitoring task during encoding, retrieval, or at both times. Older adults’ memory performance was disproportionately impaired when attention was divided at EE, but there was a similar effect of divided attention on both groups during ER.

Age deficits in EE are most pronounced when there is little environmental support to help encoding. For instance, age differences tend to be larger when young and older adults intentionally try to encode a list of study items than when a deep semantic processing task is used to guide encoding. In a study by Craik and colleagues, young and older adults encoded a list of words either with or without an associative, short descriptive phrase. Age deficits were less pronounced when the encoded words were accompanied by the descriptive phrases. Similarly, age differences in the encoding of associations between study items are much greater when there is no apparent link between the elements. For example, Smith et al. found that age differences in recall of a target picture to a context picture was better when sentences were generated that integrated the pictures or when there was already a pre-existent relationship between the pictures. They interpreted these findings in terms of age differences in self-initiated processing.

As mentioned, an alternative interpretation of age deficits in encoding of contextual information is that older adults show selective deficits in associative memory or binding, which may be related to reduced MTL function. Evidence for a deficit in binding comes from studies showing that older adults consistently exhibit age-related deficits on tasks requiring binding, even when memory for individual features is intact. Chalfonte and Johnson (1996) tested age differences in encoding of both colour and item information across three experiments. While no effect of age was found for individual features, older adults exhibited significant deficits in recognition for combined features compared to younger adults. Additionally, age differences in memory for bound features persisted across various encoding instructions. Similar results were reported by Mitchell et al. who also interpreted results as an age-related deficit in co-joining/binding features in memory. Recent studies have indicated that this associative deficit is not limited to arbitrary
associations (e.g. word–colour, item–location), but also more ecologically valid/meaningful pairings such as name–face associations\textsuperscript{11,32}. Thus, available evidence suggests that, even though older adults show deficits in general memory performance, this deficit is greater for associative memory.

**Episodic retrieval** Despite the evidence suggesting greater deficits in EE, age-related memory deficits are present during ER as well. In line with the findings on WM, age differences in retrieval become larger on tasks that put a greater demand on executive functions. Older adults experience more difficulties on free recall and source memory tasks, which require a completely self-initiated search, than on recognition tasks, in which the study item is provided and one merely has to decide whether it was part of a previously studied list or not\textsuperscript{33–35}. One explanation for this finding is that older adults do not spontaneously produce retrieval cues to guide the search process.

In line with this idea, several studies have found that age deficits reduced when cues are provided. That is, older adults benefit when provided with environmental support at retrieval\textsuperscript{27,36}. In the Park et al. study, older adults showed no age deficit following incidental word encoding when retrieval involved an implicit word–stem completion task. Given the first 2–4 letters of the studied word, older adults showed equivalent performance to young when asked to complete the word–stem. The benefit of increased environmental support leads to the distinction between differential decline of familiarity and recollection processes.

According to dual-process models, recognition memory can be based on the recovery of specific contextual details (recollection) or on the feeling that an event is old or new in the absence of confirmatory information (familiarity). Several studies have reported an increased reliance on familiarity processes in older adults during item recognition\textsuperscript{37,38}. For example, Parkin and Walter\textsuperscript{39} used the remember/know (R/K) paradigm in which participants indicate whether their recognition judgement was based on recollection (R) or familiarity (K). They found that older adults made fewer R responses and more K responses than younger adults. Furthermore, the extent to which older adults relied on familiarity-based recognition correlated with neuropsychological indices of frontal lobe dysfunction.

In line with the aforementioned deficits in associative encoding, older adults are also less accurate in recalling information associated with the context in which an item was encoded, including item colour, case, or font of words\textsuperscript{40}, domain presentation (e.g. auditory or visual)\textsuperscript{41}, and speaker gender\textsuperscript{42}. For example, when given a list of made-up facts (e.g. 'Bob Hope's father was a fireman') and tested on them a week later, both younger and older adults can successfully recall the items, but older adults are impaired at knowing where they had first learned the information\textsuperscript{43}. Similarly, older adults are impaired at knowing where on a computer screen an item was presented, though they have little problem in recognition of items themselves\textsuperscript{44}. Thus, impaired memory for context appears to exceed memory impairments for individual items. A prevailing theory accounting for these context deficits involves age-related difficulties in binding pieces of information in memory.
2.2 Brain changes

The effects of ageing on the brain occur at many levels, from genes to gross anatomy. Reviewing this large research domain is beyond the scope of this chapter. Here, we only mention two examples of cerebral ageing measures that have been directly related to cognitive decline: brain atrophy and dopamine deficits.

2.2.1 Brain atrophy

In post-mortem and *in vivo* studies, the brains of older adults tend to have lower volumes of gray matter than young adult brains\(^{45}\). These volume declines are not only related to a loss of cells, but can also be ascribed to lower synaptic densities in older adults\(^{46}\). Cross-sectional studies suggest that the volume of gray matter declines linearly with ageing, whereas white matter volume increases during young age, plateaus during young adulthood and middle age, and declines during old age — an inverted U function\(^{47}\).

Apart from differential age effects on gray and white matter volume, the relation between age and brain volume is also not uniform across different brain regions. The region most affected is the PFC, whereas other regions, such as the occipital cortex, are relatively unaffected by the ageing process\(^{48}\).

PFC volume has been seen to decrease at an average rate of 5% per decade beginning in the 20s\(^{47}\), largely due to decreases in synaptic density. The disproportional effect of ageing on PFC volume, together with the finding that age differences tend to be larger on tasks assumed to depend on PFC function, has led to the proposal that age deficits are primarily the result of frontal decline (for a review, see\(^{9}\)). However, other brain regions, including the basal ganglia\(^{49,50}\) and the thalamus\(^{51-53}\) also show a pronounced decline in brain volume with increasing age. In fact, in the last decades of normal life, volumetric changes in PFC do not differ from those in other neocortical areas\(^{54,55}\).

Furthermore, MTL volume also declines with age, even though not all structures are equally affected. The hippocampus exhibits a significant volume loss of 2–3% per decade, whereas the rhinal cortex appears to be much less affected by healthy ageing\(^{56}\). For instance, a recent cross-sectional study by Raz and colleagues\(^{56}\) found substantial age-related shrinkage not only in the prefrontal cortex (Fig. 1a) but also in the hippocampus (Fig. 1b), which was greatest in individuals with hypertension. In contrast, mean age-related shrinkage of the rhinal cortex was minimal (Fig. 1c).

![Fig. 4.1](image-url) Longitudinal changes in volumes of prefrontal cortex (a), hippocampus (b), and rhinal cortex (c) as a function of baseline age. (Reproduced with permission from Oxford University Press\(^{56}\)).
Several studies have suggested that the decline in hippocampal volume contributes to age deficits in WM. For instance, Golomb et al. investigated the link between hippocampal atrophy and memory performance in a group of healthy older adults. They found that, after controlling for such factors as age, education, and vocabulary skills, individuals with hippocampal atrophy performed more poorly on memory tests, compared to those with no decline. Furthermore, as part of a longitudinal study on memory function, Golomb et al. found a significant correlation between hippocampal atrophy across a 3.8 year span and decline in memory performance in a group of older adults (mean age = 68.4 years).

2.2.2 Dopamine deficits

Ageing affects not only brain anatomy but also brain physiology, including the function of neurotransmitter systems such as serotonin, acetylcholine, and dopamine. Associated with volume decrements in PFC are decreases in dopamine (DA) concentration and transporter availability. Additionally, dopamine D2 receptor density declines at a rate of 8% per decade beginning in the 40s. There is abundant evidence that dopamine (DA) systems play an important role not only in motor but also in higher-order cognitive functions. DA function can be measured in vivo using PET. There is strong evidence of age-related losses in post- and presynaptic DA markers, which may reflect decreases in the number of neurons, the number of synapses per neuron, and/or the expression of receptor proteins in each neuron. D1 and D2 receptor binding declines from early adulthood at a rate of 4–10% per decade, and this decline is correlated with the decline of dopamine transporter, possibly reflecting a common causal mechanism.

DA deficits in Parkinson’s disease (within the fronto-striatal system) are accompanied by reduction in processing speed, affecting WM. Thus, it has been argued that this form of pathological ageing may be integral in composing a model for fronto-striatal cognitive deficits observed in normal ageing. In support of this idea, cognitive performance on a wide range of tasks has been shown to correlate with DA functioning, exhibiting a critical role of DA in cognitive processes. In tasks involving episodic memory and perceptual speed, decreased performance with ageing was significantly correlated with D2 receptor availability and binding. For instance, Volkow and colleagues used PET to examine the relationship between brain dopamine activity and tasks of motor and cognitive functioning across healthy individuals ranging in age between 24 and 86 years. Availability of D2 receptor correlated with tasks mediated by frontal brain regions (e.g. Wisconsin Card Sorting Test, Stroop Colour–Word Test). While the availability of D2 receptors declined with age, these correlations remained significant after controlling for age effects, suggesting that DA may influence cognition irrespective of age.

3. Functional neuroimaging studies of WM and EM

Cognitive ageing studies have described the effects of ageing on behavioural performance, and neurobiological studies have characterized the effects of ageing on the brain. Functional neuroimaging studies provide a bridge between these two domains by directly measuring age-related differences in brain activity during the performance of cognitive tasks. In general, these studies find brain regions that show weaker activity...
in older than in younger adults, as well as regions that are recruited by older adults to a greater extent than young adults. Whereas age-related decreases in activation are usually attributed to cognitive deficits in older adults, age-related increases in activation are often interpreted as reflecting compensatory mechanisms in the ageing brain.

Regarding WM and EM functions, the most critical regions are PFC and MTL. Functional neuroimaging studies of cognitive ageing frequently find age-related changes in these two regions. In the case of PFC, the most consistent finding has been an age-related reduction in lateralization. This evidence has been conceptualized in a model called Hemispheric Asymmetry Reduction in Older Adults (HAROLD) which states that, under similar conditions, PFC activity tends to be less lateralized in older than in younger adults\(^69\). This model is supported by functional neuroimaging, electrophysiological, and behavioural evidence in the domains of episodic memory, semantic memory, working memory, perception, and inhibitory control\(^70\). In the case of MTL, the most consistent finding has been an age-related reduction in activity, particularly during EM studies. However, recent studies suggest that not all MTL regions show reduced activity in older adults. Actually, some MTL regions show preserved or increased activity in older adults, possibly reflecting differential age effects on various EM processes.

In this section, we first review the effects of ageing on PFC activation for both WM and EM tasks. Then, we turn to the effects of ageing on MTL activation as it relates to these cognitive processes. Although the number of studies is still too scarce to identify clear patterns in the data and a considerable amount of variability still remains unexplained, we try to emphasize the most consistent findings across studies. Table 4.1 presents an overview of reported age differences in PFC and MTL activity grouped by memory domain and ordered by place of discussion in this review section.

### Prefrontal cortex

#### Working memory

Imaging studies of ageing and WM function have shown altered patterns of activation in older compared to younger adults, particularly in frontal regions. Generally, ageing is associated with increases in task-related PFC activity, which is in turn associated with better performance\(^71,72\). Hence, increases in PFC activation during WM tasks have been usually interpreted as compensatory. Additionally, PFC activity in older adults is not only greater overall but is often more bilateral, exhibiting the aforementioned HAROLD pattern.

Age-related increases in PFC activity were found by Grossman et al.\(^73\) in a study of sentence comprehension that manipulated verbal WM demands (short vs. long antecedent noun — gap linkage). Despite similar recruitment of a semantic network across age groups, there were age differences in recruitment of areas associated with a verbal WM network. Compared to younger adults, older adults showed less activation in the left parietal cortex, but increased activation in the left premotor cortex and dorsal portions of left inferior PFC. This up-regulation of PFC areas within the verbal WM network was viewed as compensatory for older adults, whose performance did not differ from that of younger participants.
Table 4.1  Age differences in PFC and MTL activity during working memory, episodic encoding, and retrieval.

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>PFC</th>
<th>MTL</th>
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<td>LEFT</td>
<td>RIGHT</td>
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<tr>
<td>WORKING MEMORY</td>
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<td>F Grossman 02</td>
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<td>F Rypera 00</td>
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<td>●</td>
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<tr>
<td>F Rypera 01</td>
<td>●  ●</td>
<td>●</td>
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<tr>
<td>F Reuter-L. 00</td>
<td>●  ●</td>
<td>●</td>
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<tr>
<td>P Reuter-L. 00</td>
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<td>●</td>
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<tr>
<td>P Park 03</td>
<td>●  ●</td>
<td>●</td>
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<tr>
<td>F Cabeza 04</td>
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<td>●</td>
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<tr>
<td>F Mitchell 00</td>
<td>●  ●</td>
<td>●</td>
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<tr>
<td>P Grady 06</td>
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<td>●</td>
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<tr>
<td>P Grady 95</td>
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<tr>
<td>EPISODIC MEMORY ENCODING</td>
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<td>P Cabeza 97</td>
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<td>P Anderson 00</td>
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<td>F Stebbins 02</td>
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<td>F Rosen 02</td>
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<td>F Daselaar 03b</td>
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<td>F Morcom 03</td>
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<td>F Gutcheese 06</td>
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<td>P Grady 02</td>
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<td>P Grady 95</td>
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<td>F Logan 02 exp 1</td>
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<td>F Logan 02 exp 2</td>
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<td>EPISODIC MEMORY RETRIEVAL</td>
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<td>P Cabeza 97</td>
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<td>P Madden 99</td>
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<td>P Cabeza 00</td>
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<td>F Daselaar 03b</td>
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<td>F Schacter 96</td>
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<td>F Schacter 96</td>
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<td>P Bäckman 97</td>
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<td>P Cabeza 00</td>
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<td>F Cabeza 02</td>
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<td>F Dasalaar 06</td>
<td>●  ●</td>
<td>●</td>
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Symbols: ● = regions more activated or activated only by young adults; ○ = regions more activated or activated only by old adults.

Age-related increases in PFC activity were also found in studies by Rypma and colleagues. In one study, Rypma and D'Esposito differentiated the effects of ageing on encoding, maintenance, and retrieval phases of WM using event-related FMRI. The main result was that older adults showed reduced dorsolateral PFC activity during the retrieval phase but ventrolateral PFC activity was similar to young adults during all three phases. These results suggest that the retrieval phase of WM is more sensitive to ageing than encoding and maintenance phases.
In another study, Rypma et al.\textsuperscript{74} examined verbal WM for different memory loads (one vs. six letters). This contrast yielded three main findings. First, left-lateralized ventrolateral PFC activity was similar in younger adults and older adults. Second, right-lateralized dorsolateral PFC activity was weaker in older than in younger adults. Finally, a left anterior PFC region was more activated in older adults than in younger adults. The authors suggested that ageing impairs executive aspects of WM mediated by dorsolateral PFC but not maintenance operations (e.g. phonological loop) mediated by left ventrolateral PFC. Results are consistent with the aforementioned dissociation between dorsolateral and ventrolateral PFC. Additionally, the age-related increase in left PFC activity was attributed to functional compensation.

As noted, several imaging studies have not only identified increased PFC activations in healthy ageing but, more specifically, an age-related reduction in hemispheric asymmetry (HAROLD). For example, Reuter-Lorenz et al.\textsuperscript{71} used a maintenance task in which participants maintained four letters in WM and then compared them to a probe letter. As shown in Fig. 4.2, young adults showed left-lateralized activity, while older adults showed bilateral activity. They interpreted this HAROLD pattern as compensatory. Consistent with this interpretation, the older adults showing the bilateral activation pattern were faster in the verbal WM task than those that did not. In addition to the verbal WM condition, they also included a spatial WM task. In this task, younger adults activated right PFC and older adults additionally recruited left PFC. Thus, even though age-related increases were in opposite hemispheres, both verbal and spatial WM conditions yielded the HAROLD pattern (Fig. 4.2). This finding supports the generalizability of the HAROLD model to different kinds of stimuli. A follow-up study including additional participants\textsuperscript{75} found bilateral activations in older adults not only in PFC but also in parietal regions.

Park et al.\textsuperscript{76} found similar age-related bilateral PFC activity in a study involving processing of complex visual scenes. Participants maintained scenes in working memory or viewed

**Fig. 4.2** Young participants show left-lateralized PFC activity during verbal WM and right PFC activity during spatial WM, whereas older adults show bilateral PFC activity in both tasks: the HAROLD pattern.\textsuperscript{137} (Reproduced with permission from MIT Press)
them continuously. During the probe, older adults showed greater ventral PFC activity than younger adults, bilaterally. Although there was a trend for PFC activity to be more bilateral in older adults (i.e. HAROLD), the difference was not significant. The age-related increase in ventral PFC activity was attributed to compensation and/or retrieval effort.

Cabeza et al.\textsuperscript{77} also found more bilateral PFC activation in older adults during verbal WM compared to left-lateralized activation in younger adults using a word delayed–response test. Interestingly, the older adults additionally showed a decrease in occipital activity, which was correlated with an increase in right PFC activity. They interpreted the occipital reduction as a visual processing deficit, whereas the increase in right PFC (HAROLD) was suggested to reflect compensation for the visual deficit.

In summary, WM studies often found that older adults show reduced activity in the PFC regions engaged by younger adults but greater activity in other PFC regions, such as contralateral PFC regions (i.e. the PFC hemisphere less engaged by younger adults). In some cases\textsuperscript{71}, contralateral recruitment led to a more bilateral pattern of PFC activity in older adults (i.e. HAROLD). In general, age-related increases in PFC activity were attributed to compensatory mechanisms.

3.1.2 Episodic encoding

Functional imaging studies of EE and ageing have used both incidental and intentional encoding tasks and a wide variety of stimuli. Despite this variability in methods and stimuli, PFC findings have been quite consistent: older adults typically show reduced left PFC activity compared to younger adults. We first discuss studies investigating intentional encoding of material. Then we will focus on studies that examine the influence encoding instruction has on activation differences in ageing.

In a study examining the intentional encoding of word pairs, Cabeza et al.\textsuperscript{78} found that older adults showed less activity in the left PFC compared to younger adults. Importantly, they also noted the younger adults selectively recruited the left PFC whereas older adults showed equivalent activity in left and right PFC (i.e. HAROLD). Since younger adults and older adults had similar memory scores, they interpreted the additional recruitment of the right PFC by older adults as compensatory. Similarly, Anderson et al.\textsuperscript{79} studied intentional encoding of moderately associated word pairs under conditions of full and divided attention. During full attention, the older adults showed reduced activity in the left PFC as well as increased activity in the right PFC, leading to bilateral frontal activity in older adults (i.e. HAROLD).

Age differences in PFC activation have also been shown when investigating levels of processing at encoding. When comparing deep and shallow encoding of words, Stebbins et al.\textsuperscript{80} reported greater activity in both younger adults and older adults for the deep relative to the shallow encoding condition. However, the older adults showed decreased activation in the left PFC. Furthermore, decreased performance on neuropsychological tests correlated with reduced PFC activity. As a result of the reduced left PFC activity, PFC activity in older adults was more symmetric than in younger adults, again in accord with the HAROLD model.

Rosen et al.\textsuperscript{81} also studied deep and shallow encoding of words in younger adults and older adults. However, they distinguished between older adults with high and low memory
scores based on a neuropsychological test battery. They reported equivalent left PFC activity and greater right PFC activity in the old-high group relative to younger adults. In contrast, the old-low group showed reduced activity in both the left and right PFC. As a result, the old-high group showed a more bilateral pattern of PFC activity than younger adults (HAROLD).

Similarly, Daselaar et al.\textsuperscript{82} compared groups of high- and low-performing old adults on a verbal encoding/recognition task, who were divided, post hoc, based on their memory scores. During the semantic encoding task (pleasant/unpleasant decisions) all groups showed left lateralized activations patterns, but PFC activity was slightly less lateralized in the low-performing elderly, and even less so in the high-performing elderly. Consistent with the results of Cabeza et al.\textsuperscript{83}, these findings support the compensatory interpretation of HAROLD.

Morcom et al.\textsuperscript{83} used event-related fMRI to study subsequent memory for semantically encoded words. Recognition memory for these words was tested after a short and a longer delay. At the short delay, performance in older adults was equal to that of younger adults at the long delay. Under these conditions, activity in the left inferior PFC was greater for subsequently recognized than forgotten words in both age groups. Conversely, older adults showed greater right PFC activity than younger adults resulting in a more bilateral pattern of frontal activity (HAROLD).

Finally, Gutchess et al.\textsuperscript{84} studied subsequent picture memory using a deep processing task. The older adults showed increased activity in the left PFC. Since picture encoding in younger adults was associated with bilateral PFC activity, these findings suggest a selective recruitment of the left PFC, which may be compensatory.

One question arises from these studies: What effect, if any, does encoding strategy play in age-altered PFC activations? The following three studies addressed this issue by directly comparing incidental to intentional instructions at encoding.

Grady and colleagues (not included in Table 4.1)\textsuperscript{85} compared intentional versus incidental encoding conditions across various stimuli (e.g., words, pictures). They scanned participants during shallow (uppercase/lowercase, picture size), deep (living/non-living), and intentional encoding conditions. Overall, picture encoding resulted in greater activity in visual and MTL regions, while word encoding yielded greater activity in the left PFC and left lateral temporal cortex. However, deep encoding produced greater left PFC activity, while intentional encoding yielded greater right PFC activity. Though older adults showed the same patterns, the overall level of activity was reduced. Interestingly, they did not find a difference in deep versus intentional encoding of pictures, indicating that age differences were greater for words than for pictures.

The same research group performed another study comparing intentional and incidental encoding conditions, this time using faces as study items\textsuperscript{86}. Convergent with their earlier study investigating intentional face encoding\textsuperscript{87}, older adults showed decreased activity in the left PFC compared to younger adults and diminished connectivity between frontal and MTL areas during both encoding conditions.

However, despite the lack of activation differences across encoding instructions mentioned above, a more recent study did find age-related frontal differences for intentional
encoding instructions. During self-initiated encoding instructions, Logan et al.\textsuperscript{88} reported that older adults compared to younger adults showed less activity in the left PFC, but greater activity in the right PFC, resulting in a more bilateral activity pattern (HAROLD). Results were similar for intentional encoding of both verbal and non-verbal material. Interestingly, further exploratory analyses revealed that this pattern was present in a group of old-older adults (mean age = 80), but not in a group of young-older adults (mean age = 67), suggesting that contralateral recruitment occurs very late in life (Fig. 4.3).

To summarize encoding studies, the most consistent finding was an age-related reduction in left PFC activity. This finding was more frequent for intentional than for incidental encoding studies suggesting that the environmental support provided by a deep semantic encoding task may attenuate the age-related decrease in left PFC activity. This effect was found within subjects in the study by Logan et al.\textsuperscript{88}. The difference between intentional versus incidental encoding conditions suggests an important strategic component in age-related memory decline. The reduction in left PFC activity was often coupled with an increase in right PFC activity, leading to a bilateral pattern of PFC activity in older adults (HAROLD). Importantly, extending to encoding a finding originally reported for retrieval\textsuperscript{89}, two studies that divided older adults into high and low performers found the HAROLD pattern only in the high-performing group\textsuperscript{81,82}. These findings provide direct support for the compensation account of HAROLD.

3.1.3 Episodic retrieval

As noted previously, age-related deficits in episodic retrieval tend to be more pronounced for recall and context memory tasks than for recognition tasks\textsuperscript{89}. However, considerable differences in activity have also been observed during simple recognition tasks. We will

![Images showing brain activity in different age groups: Young, Young-old, Old-old.]

**Fig. 4.3** Young and young-old adults show left-lateralized PFC activity during intentional encoding of words, whereas old-old adults show bilateral PFC activity (HAROLD) (Reproduced with permission from Elsevier Publishers\textsuperscript{138}.)
first review studies looking at recognition processes and then examine those that focus on recall and different forms of context memory.

The face encoding study by Grady et al. included also a face recognition test. During this task, older adults showed reduced activity in parietal and occipital regions but equivalent activity to young adults in the right PFC. This last finding contrasts with the age-related reduction in left PFC activity found in the same study during face encoding. Based on these results, the authors suggested that age effects are more pronounced on encoding than on retrieval. As noted below, however, many subsequent PET and FMRI studies have found reliable age-related changes in PFC activity during episodic retrieval.

The word-pair encoding study by Cabeza et al. included also a word-pair recognition task. During this task, older adults showed reduced activity in the right PFC but increased activity in other brain regions, such as the precuneus. The age-related reduction in the right PFC contrasts with the lack of age effects in this region's activity in Grady et al.'s (1995) study. This inconsistency could reflect differences in stimuli (faces vs. words) or retrieval processes (recognition of items vs. recognition of pairs).

The age-related reduction in right PFC activity during recognition was replicated by Madden et al. using a single-word recognition task. Additionally, this study found an age-related increase in the left PFC. This age-related increase extended to recognition, a finding previously reported for recall by Cabeza et al. which is reviewed below. As in the previous recall study, the age-related increase in the left PFC led to a more bilateral pattern in older adults (i.e. HAROLD). In a subsequent study, Madden et al. re-analysed the recognition data using a stepwise regression method that distinguished between exponential (tau) and Gaussian (mu) components of RT distributions. Young adults showed a correlation between mu and right PFC activity, whereas the older adults showed correlations in left and right PFC regions related to both mu and tau. Since tau is associated with task-specific decision processes, and mu, with residual sensory coding and response processes, the authors concluded that attentional demands were greater for older adults, leading to the recruitment of additional regions. These findings suggest that the retrieval network is more widely distributed in older adults.

Daselaar et al. used event-related FMRI to study recognition of words in younger adults and older adults. Based on recognition performance (high/low) in the scanner, older adults were divided into old-high and old-low groups. During recognition compared to baseline, the old-low group showed much increased activity throughout the brain relative to the other groups. In addition, the old-low group and younger adults showed bilateral PFC activity, whereas the old-high group showed a more left lateralized pattern of frontal activity. In other words, the old-low group showed a non-selective increase in global brain activity, whereas the old-high group showed selective recruitment of the left PFC. The authors interpreted these findings in terms of strategic retrieval differences. Interestingly, when correctly recognized old words were compared to correctly rejected new words, these group differences disappeared. The difference in activity between these two trial types is generally considered to be a correlate of retrieval success. Hence, these findings suggest that age differences in episodic recognition reflect strategic differences rather than a change in the processes supporting the actual recovery of information.
Like recognition, memory studies employing cued and free recall tasks have seen a difference in activation patterns across age. Age differences exist for both single item recall and recall of multiple items and/or features. During recall of a previously studied word list, Schacter et al.\(^{92}\) scanned young and old subjects under different levels of performance. High and low levels of recall were produced by varying encoding conditions. In the high-minus-low contrast, both groups showed similar hippocampal activations. In the low-minus-high contrast, bilateral anterior PFC regions were more activated in younger than in older adults, whereas left posterior PFC areas were more activated in older adults. These findings support the idea that elderly use different functional networks at retrieval than younger adults.

The aforementioned word-pair study by Cabeza et al.\(^{78}\) included not only a recognition test but also a cued-recall test. During recall, older adults showed weaker activity in the anterior cingulate and left temporal cortex. In addition, consistent with Schacter et al., older adults showed weaker activations in the right PFC than the younger adults. Conversely, older adults showed greater activity than younger adults in the left PFC. The net result was that PFC activity during recall was right lateralized in younger adults but bilateral in older adults. The authors noted this change in hemispheric asymmetry and interpreted it as compensatory. This was the first study identifying the HAROLD pattern and the first one suggesting the compensatory interpretation of this finding. This study also compared age-related changes in activity during recall and recognition. These changes were more pronounced during recall than during recognition, consistent with behavioural evidence that recall is more sensitive to ageing.

Bäckman et al.\(^{93}\) found a similar result as Cabeza et al.\(^{78}\) using word-stem cued recall instead of word-pair cued recall: younger adults activated the right PFC whereas older adults activated both the left and right PFC (HAROLD). Also using word pairs, Anderson et al.\(^{79}\) investigated the effects of divided attention on cued recall. They reported negligible effects of divided attention in both groups. However, under full attention conditions, older adults showed weaker activations primarily in the right PFC but stronger activations primarily in the left PFC, suggesting an attenuation of the right-lateralized pattern shown by younger adults (HAROLD).

Cabeza et al.\(^{94}\) investigated item and temporal-order memory tasks. In the item task, a word pair was presented consisting of one studied word and one new word, and participants indicated which word was studied. In the temporal-order task, both words were studied, and participants indicated which of the two words appeared later in the study list. They reported that younger adults showed increased activation in the right PFC for temporal-order compared to item memory, whereas older adults did not. In contrast, the activations during item memory were relatively unaffected by age. These findings are in line with the hypothesis that memory deficits in older adults are due to PFC dysfunction, and that context memory is more heavily dependent on the frontal lobes than item memory.

In another study of context memory by Cabeza and colleagues\(^{69}\), younger adults, high-performing older adults (old-high), and low-performing older adults (old-low) studied words presented auditorily or visually. During scanning, they were presented with words
visually and made either old/new decisions (item memory) or heard/seen decisions (context memory). Consistent with their previous results, younger adults showed right PFC activity for context trials, whereas older adults showed bilateral PFC activity (HAROLD). Importantly, however, this pattern was only seen for the old-high adults, supporting a compensation account of the HAROLD pattern (Fig. 4.4).

Summarizing the studies on retrieval, the HAROLD pattern has been found more frequently in studies using more challenging recall and context memory tasks than during simple item recognition. These findings suggest a three-way interaction between age, task difficulty, and frontal laterality. Importantly, distinguishing between old-high and old-low adults, the study by Cabeza et al.65 provided direct evidence for the compensation account of HAROLD.

3.2 Medial temporal lobes

Frontal activations in ageing show both reductions and increases across ageing, as well as shifts in lateralization of activation. On the other hand, activation within the MTL generally shows age-related decreases compared to that seen in younger adults. However, some studies show a shift in the foci of activation from the hippocampus proper to more parahippocampal regions in ageing. Evidence for such a shift will be presented below where appropriate and discussed further in the conclusions.

3.2.1 Working memory

In WM tasks, older adults tend to show reductions in hippocampal activity associated with maintenance operations. Mitchell et al.95 investigated a WM paradigm with an important episodic encoding component. In each trial, participants were presented with an object in a particular screen location and had to hold in WM the object, its location, or both (combination trials). Combination trials can be assumed to involve not only

![Image](image-url)
WM maintenance but also the binding of different information into an integrated memory trace (associative memory encoding). Older adults showed a deficit in accuracy in the combination condition but not in the object and location conditions. Two regions were differentially involved in the combination condition in younger adults but not in older adults: a left anterior hippocampal region and an anteromedial PFC region (right BA 10) (Fig. 4.5). According to the authors, a disruption of a hippocampal–PFC circuit may underlie binding deficits in older adults.

Older adults also exhibit difficulty maintaining hippocampal activation across long delays. Grady et al.\textsuperscript{36} investigated a face WM task with varied intervals of item maintenance (1–21 secs). As the delay extended from 1 to 6 sec, left hippocampal activity increased in younger adults but decreased in older adults, which implies that older adults have difficulties initiating memory strategies mediated by MTL or sustaining MTL activity beyond very short retention intervals.

In addition to showing greater ventral PFC activation while maintaining faces in WM, older adults in the aforementioned Park et al.\textsuperscript{76} also showed an age-related reduction in hippocampal activity. The left hippocampus was more activated in the viewing
than in the maintenance condition in younger adults, but not in older adults. As in Mitchell et al.'s\textsuperscript{9,5} study, the age-related reduction in hippocampal activity was attributed to deficits in associative encoding.

Three nonverbal working memory studies\textsuperscript{7,6.95,96} found age-related decreases in hippocampus activity, whereas no verbal working memory study found such decreases. It is possible that nonverbal tasks were more dependent on hippocampal-mediated relational memory processing and, hence, more sensitive to age-related deficits in these regions. Additionally, age-related differences in activation during maintenance tasks support the theory that age differences in 'simple' WM do exist and are indeed undetectable at the behavioural level.

3.2.2 Episodic encoding

In their study examining face encoding, Grady et al.\textsuperscript{87} found that older adults showed less activity in the left PFC and MTL than younger adults. Furthermore, they found a highly significant correlation in younger adults, but not in older adults, between hippocampus and left PFC activity. Based on these results, they concluded that encoding in older adults is accompanied by reduced neural activity and diminished connectivity between PFC and MTL areas.

Daselaar et al.\textsuperscript{97} investigated levels of processing in ageing using a deep (living/nonliving) vs. shallow (uppercase/lowercase) encoding task. Despite seeing common activation of regions involved in a semantic network across both age groups, activation differences were seen when comparing levels of processing. Older adults revealed significantly less activation in the left anterior hippocampus during deep relative to shallow classification. Researchers concluded that under-recruitment of MTL regions contribute, at least in part, to age-related impairments in encoding.

Similarly, the same group showed decreased activity in the MTL for poor-performing older adults compared to young and high-performing elderly. Despite the equivalent activation that was shown in PFC activation in their verbal encoding/recognition task, Daselaar et al.\textsuperscript{82} found that the older adults showed decreased activity in the left hippocampus/parahippocampal cortex during successful encoding of words (Fig. 4.6). Based on these findings, they concluded that MTL dysfunction during encoding is an important factor in age-related memory decline.

Similar to Daselaar et al.\textsuperscript{82}, Gutchess et al.'s\textsuperscript{84} study of subsequent picture memory observed reduced activity in the MTL for subsequently remembered items, even when older adults were not divided into high- and low-memory groups. Additionally, older adults exhibited a significant negative correlation between inferior frontal and parahippocampal activity, whereas younger adults did not. Results suggest that those older adults exhibiting the least involvement of the parahippocampus conversely activated inferior frontal areas the most. Data suggest that prefrontal regions could be activated to compensate for declines in MTL activations in older adults.

Age-related reductions in MTL activity\textsuperscript{82,84,97} indicate that, besides frontal changes, reduced MTL function also contributes to age-related memory decline. Increased PFC activity in older adults may be compensatory, offsetting reduction in MTL activation.\textsuperscript{84}
Fig. 4.6 Young adults and older adults with high memory performance (old-high) exhibit similar activation in the hippocampus/parahippocampal cortex, while older adults with low memory performance (old-low) exhibit less hippocampal/parahippocampal activation during successful encoding. (Reproduced with permission from Oxford University Press.)
3.2.3 Episodic memory retrieval

Cabeza et al. investigated the effects of ageing on several cognitive tasks including a verbal recognition task. Within the medial temporal lobes, they found a dissociation between a hippocampal region which showed weaker activity in older adults than in younger adults and a cortical MTL region, which showed the converse pattern. Given evidence that hippocampal and parahippocampal regions are respectively more involved in recollection vs. familiarity, this finding is consistent with the notion that older adults are more impaired in recollection than in familiarity. Actually, the age-related increase in parahippocampal cortex suggests that older adults may be compensating for recollection deficits by relying more on familiarity. Supporting this idea, older adults had a larger number of ‘know’ responses than younger adults and these responses were positively correlated with the parahippocampal activation.

A recent follow-up study by the same group showed a similar pattern of results. Young and older adults made old/new judgements about previously studied words followed by a confidence judgement from low to high. These responses were then combined into a three-point perceived oldness scale (level 1 = ‘new’, level 2 = ‘probably old’, level 3 = ‘definitely old’). There is a considerable amount of evidence that familiarity-based responses increase gradually as a function of perceived oldness, whereas recollection-based responses are primarily associated with the highest level of perceived oldness. For example, the probability of ‘know’ responses increases monotonically from ‘new’ to ‘definitely old’ trials, whereas the vast majority of ‘remember’ responses are clustered around ‘definitely old’ trials. Accordingly, using parametric fMRI analyses with perceived oldness as a covariate, recollection-related activity was defined as an exponential function in which activity remains low for levels 1 and 2 and increases sharply for level 3 (i.e. definitely old trials). In contrast, familiarity was defined as a linear increase or decrease as a function of perceived oldness. The results revealed a double dissociation within MTL. Recollection-related activity in the hippocampus was reduced in older adults as indicated by a sharper exponential increase of the perceived oldness function in young adults (Fig. 4.7a). In contrast, familiarity-related activity (linear decrease) in the rhinal cortex was augmented in older adults as indicated by the steeper negative slope of the perceived oldness function (Fig. 4.7b). In addition, age dissociations regarding recollection and familiarity were found within parietal and posterior midline regions. Finally, ageing reduced functional connectivity within a hippocampal-retrosplenial/parietotemporal network, but increased connectivity within a rhinal-frontal network. These findings indicate that older adults compensate for hippocampal deficits by relying more on the rhinal cortex, possibly through a top-down frontal modulation. Hence, consistent with their previous findings, these results suggest a greater reliance on familiarity-based recognition in older adults.

In addition to increases in activity in the left PFC during word-stem cued recall, Bäckman and colleagues found increased MTL activation in older adults. Just as the increased left PFC activation resulted in more bilateral frontal activation for older adults, increased activation in the left MTL had the same effect. Compared to younger adults,
Fig. 4.7 The effects of ageing yielded a double dissociation between two MTL sub-regions: whereas recollection-related activity (exponential increase) in the hippocampus was attenuated by ageing, familiarity-related activity (linear decrease) in the rhinal cortex was enhanced by ageing. The hippocampal exponential rate parameter (λ) provides a measure of the sharpness of the exponential increase of the perceived oldness function in the hippocampus. The rhinal slope parameter provides a measure of the steepness of the perceived oldness function in the rhinal cortex. (Reproduced with permission from Oxford University Press101.)
older adults showed more bilateral MTL activity. It should be noted that this bilateral
activation was not accompanied by increased performance — older adults recalled only
about half as many words as did younger adults.

This HAROLD pattern within MTL was also observed in a recent study using event-
related fMRI. Maguire and Frith[104] investigated the recall of autobiographical events
gathered in a pre-scan interview. Although the groups activated largely the same regions,
they observed a striking difference in the MTL. Younger adults showed left-lateralized
hippocampal activity, whereas older adults showed bilateral activity in the MTL. These
findings suggest that HAROLD extends beyond the PFC not only to other cortical
regions (as shown by several studies) but also to subcortical areas.

In sum, retrieval studies have found both increases and decreases in MTL activity. The
findings by Cabeza and colleagues suggest that some of these increases reflect a shift from
recollection (hippocampus) to familiarity-based retrieval (parahippocampal cortex).

3.3 Discussion

In summary, our review of functional neuroimaging studies of cognitive ageing has iden-
tified considerable age-related changes in activity during WM, EE, and ER tasks not only
in the PFC, but also in the MTL. These findings suggest that functional changes in both
PFC and MTL play a role in age-related memory deficits. Focusing first on PFC findings,
the studies indicated both age-related reductions and increases in PFC activity. During
WM tasks, older adults show reduced activity in the PFC regions engaged by young
adults, but greater activity in other regions, such as contralateral PFC regions. The latter
changes often resulted in the more bilateral pattern of PFC activity in older than younger
adults known as HAROLD[71,76,77,105]. In general, age-related PFC increases and HAROLD
findings have been attributed to functional compensation in the ageing brain. During EE
tasks, the most consistent finding has been a reduction in left PFC activity. This finding is
more frequent for intentional than for incidental encoding tasks. The age-related reduc-
tion in left PFC activity was often coupled with an age-related increase in right PFC
activity (i.e. HAROLD). Finally, ER was also associated with HAROLD, and this pattern
was found more often in studies using more challenging recall and context memory tasks
than during simple item recognition tasks.

Age-related changes in PFC activity are generally in line with the resource deficit theory
of cognitive ageing[10]. As described at the beginning of the chapter, this theory postulates
that ageing reduces attentional resources and, as a result, older adults have greater diffi-
culties with cognitive tasks that provide less environmental support and, hence, require
greater self-initiated processing. Given the critical role of the PFC in managing atten-
tional resources, this view predicts that age-related changes in PFC activity will be larger
for tasks involving greater self-initiated processing and/or less environmental support.
The results are generally consistent with this prediction. During EE, age-related decreases
in left PFC activation were found frequently during intentional encoding conditions
(which provide less environmental support) but rarely during incidental encoding condi-
tions (which provide greater environmental support). Similarly, during ER, age-related
differences in PFC activity were usually larger for recall and context memory tasks
(which require keeping information in mind) than for keeping information in working memory
as well as for other memory tasks.

However, contrary to resource deficit theory, older adults have shown less age-related
declines in hippocampal activity during tasks involving time-based memory. For instance,
hippocampal activity during time-based memory tasks has been shown to decline in healthy
older adults but not in patients with AD[77,105]. This finding highlights the potential for
inhibitory brain plasticity in older adults.

In general, age-related declines in hippocampal activity are associated with poorer
recognition memory performance[77,105]. However, this relationship is not always
strongly supported. For instance, in a recent study, elderly participants who showed
greater hippocampal atrophy and poorer memory performance on a recognition memory
task were still able to learn new information and perform well on a delayed recall task[76].

Overall, the relationship between hippocampal activity and memory performance is
complex and likely influenced by multiple factors, including age, health, and individual
variables. Further research is needed to clarify these relationships and understand the
role of hippocampal activity in memory processing in older adults.
(which require greater cognitive resources) than for recognition memory tasks (which require less cognitive resources). Thus, in general, age effects on PFC activity tend to increase as a function of the demands placed on cognitive resources. This finding is in keeping with aforementioned evidence that the anatomical integrity of the frontal lobes, as well as the dopamine modulation of this region, show significant decline with ageing.

However, not all age-related changes on PFC activity suggested decline; on the contrary, many studies found age-related increases in PFC that suggested compensatory mechanisms in the ageing brain. In particular, several studies found, in older adults, activations in contralateral PFC regions not activated by young adults. Activity-benefit correlations and experimental comparisons between high- and low-performing older adults demonstrated the beneficial contribution of these regions to memory performance in older adults. In this respect, it is important to note that resource deficit and compensatory interpretations are not incompatible. Actually, it is reasonable to assume that the recruitment of additional brain regions (e.g. in the contralateral PFC hemisphere) reflects an attempt to compensate for reduced cognitive resources. Moreover, age-related decreases suggestive of resource deficits and age-related increases suggestive of compensation have been often found in the same conditions. For example, EE studies have shown age-related decreases in left PFC activity coupled with age-related increases in right PFC activity. These changes often lead to a dramatic reduction in hemispheric asymmetry in older adults (i.e. HAROLD) which is, overall, the most consistent finding across different memory domains.

Turning to MTL findings, several studies have found age-related decreases in hippocampal and parahippocampal regions. During WM, older adults demonstrate decline in hippocampal activation during encoding of multiple features. During EE, however, declines in hippocampal activation are also seen for encoding of individual features in healthy older adults. Finally, during ER, some studies found decreases in hippocampal activity, but also greater activity in older than younger adults in parahippocampal regions, or contralateral MTL regions, which may be compensatory.

In general, age-related changes in MTL activity are consistent with the associative deficit theory. As noted in the first part of the chapter, this hypothesis postulates that age-related memory deficits are primarily the results of difficulties in encoding and retrieving novel associations between items. Given that relational memory has been strongly associated with the hippocampus, this hypothesis predicts that older adults will show decreased hippocampal activity during memory tasks, particularly when they involve associations. Consistent with this hypothesis, age-related reductions in hippocampal activity were found in WM tasks involving maintenance of complex visual scenes and objects paired with specific locations. Also, EE studies found these reductions during the encoding of complex scenes, which involve associations among picture elements, and during deep encoding of words, which involve identification of semantic associations. Finally, a recent study specifically associated age-related reductions in hippocampal activity to recollection, which involves recovery of item-context associations (see Fig. 4.7). Yet, it should be noted that age-related changes in MTL activity were often accompanied by concomitant changes in PFC activity. Hence, in these cases,
it is unclear whether such changes signal MTL dysfunction or whether they are the result of a decline in efficient memory strategies mediated by PFC regions. However, studies using incidental encoding tasks with minimal strategic requirements have also identified age differences in MTL activity without significant changes in PFC activity (see Fig. 4.6)82,97.

As in the case of PFC, not all age-related changes in MTL activity suggest decline; several findings suggest compensation. First, similar to the bilateral pattern frequently observed in PFC, older adults have also demonstrated bilateral hippocampal recruitment while performing memory retrieval tasks104. Second, during ER, older adults have been found to show reduced activity in the hippocampus but increased activity in other brain regions such as the parahippocampal gyrus77 and the rhinal cortex101. These results were interpreted as a recruitment of familiarity processes mediated by parahippocampal regions in order to compensate for the decline of recollection processes that are dependent on the hippocampus proper.

As mentioned at the beginning of this chapter, one of the biggest challenges in cognitive ageing research is to isolate the effects of healthy ageing from those of pathological ageing (e.g. AD). A general review of the structural neuroimaging literature suggests that healthy ageing is accompanied by greater declines in frontal regions compared to the MTL47. In contrast, pathological ageing is characterized by greater decline in the MTL than in frontal regions109,110. In fact, functional neuroimaging evidence suggests that prefrontal activity tends to be maintained or even increased in early AD111. Thus, these findings suggest that memory decline in healthy ageing is more dependent on frontal than MTL deficits, whereas the opposite pattern is more characteristic of pathological ageing79. In view of these findings, clinical studies aimed at an early diagnosis of age-related pathology have mainly targeted changes in the MTL112. Yet, the studies reviewed in this chapter clearly indicate that healthy older adults are also prone to MTL decline. Hence, rather than focussing on MTL deficits alone, diagnosis of age-related pathology may be improved by employing some type of composite score reflecting the ratio between MTL and frontal decline.

In terms of MTL dysfunction in healthy and pathological ageing, it is also critical to assess the specific type or loci of MTL dysfunction. As noted, a decline in hippocampal function can be seen in both healthy ageing and AD. Thus, even though hippocampal volume decline is an excellent marker of concurrent AD113,114, it is not a reliable measure for distinguishing normal ageing from early stages of the disease47. In contrast, substantial changes in the rhinal cortex are present in early AD patients with only mild impairments115–118, but not in healthy ageing (see Fig. 4.1c)56. In a discriminant analysis, Pennanen and colleagues119 showed that, although hippocampal volume is indeed the best marker to discriminate AD patients from normal controls, the volume of the rhinal cortex is much better in distinguishing between incipient AD (mild cognitive impairment — MCI) and healthy ageing. Finally, it should be noted that, despite the rigorous screening procedures typical of functional neuroimaging studies of healthy ageing, it remains possible that early symptoms of age-related pathology went undetected in some of the studies reviewed in this chapter.

4. Is: Tab: One is the fact complex bl involving age-related decrement in memory and executive function, and significant a greater ability to maintain task performance in older age than in young adults (associations...)

The results which are the focus of interest can be employed because it during low-level tasks also show evidence and of past deactivation in young differences in resource levels. Second, the task is not simply pure i further resources in the substrata and analytic...
4. **Issues**

4.1 **Tasks and design**

One issue with regards to assessing age-related deficits in performance and activation is the fact of what one is testing. Cognitive tasks are never ‘pure’; they always involve a complex blend of different cognitive operations. For example, as noted above, WM tasks can involve both encoding and retrieval operations. And within those operations are levels of maintenance, processing, etc. The same is true for all cognitive functions. Thus, when an age-related difference in activation is found, it is important to determine which component of the task is responsible for the difference. This type of task analysis could help explain some inconsistencies in the literature. For example, Cabeza et al.\(^7\) found a significant age-related reduction in PFC activity during verbal recognition, whereas Madden et al.\(^9\) did not. Given that recognition memory involves both recollection and familiarity\(^9\), and that recollection is sensitive to ageing\(^10\), the inconsistent findings could reflect a greater recollection component in the recognition task investigated by Cabeza et al. (associative recognition) than in the one studied by Madden et al. (item recognition).

The standard solution to the problem of task complexity is the subtraction method, which compares target and control conditions assumed to differ primarily in the process of interest. There are two main problems with this method, and both are magnified by group contrasts. First, activations reflect both the target condition and control condition employed. Thus, older adults may show weaker activations than young adults not because they did not engage a region during the target task but because they also engaged it during the control task\(^12\). This problem is attenuated, but not eliminated, by using low-level baselines (e.g. the fixation period in event-related FMRI studies) which may also show age-related differences. For example, Lustig et al.\(^12\) scanned younger adults and older adults during a semantic classification task, which was intermixed with blocks of passive rest. They found that older adults showed less activity during rest (task-related deactivation) in posterior midline regions. These regions are commonly activated in younger adults during low-level baseline conditions\(^12\). Lustig et al. proposed that age differences in rest activity reflect a less efficient allocation in older adults of available resources to task-relevant processes.

Second, the subtraction method rests on the assumption that the extra component of the target condition does not affect the components shared with the control condition pure insertion assumption\(^12\). This assumption is problematic (e.g. see\(^12\)) and may be further violated when the inserted task components interact with limitations in cognitive resources in older adults. To address this problem, future studies should complement subtraction analyses with other methods such as parametric manipulations, multivariate analyses, and activity–performance correlations.

4.2 **Subjects**

One important aspect of study design is the selection of older adults. On the one hand, one would like to select older adults who are perfectly healthy and who are matched to younger adults in all possible variables except age. One the other hand, one would like to
investigate a sample of older adults that is representative of the general population. This is a general problem of cognitive ageing research, but some aspects of it are particularly thorny in functional neuroimaging studies, such as screening criteria and the sub-population of older adults investigated.

Regarding health screening, not all researchers agree on concrete inclusion/exclusion criteria. Most do agree that participants with high blood pressure should be excluded; hypertension may not only alter blood flow measures but it is also associated with covert cerebrovascular damage\textsuperscript{127}. Also, while most studies exclude participants taking medications that could alter blood flow, there are no clear guidelines about which drugs to exclude for. Likewise, participants are usually excluded if they show pronounced atrophy or white-matter damage in MRI scans, but the boundary between normal and abnormal structural changes is not clear. Thus, there is an urgent need for studies assessing the effect of the various subject-related factors on haemodynamic measures — as this could lead to greater variability in activation. For example, Jennings et al.\textsuperscript{128} found, during a WM task, hypertensive older adults showed different activation patterns than normotensive older adults.

There is also a wide range within older adults, both quantitatively and qualitatively. Quantitatively, older adults may differ in level of cognitive performance, with some older adults performing as well as younger adults and others showing significant deficits. This variability in age-related cognitive decline difference may account for some inconsistencies in the imaging literature (see discussion about performance differences below). Qualitatively, older adults may differ regarding the particular neurocognitive component in which they are most impaired. As shown by Glisky and collaborators\textsuperscript{129,130}, some older adults may be more affected on PFC-mediated executive functions, whereas other older adults may be more affected in MTL-mediated memory functions. Obviously, the proportion of these two patterns in the sample investigated is likely to affect what age effects one finds. Thus, future studies should try to characterize different levels of performance and ageing patterns and investigate their effect on brain activation patterns.

4.3 Performance

Brain activity can vary as a function of performance measures (e.g. accuracy\textsuperscript{131}, reaction time\textsuperscript{72}). Therefore, in functional neuroimaging studies, if older adults perform more poorly than younger adults, it is unclear whether differences in activation between older adults and younger adults reflect the age effects or dissimilarities in performance. This is a typical ‘chicken and egg’ problem: do older adults perform poorly because their brain activity is different, or is their brain activity different because they perform poorly?

One approach to this problem is to match performance in young and old groups by manipulating tasks\textsuperscript{83,101} or by scanning high-functioning elderly who naturally perform as well as young adults (e.g. see\textsuperscript{78}). When cognitive performance is similar in the young and old groups, group differences in brain activity can be safely attributed to ageing. The main problem of this approach is that when performance differences are eliminated, it becomes more difficult to relate activation findings to the cognitive deficits typically displayed by older adults. Another solution is to use group tasks matched for performance, as is present in the study of older adults.

Another approach is to control for age differences using additional task trials without the need for covariate correction (which is beyond the scope of this chapter).

4.4 Age-related brain differences vs. task performance

After systematically controlling for age in functional neuroimaging studies, it is possible to distinguish age-related brain differences from task performance differences. This may be done by assessing the effect of age on the performance of different cognitive processes and tasks and relating these differences to age-related brain differences.

Determine First, if there are performance differences between different age groups (e.g. different tasks) that are related to cognitive function. If so, determine whether these differences relate to different regions of the brain. This can be done by using appropriate statistical methods (e.g. ANOVA, MANOVA) to assess the relationship between age and brain activation differences.

Integrate the results of these analyses into a model that relates age-related brain differences to the cognitive performance differences observed in the study. This model should take into account the age-related changes in brain structure and function, as well as the performance differences observed in the study. This model can then be used to interpret the results of future studies in this area.
older adults. A possible solution to this problem is to have an 'easy' and a 'difficult' version of the task, and compare younger adults and older adults both when performance is matched (e.g. young adults-difficult vs. old adults-easy) and when an age-related deficit is present (e.g. young adults-difficult vs. old adults-difficult or young adults-easy vs. old adults-easy)

Another way to address the problem of performance differences is to use event-related fMRI designs and analyse only correct trials in both groups. This method does not eliminate differences in RTs, unless the number of trials is sufficiently large to allow selecting trials with similar RTs in the two groups. An alternative solution is to enter RTs as a covariate in the analyses, but risks eliminating activity associated with processes of interest (which are usually correlated with RTs).

4.4 Activations
After subjects have been appropriately selected, task components suitably analysed, and performance differences properly controlled, researchers are still faced with the fundamental problem of interpreting the age-related differences in activation they have found. This more general issue can actually be divided into three tasks: determining what kind of age-related activation differences were found; interpreting ageing effects on a particular brain region; and evaluating global network changes.

Determining the kind of age-related activity difference found is not a trivial problem. First, one must determine whether younger adults and older adults engage the same region to different degrees (quantitative difference) or different brain regions (qualitative difference). The interpretation of these two patterns is different but distinguishing between them is not easy. For example, quantitative differences may appear as qualitative due to threshold effects. Also, when younger adults and older adults activate adjacent areas (e.g. BA 9 vs. BA 46), the finding may be described as the 'same' activation in different locations or as 'different' activations. Second, another knotty problem is whether age-related differences in activation reflect changes in neural architecture or changes in cognitive architecture. In other words, did younger adults and older adults engage different regions to perform the same cognitive operations or did they recruit different regions to perform different cognitive operations? If one wants to know if the neural correlates of process A change with age, it is critical that both groups engage process A to the same extent. At the same time, if ageing is associated with a shift from process A to process B, then the neural correlates of both processes should be investigated in both groups. The main problem, of course, is how to determine exactly the processes engaged by human subjects, since cognitive tasks can be performed in many different ways and introspective reports provide very limited information about the actual operations performed by the subjects.

Interpreting age-related differences in activation is also complex. In general, age-related decreases in activation have been interpreted as detrimental and age-related increases as beneficial. Unfortunately, the relation between neural activity and cognitive performance is not so simple; less activity may reflect more efficient processing, and more activity may reflect unnecessary or even disruptive processes.
could help interpret activation differences if one assumes that activations positively correlated with performance are beneficial and those negatively correlated with performance are detrimental. However, an activation may be beneficial for performance but be negatively correlated with performance across subjects when the region is recruited by participants who have difficulty with the task. To explain using an analogy, a walking-stick helps walking performance but its use is negatively correlated with walking performance (because it is used by those who have difficulty walking). Event-related designs can also help distinguish between beneficial and detrimental interpretations if one assumes that activity during successful trials is beneficial and activity during unsuccessful trials is detrimental. Yet, again, a region may be beneficial for performance but only for demanding trials, which have a greater chance of being unsuccessful.

Finally, although most studies have interpreted age-related differences in terms of local changes (e.g., PFC dysfunction), these differences may also reflect global network changes. For example, using structural equation modelling, we have found that age-related changes in the activity of a left PFC region during episodic encoding and retrieval were partly due to age-related changes in the interactions between this region and other components of the episodic memory network. Thus, one of the main challenges for future imaging studies of cognitive ageing is to investigate not only local changes but also changes in functional connectivity.

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References


