Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory

M. Natasha Rajah and Mark D’Esposito

Helen Wills Neuroscience Institute and Department of Psychology, University of California, Berkeley, CA, USA

Correspondence to: M. N. Rajah, PhD, Helen Wills Neuroscience Institute, 132 Barker Hall MC #3190, University of California, Berkeley, CA 94720-3190, USA
E-mail: mnrajah@berkeley.edu

Several neuroimaging studies of cognitive ageing have found that age-related deficits in working memory (WM) and episodic memory abilities are related to changes in prefrontal cortex (PFC) function. Reviews of these neuroimaging studies have generally concluded that with age there is a reduction in the hemispheric specialization of cognitive function in the frontal lobes that may either be due to dedifferentiation of function, deficits in function and/or functional reorganization and compensation. Moreover, previous reviews have considered the PFC as homogeneous in function and have not taken into account the possibility that region specific changes in PFC function may occur with age. In the current review we performed a qualitative meta-analytic review of all the functional magnetic resonance imaging ageing studies and positron emission tomography ageing studies of WM and episodic memory that report PFC activation, to determine if any region-specific changes occur. The results indicated that in normal ageing distinct PFC regions exhibit different patterns of functional change, suggesting that age-related changes in PFC function are not homogeneous in nature. Specifically, we hypothesize that normal ageing is related to the differentiation of cortical function in a bilateral ventral PFC and deficits in function in right dorsal and anterior PFC. As a result of these changes, functional compensation in left dorsal and anterior PFC may occur. We hope that future studies will be conducted to either confirm or counter these hypotheses.

Keywords: ageing; compensation; dedifferentiation; episodic memory; working memory

Abbreviations: BA = Brodmann area; EM = episodic memory; MFG = middle frontal gyrus; PFC = prefrontal cortex; WM = working memory


Introduction

Ageing is related to the deterioration of numerous biological systems and functions in the human body. The underlying cause of senescence has been investigated at numerous levels of analysis and has been attributed to a variety of possible factors: changes in cellular metabolism, cell structure, cell–matrix interactions, neurotransmitter systems and the rate and accuracy of DNA replication (Osiewacz and Hamann, 1997; Ladislas, 2000; Labat-Robert, 2001; Campisi, 2003; Troen, 2003; Cabeza et al., 2005). With the increasing availability of brain imaging technologies, such as blood-oxygen-level-dependent functional MRI (BOLD fMRI) and positron emission tomography (PET), much of the recent research on ageing has focused on investigating the relationship between age-related changes in brain structure/function and concomitant changes in cognitive/behavioural abilities (Gabrieli, 1996; Grady et al., 1995; Madden et al., 1999; Raz, 2000; Cabeza, 2002; Craik and Grady, 2002; Della-Maggiore et al., 2002; Grady, 2002; Reuter-Lorenz, 2002; Gazzaley and D’Esposito, 2003; Buckner, 2004; Park et al., 2004). Though it can be argued that the neuroimaging approach cannot inform us on the direct underlying cellular or physiological causes of senescence, due to the gross level of anatomic
and functional changes that they measure; functional neuroimaging studies of cognition in healthy young adults indicate that these techniques provide valuable, non-invasive, methods for gaining insight into how regional changes in neural structure and function relate to cognition and behaviour (Cabeza and Nyberg, 2000; D’Esposito, 2000; Duncan and Owen, 2000; Rugg et al., 2002; Friston, 2005). Moreover, recent findings indicate that the signals measured by BOLD fMRI and PET techniques are coupled to ‘real’ changes in neural activity. Thus, if one is interested in understanding how age-related changes in cognition and behaviour may be related to gross changes in neural structure and function, then neuroimaging is a valid technique to use (Braver and Barch, 2002; Della-Maggiore et al., 2002; Grady, 2002; Reuter-Lorenz, 2002; Tisserand et al., 2002; Gazzaley and D’Esposito, 2003; Johnson et al., 2004; Raz et al., 2004; Cabeza et al., 2005).

**Concerns with using functional imaging to examine age-related differences in brain function**

However, when using BOLD fMRI and PET techniques to examine age differences in brain activity one must keep in mind that normal ageing affects the cerebrovascular system, which in turn affects the neurovascular coupling that is the basis of the signals measured by these techniques (D’Esposito et al., 2003). For example, the cerebrovascular changes observed in normal ageing have been shown to decrease the signal-to-noise ratio, the amplitude and the spatial extent of the BOLD response measured in the healthy elderly (Taoka et al., 1998; D’Esposito et al., 1999a; Hesselmann et al., 2001; Huettel et al., 2001). In addition, normal ageing has been associated with a lag in the time-to-peak of the BOLD response (Taoka et al., 1998); however, the overall shape of the BOLD response does not change with age (D’Esposito et al., 1999a, Huettel et al., 2001). Therefore, one must be careful in interpreting age-related changes in functional activity, as measured by fMRI and PET, since the observed age differences in brain activity may be confounded by group differences in cerebral vascular function. This is especially true when interpreting age-related deficits in brain activity since these deficits may not mean that elderly subjects exhibit deficits in regional neural activity, but may instead be due to changes in neurovascular coupling which in turn causes decreases in signal-to-noise ratio, signal amplitude or signal spatial extent.

**Addressing confounds due to age-related differences in cerebral vascular function**

Overall, researchers in the field of cognitive neuroscience of ageing have successfully used both statistical and experimental manipulations to control for the aforementioned confounds (Buckner et al., 2000; D’Esposito et al., 2003; Gazzaley and D’Esposito, 2003). For example, investigators generally do not test for between-group differences in task-related brain activity in functional neuroimaging studies of ageing. Instead, within-group differences in task-related activity are examined, followed by tests of group-by-task interactions (Hazlett et al., 1998; Madden et al., 1999; Reuter-Lorenz et al., 2000; Rypma and D’Esposito, 2000; Dolcos et al., 2002; Idaka et al., 2002; Morcom et al., 2003). Investigators have also used multivariate statistics and brain-behaviour correlation methods to control for the confounding effects of age-related changes in neurovascular coupling (Cabeza et al., 1997; Madden et al., 1999, 2002; McIntosh et al., 1999; Anderson et al., 2000; Della-Maggiore et al., 2000; Grady et al., 2002; Schiavetto et al., 2002; Morcom et al., 2003; Lustig and Buckner, 2004). In addition, parametric experimental designs are helpful in dissociating age-related differences in brain activity that are related to the parametric changes in task performance and not to age differences in cerebral vasculature or other experimental confounds (i.e. motor flexibility or fatigue; Grady et al., 1999; Buckner et al., 2000; Gould et al., 2003). Therefore, by controlling for these possible confounds several functional neuroimaging studies have contributed valuable information to the field of cognitive ageing and how age-related changes in brain structure and function may be related to the cognitive and behavioural deficits that occur with age (Craik and Grady, 2002; Cabeza et al., 2005).

**Theoretical issues in examining age-related changes in PFC function: functional compensation and dedifferentiation perspectives**

One of the brain regions exhibiting a strong age-related change in structure and function, which also impacts cognition and behaviour, is the prefrontal cortex (PFC) (Lapidot, 1987; Morgan, 1987; Nielsen-Bohlman and Knight, 1995; de Brabander et al., 1998; Langley and Madden, 2000; Raz, 2000; West, 2000; Grachev and Apkarian, 2001; Braver and Barch, 2002; Cabeza, 2002; Craik and Grady, 2002; Della-Maggiore et al., 2002; Grady, 2002; Reuter-Lorenz, 2002; Tisserand et al., 2002; Uylings and de Brabander, 2002; Gazzaley and D’Esposito, 2003; Peters and Rosene, 2003; Buckner, 2004). For example, in vivo and post-mortem studies of humans and primates have shown that the strongest age-related cerebral cortical change is PFC grey matter and white matter reductions (Raz, 2000; Tisserand et al., 2002). In addition, functional neuroimaging studies have reported age-related changes in PFC activation and its functional connectivity with posterior cortical regions across a variety of cognitive tasks (Grady et al., 1994, 1999; Cabeza et al., 1997; Madden et al., 1999; McIntosh et al., 1999; Della-Maggiore et al., 2000; Rypma and D’Esposito, 2000; Schreurs et al., 2001; Idaka et al., 2002). Behaviourally, the PFC is involved in a variety of cognitive operations, including: working memory (WM), episodic memory (EM), inhibition, monitoring, strategic...
organization and planning (Stuss and Knight, 2002). However, since memory impairment is one of the hallmarks of ageing, the majority of neuroimaging studies in this area have focused on age-related changes in PFC function during WM and EM task performance (Craik and Salthouse, 2000).

Age-related increases and decreases in activation during WM and EM tasks have been reported in a variety of PFC regions including the ventrolateral, dorsolateral and anterior PFC (Nielsen-Bohlman Knight, 1995; Trott et al., 1997; Grady et al., 1998; Madden et al., 1999; Reuter-Lorenz et al., 2000; Rypma et al., 2001; Cabeza, 2002; Wegesin et al., 2002; Morcom et al., 2003). Often, when these age-related changes in PFC activity are observed, the older subjects also perform poorer than young subjects on the WM and EM tasks used (Anderson et al., 2000; Cabeza et al., 2000; Rypma et al., 2001). However, even in the absence of behavioural differences, studies have reported WM-related and EM-related differences in PFC activation in young versus old subjects (Cabeza et al., 1997; Rypma and D’Esposito, 2000).

Reviews of the cognitive neuroscience literature of memory and ageing have generally considered cognitive mechanisms underlying age-related deficits in WM and EM and viewed the PFC as a homogeneous region (Li et al., 2001; Braver and Barch, 2002; Cabeza, 2002; Cabeza et al., 2002; Della-Maggiore et al., 2002; MacPherson et al., 2002; Reuter-Lorenz, 2002; Gazzaley and D’Esposito, 2003; Ramnani and Owen, 2004; Reuter-Lorenz, 2002). For example, Cabeza (2002) observed that there is reduced lateralized PFC activity across WM and EM tasks with age and proposed the hemispheric asymmetry reduction in old adults (HAROLD) model, which has been supported by subsequent experimental findings. However, this model does not address whether these laterality effects are specific to particular brain regions or common to all brain regions; including the PFC and its various subdivisions. Also, the HAROLD model does not specify whether the underlying neural mechanisms for age-related reductions in lateralized activity are due to functional compensation (Cabeza, 2002; Reuter-Lorenz et al., 2000, 2002), primary deficits in function (Lapidot, 1987; McDowell et al., 1994), dedifferentiation of function (Li et al., 2001; Lindenberger et al., 2001), or some combination of these mechanisms.

According to the functional compensation view, age-related decreases or absences in activation reflect deficits in brain function (Cabeza, 2002; Cabeza et al., 2002, 2004) and the concomitant increases in activation reflect either successful compensation for these deficits, when there are no age-differences in performance, and ‘attempted’ compensation for these deficits, when there is an age-related decrement in performance (Cabeza, 2002; Cabeza et al., 2000; Grady, 2002; Grady et al., 1999; Madden et al., 1999; Reuter-Lorenz et al., 2000). It is unclear from a compensation perspective whether these compensatory activations reflect the recruitment of different regions and processes, which assumes that regional process-specificity does not change with age, or whether these changes reflect alterations in the processes mediated by the recruited regions, which assumes that as a result of neural plasticity, regional process-specificity changes with age.

Investigators have interpreted age-related changes in brain activation patterns to support both compensation perspectives. For example, in a PET study investigating age-related differences in visual memory for sinewave gratings, McIntosh et al. (1999) found that older subjects performed equivalently to young subjects, but recruited a different neural network to perform the task. It was concluded that these changes reflected age-related reorganization of cortical function. In contrast, Cabeza et al. (2003, 2004) argue that if the production-monitoring distinction for respective left/right PFC activation during EM retrieval is true, then increased bilateral PFC activity in older subjects may reflect compensatory use of production processes when monitoring processes fail and vice versa. This conclusion assumes that regional process-specificity is maintained across lifespan.

According to the dedifferentiation view, age-related changes in functional activations reflect deficits in neurotransmission, which in turn cause decreases in signal-to-noise ratio and less distinct neural representations (Li et al., 2001). It follows, that decreases in activation reflect a deficit due to reductions in regional process-specificity. Increases in activity reflect generalized spreading of activity due to reduced specialization of function, which may or may not be compensatory. Therefore, this view suggests that overall there is no change in regional process-specificity in cortical function across lifespan, but that this specificity becomes more generalized with normal ageing.

Therefore, age-related changes in PFC function may be due to primary deficits in function, functional compensation (with or without reorganization of function) and dedifferentiation of function. The functional compensation and dedifferentiation perspectives both assume that there are primary deficits in function with age that precipitate functional compensation. However, the functional compensation perspective does not state precisely what neural changes precipitate deficits in function, whereas the dedifferentiation perspective does. According to the dedifferentiation perspective age-related deficits in function are due to deficits in neurotransmission resulting in noisier internal cortical representations (deficits in function). The functional compensation and dedifferentiation perspectives also differ in how they interpret age-related increases in PFC function. According to the former perspective age-related increases in PFC activity are compensatory. According to the latter perspective these age-related increases in activity may not always be compensatory, since age-related reductions in regional process-specificity may result in aberrant neural activity. In some cases this may benefit task performance (compensation) and in other cases it may be detrimental to task performance. Therefore, the dedifferentiation perspective does not neglect the possibility that age-related increases in PFC activity may be compensatory.
Structural and functional heterogeneity in the human PFC

One problem shared by both the functional compensation and dedifferentiation perspectives is that they treat the PFC as one homogeneous region. However, there is evidence that the PFC is neither structurally nor functionally homogeneous (Brodmann, 1909; Economo and Koskinas, 1925; Pandya and Yeterian, 1985; Petrides and Pandya, 1994; D’Esposito et al., 1999b; Cabeza and Nyberg, 2000; Duncan and Owen, 2000). The PFC in humans compromises most of the frontal lobes and is located rostral to the central sulcus, anterior to the Sylvian fissure and excludes primary and association motor cortices. Structurally, the PFC consists mostly of neocortex which has six cellular layers (Talairach and Tournoux, 1988). Traditionally, neuroscientists have subdivided the PFC into the following ‘classical’ regions based on gross anatomic markers: orbitofrontal cortex, dorsolateral PFC, ventrolateral PFC, anterior PFC and medial PFC (Luria, 1962; Milner and Petrides, 1984; Mesulam, 1986; Morecraft et al., 1993; Petrides and Pandya, 1999, 2002; Petrides et al., 2002; Ongur et al., 2003). However, variation in cytoarchitecture has also been used to define distinct structural regions within the PFC (Brodmann, 1909; Economo and Koskinas, 1925; Bonin and Bailey, 1947; Petrides and Pandya, 1994, 1999, 2002; Ongur et al., 2003). For example, by using the Nissl staining method and light microscope Brodmann (1909) examined laminar differences in the human PFC and defined the following cytoarchitectonic areas, referred to as Brodmann areas (BA): 8, 9, 10, 11, 12, 44, 45, 46 and 47. Additional cytoarchitectonic maps of human and primate frontal lobes have also been defined (Economo and Koskinas, 1925; Walker, 1940; Bonin and Bailey, 1947; Petrides and Pandya, 1994, 1999, 2002); however, the Brodmann map has been the most widely used in expressing functional and structural neuroimaging results of humans. The Brodmann map of the human PFC has been superimposed on the traditional subdivisions of the human PFC (see Fig. 1) and cognitive neuroscientists often use both methods when discussing structural subdivisions within the human PFC.

Therefore, it is generally accepted that there is structural heterogeneity within the human PFC. Due to these structural differences it has also been suggested that there is functional heterogeneity in the roles played by distinct PFC regions in human cognition and behaviour. The arguments for functional heterogeneity of the PFC are supported by retrograde and anterograde tracer studies that have shown distinct patterns of cortico-cortical connectivity for dorsolateral, ventrolateral, orbitofrontal and medial PFC with posterior cortical regions (Carmichel and Price, 1998; Petrides and Pandya, 1999, 2002; Ongur and Price, 2000; Stefanacci and Amaral, 2002; Ongur et al., 2003). For example, Petrides and Pandya (1999, 2002) have shown that the dorsal and medial PFC regions are reciprocally connected with the posterior cortical regions involved in visuospatial processing, such as: superior parietal lobule, caudal portions of inferior parietal lobule, dorsal and medial occipital cortex, and caudal parietotemporal regions. In contrast, orbital and ventrolateral PFC regions are reciprocally connected with posterior cortical regions involved in object perception and identification such as inferotemporal cortex. Therefore, it has been suggested that due to these different patterns of anatomical connectivity, the dorsal and medial areas of PFC are involved in visuospatial processing whereas the orbital and ventrolateral area of the PFC are involved in object meaning (Petrides and Pandya, 1999, 2002).

Evidence for the functional heterogeneity of the PFC also emerges from neuropsychological examinations of patients with frontal lobe damage (Petrides, 1983, 1996; Shimamura, 1995; Stuss and Alexander, 2000; Stuss et al., 2001; Mesulam, 2002; Stuss et al., 2002a; Fellows and Farah, 2003; Bechara, 2004; Roberts et al., 2004], lesion studies of non-human primates (Passingham, 1972, 1975; Mishkin, 1978; Mishkin and Manning, 1978; Dias et al., 1996, 1997; Collins et al., 1998; Petrides, 2000; Mesulam, 2002), physiological studies of regional differences in neurotransmitter modulation (Robbins, 2000; Castner et al., 2004; Seamans and Yang, 2004) and from neuroimaging studies examining cognitive function in healthy young adults (Cabeza and Nyberg, 2000; D’Esposito et al., 2000; Duncan and Owen, 2000; Rugg et al., 2002; Gilboa, 2004). For example, based on lesion studies of both human and non-human primates, Petrides (1994, 1996, 2002) has found that damage to the mid-ventrolateral PFC versus damage to the mid-dorsolateral PFC produces dissoluble deficits on memory performance. Specifically, he
argues that mid-ventrolateral PFC damage produces deficits in the active selection, comparison and judgement during retrieval in both WM and EM tasks (Petrides, 2002). In contrast, mid-dorsolateral PFC damage produces deficits in monitoring task performance during WM and EM tasks.

Similar dissociations in function have been observed in functional neuroimaging studies of WM and EM in healthy young adults (Cabeza and Nyberg, 2000; D’Esposito et al., 2000; Rugg et al., 2002, 2003; Wheeler and Buckner, 2003). For example, several studies have shown that manipulating information within WM activates the dorsolateral PFC whereas maintaining information within WM activates the ventrolateral PFC (D’Esposito, 1999a; 2000). EM studies have consistently reported left inferior PFC activity during encoding and bilateral dorsolateral and right anterior PFC activity during retrieval. In general, the focus of recent functional imaging studies has been on dissociating the functional contributions of the ventrolateral, dorsolateral and anterior PFC during EM and WM (Ranganath et al., 2000; Dobbins et al., 2003, 2004; Rugg et al., 2003). Therefore, in addition to structural heterogeneity, the neuropsychological and neuroimaging findings suggest that there is also functional heterogeneity between the ventral, dorsal and anterior PFC regions.

Examiner region-specific changes in PFC function with age

We argue that neuroscience-based models of cognitive ageing must consider the above evidence that the PFC is neither structurally nor functionally homogeneous; especially since recent in vivo volumetric studies report that there are regional differences in age-related cortical atrophy. For example, studies have consistently reported volume reductions in lateral and orbital PFC with age (Raz et al., 1997; Salat et al., 2001; Tisserand, 2002, 2004). Given these reports of region-specific changes in the PFC structure with age, it is important that region-specific changes in PFC functions with age also be examined. In fact, several cognitive ageing studies have identified different patterns of activity and cortical atrophy in the ventral versus dorsal PFC across WM and EM tasks with age (Madden et al., 1999; Anderson et al., 2000; Cabeza et al., 2000; Raz, 2000; Schiavetto et al., 2002; Tisserand et al., 2002; Daselaar et al., 2003). However, to date, there has not been a review examining regionally-specific patterns of age-related changes in PFC function. Moreover, previous reviews have not considered the possibility that with age, distinct PFC regions may differentially reflect primary deficits in function, dedifferentiation of function and functional compensation with or without functional reorganization, respectively. These are the goals of the current review.

Unlike previous reviews of this literature, we have systematically tabulated age-related functional changes within distinct PFC regions, across tasks, to test the aforementioned hypotheses. Since the majority of the neuroimaging studies on cognitive ageing have utilized WM and EM tasks, we focus on these studies. We perform a qualitative meta-analytic review of all fMRI and PET studies archived by PubMed in the area of ageing, WM and EM that report PFC activation. Our goal is to examine age-related changes in the functional contributions of the ventral, dorsal and anterior PFC. We focus on these three subdivisions of the PFC since there is evidence that they are structurally distinct and also functionally distinct, within the context of WM and EM tasks (Petrides and Pandya, 1999, 2002; Ranganath and Paller, 1999; Cabeza and Nyberg, 2000; D’Esposito et al., 2000; Ranganath et al., 2000; Dobbins et al., 2002; Mesulam, 2002; Petrides et al., 2002; Rugg et al., 2002; Stuss et al., 2002). We predict that there will be a consistent pattern of region-specific, age-related, changes in PFC function across studies, which supports the hypothesis that ageing differentially affects distinct regions of PFC. In addition, we present some tentative predictions as to what mechanisms may cause these distinct regional changes: dedifferentiation of cortical function, deficits in cortical function or functional compensation, respectively. We hope our review will generate new hypotheses that stimulate future research in the cognitive neuroscience of ageing.

Methods

Inclusion criteria

We conducted a literature search using the keywords: ageing/age, brain, memory and imaging in PubMed for papers published between 1997 and the first half of 2004. Only studies that examined either the encoding phase, the retrieval phase, or both, in WM or EM were included in this review. Studies reviewed used either univariate or multivariate methods to analyse the imaging data. Only those studies that either used only within group analysis of young and older subjects, or, used both within and between group analyses, were included in this review.

Behavioural performance of the older subjects, relative to young, was not used to rule out study inclusion. Thus, in some studies older subjects performed equivalently to young in accuracy, whereas in others there was an age-related deficit in accuracy. Table 1 lists all 22 studies that were reviewed, the neuroimaging technique employed, a summary of the type of task employed in each study and the between-group behavioural accuracy results. We do not report the between-group behavioural reaction time results since most of the studies reviewed reported a significant between-group difference in reaction time response, with older subjects consistently responding slower than young subjects (Grady et al., 1998, 2002; Madden et al., 1999; Grossman et al., 2002; Cabeza et al., 2004). There were only two exceptions to this general finding (Daselaar et al., 2003; Morcom et al., 2003). In these two studies there were no significant between-group differences in reaction time.

Defining PFC activation

This review focuses on activations reported in the ventral PFC [Brodman area (BA) 44, 45 and 47 on inferior frontal gyrus (IFG)] dorsal PFC [BA 9 and 46 on middle frontal gyrus (MFG)], and anterior PFC [BA 9 or 10 on superior frontal gyrus (SFG)], since activations in these PFC subregions have been observed in previous neuroimaging studies of WM and EM in young subjects (Fletcher et al., 1997;
<table>
<thead>
<tr>
<th>No.</th>
<th>Study</th>
<th>Neuroimaging method</th>
<th>Cognitive task</th>
<th>Behavioural performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anderson et al. (2000)</td>
<td>PET</td>
<td>EM encoding and retrieval of word pairs under full attention and divided attention. Retrieval phase involved a forced-choice recognition task.*</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>2</td>
<td>Cabeza et al. (2004)</td>
<td>fMRI</td>
<td>Verbal WM delayed-response task, verbal EM recognition task and visual attention task.**</td>
<td>(Y = O^{***})</td>
</tr>
<tr>
<td>3</td>
<td>Cabeza et al. (2002)BB</td>
<td>PET</td>
<td>EM retrieval of word pairs. Retrieval phase involved cued recall and source retrieval.</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>4</td>
<td>Cabeza et al. (2000)</td>
<td>PET</td>
<td>EM retrieval of words. Retrieval phase involved both recognition and temporal order memory tasks.</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>5</td>
<td>Cabeza et al. (1997)BB</td>
<td>PET</td>
<td>EM encoding and retrieval of word pairs. Retrieval phase included recognition tasks and cued recall tasks.</td>
<td>(Y = O)</td>
</tr>
<tr>
<td>6</td>
<td>Daselaar et al. (2003)BB</td>
<td>fMRI</td>
<td>EM encoding and retrieval of words. Retrieval phase involved forced-choice recognition.</td>
<td>(Y = O)</td>
</tr>
<tr>
<td>7</td>
<td>Grady et al. (1999)</td>
<td>PET</td>
<td>EM encoding of words and pictures. Levels of processing manipulation incorporated into encoding phase. WM delayed match-to-sample task for faces. Delay manipulation incorporated: long versus short delay.</td>
<td>(Y = O), encoding; (Y &gt; O), post-scan recognition</td>
</tr>
<tr>
<td>8</td>
<td>Grady et al. (1998)BB</td>
<td>PET</td>
<td>EM encoding and retrieval for faces. Levels of processing manipulation during encoding. Retrieval phase involved forced-choice recognition tasks.</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>9</td>
<td>Grady et al. (2002)BB</td>
<td>PET</td>
<td>Sentence comprehension task. WM manipulation involved long versus short antecedent noun-gap linkage. Intentional EM encoding of pairs of abstract pictures.</td>
<td>(Y = O), encoding, recognition hits; (Y &gt; O), recognition false alarms</td>
</tr>
<tr>
<td>10</td>
<td>Grossman et al. (2002)</td>
<td>fMRI</td>
<td>WM delayed match-to-sample task for object, location and combination trials.</td>
<td>(Y = O)</td>
</tr>
<tr>
<td>11</td>
<td>Iidaka et al. (2001)BB</td>
<td>fMRI</td>
<td>EM encoding for words using animacy judgements</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>12</td>
<td>Jonides et al. (2000)</td>
<td>PET</td>
<td>Verbal WM item recognition task.</td>
<td>(Y = O), overall; (Y &lt; O), interference effect</td>
</tr>
<tr>
<td>13</td>
<td>Logan et al. (2002)</td>
<td>fMRI</td>
<td>Experiment 1: EM encoding for faces and words. Experiment 2: levels of processing manipulation incorporated to encoding phase.</td>
<td>(Y = O), encoding; (Y &gt; O), post-scan recognition test. Experiment 2: (Y = O)</td>
</tr>
<tr>
<td>14</td>
<td>Madden et al. (1999)BB</td>
<td>PET</td>
<td>EM encoding and retrieval of words. Retrieval phase involved forced-choice recognition.</td>
<td>(Y = O), encoding; (Y &gt; O) recognition</td>
</tr>
<tr>
<td>15</td>
<td>Mitchell et al. (2000)</td>
<td>fMRI</td>
<td>WM delayed match-to-sample for real world scenes. Examined activity differences between a WM maintenance condition and an extended visual condition.</td>
<td>(Y &gt; O)</td>
</tr>
<tr>
<td>16</td>
<td>Morcom et al. (2003)BB</td>
<td>fMRI</td>
<td>EM encoding for words using animacy judgements</td>
<td>(Y = O), encoding; (Y &gt; O), post-scan recognition</td>
</tr>
<tr>
<td>17</td>
<td>Park et al. (2003)</td>
<td>fMRI</td>
<td>WM delayed-response task for real world scenes. Examined activity differences between a WM maintenance condition and an extended visual condition.</td>
<td>(Y = O)</td>
</tr>
<tr>
<td>18</td>
<td>Reuer-Lorenz et al. (2000)</td>
<td>PET</td>
<td>WM delayed match-to-sample task for spatial and for verbal information.</td>
<td>(Y = O)</td>
</tr>
<tr>
<td>19</td>
<td>Rosen et al. (2002)BB</td>
<td>fMRI</td>
<td>EM encoding for words. Levels of processing manipulation at encoding. WM delayed-response task. Incorporated a WM load manipulation: high versus low load.</td>
<td>(Y = O), encoding; (Y &gt; O), post-scan recognition</td>
</tr>
<tr>
<td>20</td>
<td>Rypma and D’Esposito (2000)</td>
<td>fMRI</td>
<td>WM delayed-response task. Incorporated a WM load manipulation: high versus low load.</td>
<td>(Y = O)</td>
</tr>
</tbody>
</table>
D’Esposito et al., 1998, 1999b; Henson et al., 1999; Cabeza and Nyberg, 2000; Habib et al., 2003; Nyberg et al., 2003; Wager and Smith, 2003). Figure 1 presents an anatomical image of the human brain, highlighting the regional ventral, dorsal and anterior subdivisions, used in tabulating activations for this review. For each study, results from fMRI or PET activation analyses that directly compared memory tasks to a control task or to one another were examined. Only task effects yielding PFC activations in young subjects, old subjects, or both, were included in the review. PFC activations reported from higher order interaction effects that were specific to a particular study design, and therefore would not be comparable to result from other studies, were excluded from the review.

Ventral, dorsal and anterior PFC activations reported for young and older subjects from the reviewed WM studies, EM studies of encoding and EM studies of retrieval were tabulated separately by region, respectively (Tables 2–4). Each table was organized into the following columns: the study reviewed, the contrast tested, and the hemispheric location of each activation for each age group, respectively. For studies that employed multivariate partial least squares regression methods and was conducted in 6 of the 22 papers reviewed (Grady et al., 1998, 2002; Iidaka et al., 2002; Madden et al., 1999; Morcom et al., 2003; Rypma and D’Esposito, 2000). Indirect examinations of brain-behaviour relationships were conducted in three studies reviewed (Cabeza et al., 2002; Rosen et al., 2002; Daselaar et al., 2003). In these studies older subjects were split into two groups based on behavioural performance: high performers, who performed equivalently to young subjects, and low performers, who performed poorer than high performing older and young

**Table 1 Continued**

<table>
<thead>
<tr>
<th>No.</th>
<th>Study</th>
<th>Neuroimaging method</th>
<th>Cognitive task</th>
<th>Behavioural performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Schiavetto et al. (2002) PET</td>
<td>Perceptual matching baselines for object identity and object location. EM encoding and retrieval of objects. Retrieval phase involved forced choice recognition task for either object identity or location.</td>
<td>Y &gt; O</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Smith et al. (2001) PET</td>
<td>Single verbal WM delayed-response task and dual task verbal WM with mathematical operation span.</td>
<td>Y = O</td>
<td></td>
</tr>
</tbody>
</table>

List of studies included in the review. The neuroimaging-method column describes whether PET or fMRI was used in the study. The ‘Cognitive task’ column gives a brief description of the tasks tested. The ‘Behavioural performance’ column lists whether there was a significant between group difference in which the elderly performed poorer than the young (Y > O) or whether there were no significant between group differences in accuracy across tasks (Y = O). If a study produced both significant and non-significant effects it is noted for which tasks there was an effect (e.g. ‘Y > O, recognition’) and for which tasks there was no effect (e.g. ‘Y = O, encoding’). EM, episodic memory; WM, working memory. *Only the results from full attention conditions were included in this review. **Only the results from the WM and EM tasks are included in this review. ***Older subjects had fewer remember responses and more know responses compared to young subjects. BB, highlights papers that conducted either an indirect or a direct examination of brain-behaviour relationships.
### Table 2  Summary of ventral PFC activations reported across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Analytical methods</th>
<th>Contrast</th>
<th>Hemisphere</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Young</td>
<td>Old</td>
</tr>
<tr>
<td>Working memory studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabeza et al. (2004)</td>
<td>Conjunction analysis</td>
<td>WM &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Grady et al. (1998)</td>
<td>Within-group univariate</td>
<td>WM &gt; control</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Jonides et al. (2000)</td>
<td>Between-group ROI analysis</td>
<td>High &gt; low interference</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Mitchell et al. (2000)</td>
<td>Between-group ANOVA</td>
<td>Object WM main effect</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Park et al. (2003)</td>
<td>Between-group ROI analysis</td>
<td>WM retrieval &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Reuter-Lorenz et al. (2000)</td>
<td>Between-group VQI analysis</td>
<td>Spatial WM</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Rypma and D'Esposito (2000)</td>
<td>Within-group univariate</td>
<td>WM encoding &gt; fixation</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Smith et al. (2001)</td>
<td>Within-group univariate</td>
<td>Dual-task &gt; single tasks</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Episodic memory encoding studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. (2000)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; retrieval</td>
<td></td>
<td>YY</td>
<td>YY</td>
</tr>
<tr>
<td>Cabeza et al. (1997)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; retrieval</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Daselaar et al. (2003)</td>
<td>Within-group univariate SPM</td>
<td>Encoding &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Grady et al. (1999)</td>
<td>Between-group multivariate PLS</td>
<td>Levels of processing effect</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Grady et al. (2002)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; control</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Iidaka et al. (2001)</td>
<td>Within-group univariate</td>
<td>Encoding concrete unrelated words &gt; control</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Logan et al. (2002)</td>
<td>Between-group ROI analysis</td>
<td>Encoding abstract pictures &gt; control</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Madden et al. (1999)</td>
<td>Within-group univariate</td>
<td>Encoding &gt; baseline</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Morcom et al. (2003)</td>
<td>Between-group univariate</td>
<td>Encoding &gt; baseline related to subsequent memory</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Rosen et al. (2002)</td>
<td>Within-group univariate</td>
<td>Deep &gt; shallow encoding</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Schiavetto et al. (2002)</td>
<td>Between-group ROI analysis</td>
<td>Deep &gt; shallow encoding</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Episodic memory retrieval studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. (2000)</td>
<td>Between-group multivariate PLS</td>
<td>Retrieval &gt; encoding</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Cabeza et al. (2004)</td>
<td>Conjunction analysis</td>
<td>Retrieval &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Cabeza et al. (2002)</td>
<td>Within-group univariate</td>
<td>Cued recall &gt; source memory</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Cabeza et al. (1997)</td>
<td>Between-group multivariate PLS</td>
<td>Retrieval &gt; encoding</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Daselaar et al. (2003)</td>
<td>Within-group univariate SPM</td>
<td>Retrieval &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Grady et al. (2002)</td>
<td>Between-group multivariate PLS</td>
<td>Retrieval &gt; encoding</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Madden et al. (1999)</td>
<td>Within-group univariate</td>
<td>Retrieval &gt; baseline</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Schiavetto et al. (2002)</td>
<td>Between-group ANOVA</td>
<td>Retrieval &gt; encoding main effect and interaction</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Total sum of reported age-related increases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

This table presents reviewed studies that reported ventral PFC activity. Reports of ventral PFC activity are listed first by study type (first column; WM, for working memory and EM, for episodic memory). The method of neuroimaging analysis and contrast effects yielding ventral PFC activations are presented in columns two and three, respectively. The activations are organized by cerebral hemisphere (Left versus Right) and by age group (Young versus Old). Y's and O's are used to notate the activations reported in Young and Old subject groups across studies, respectively. Y, ventral PFC activity in young subjects; O, ventral PFC activity in old subjects; YY, the authors reported young only or young greater than old activity (Y > O) activity in this region for a specific task effect. The bottom row of the table represents the total weighted sum in this region for a specific task effect. OO, the authors reported old only or old greater than young (O > Y) of reported left/right ventral PFC activation in young or old subjects across the studies presented (refer to the Methods section to see how the sum was calculated).
<table>
<thead>
<tr>
<th>Study</th>
<th>Analytical methods</th>
<th>Contrast</th>
<th>Hemisphere</th>
<th>Left</th>
<th>Young</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabeza et al. (2004)</td>
<td>Conjunction analysis</td>
<td>WM &gt; baseline</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between-group univariate analysis</td>
<td>WM &gt; baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grady et al. (1998)</td>
<td>Within-group univariate analysis</td>
<td>WM &gt; control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between-group multivariate analysis</td>
<td>Long &gt; short delay</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grossman et al. (2002)</td>
<td>Between-group univariate analysis</td>
<td>Long &gt; short linkage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. (2000)</td>
<td>Between-group ANOVA</td>
<td>Object WM</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reuter-Lorenz et al. (2000)</td>
<td>Between-group VOI analysis</td>
<td>Spatial WM</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between-group VOI analysis</td>
<td>WM encoding &gt; fixation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group univariate analysis</td>
<td>WM maintenance &gt; fixation</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group univariate analysis</td>
<td>WM retrieval &gt; fixation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Across group univariate analysis</td>
<td>WM retrieval &gt; fixation</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group ROI analysis</td>
<td>WM retrieval &gt; baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group ROI analysis</td>
<td>WM retrieval &gt; High &gt; low load</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group ROI analysis</td>
<td>Dual-task &gt; single tasks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic memory encoding studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. (2000)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; retrieval</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabeza et al. (1997)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; retrieval</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grady et al. (1999)</td>
<td>Between-group multivariate PLS</td>
<td>Verbal &gt; object encoding</td>
<td>YY</td>
<td>O</td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td>Between-group multivariate PLS</td>
<td>Intentional &gt; semantic encoding</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between-group multivariate PLS</td>
<td>Levels of processing effect</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grady et al. (2002)</td>
<td>Between-group multivariate PLS</td>
<td>Encoding &gt; control</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iidaka et al. (2001)</td>
<td>Within-group univariate analysis</td>
<td>Encoding concrete unrelated words &gt; control</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group univariate analysis</td>
<td>Encoding abstract pictures &gt; control</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madden et al. (1999)</td>
<td>Within-group univariate analysis</td>
<td>Encoding &gt; baseline</td>
<td>YY</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morcom et al. (2003)</td>
<td>Between-group univariate analysis</td>
<td>Encoding &gt; baseline related to subsequent memory</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within-group univariate analysis</td>
<td>Deep &gt; Shallow Encoding</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sum of reported age-related increases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table presents reviewed studies that reported dorsal PFC activity. Reports of dorsal PFC activity are listed first by study type (first column; WM, for working memory and EM, for episodic memory). The method of neuroimaging analysis and contrast effects yielding dorsal PFC activations are presented in columns two and three, respectively. The activations are organized by cerebral hemisphere (Left versus Right) and by age group (Young versus Old). Y’s and O’s are used to notate the activations reported in Young and Old subject groups across studies, respectively. Y, dorsal PFC activity in young subjects; O, dorsal PFC activity in old subjects; YY, the authors reported young only or young greater than old activity (Y > O) in this region for a specific task effect; OO, the authors reported old only or old greater than young (O > Y) activity in this region for a specific task effect. The bottom row of the table represents the total weighted sum of reported left/right dorsal PFC activation in young and old subjects across the studies presented (refer to the Methods section to see how the sum was calculated).
Table 4  Summary of anterior PFC activations reported across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Analytical methods</th>
<th>Contrast</th>
<th>Hemisphere</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Working memory studies</td>
<td></td>
<td></td>
<td></td>
<td>YY</td>
<td>Y</td>
</tr>
<tr>
<td>Grady et al. (1998)</td>
<td>Within-group univariate</td>
<td>WM &gt; control</td>
<td>Left</td>
<td>YY</td>
<td>Y</td>
</tr>
<tr>
<td>Grossman et al. (2002)</td>
<td>Between-group multivariate</td>
<td>Long &gt; short delay</td>
<td>Right</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Mitchell et al. (2000)</td>
<td>Between-group univariate</td>
<td>Long &gt; short linkage</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Smith et al. (2001)</td>
<td>Within-group ROI analysis</td>
<td>Verbal WM &gt; control</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Episodic memory encoding studies</td>
<td></td>
<td></td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Daselaar et al. (2003)</td>
<td>Within-group univariate SPM</td>
<td>Encoding &gt; baseline</td>
<td>Left</td>
<td>YY</td>
<td></td>
</tr>
<tr>
<td>Grady et al. (1999)</td>
<td>Between-group multivariate</td>
<td>Verbal &gt; object encoding</td>
<td>Right</td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Grady et al. (2002)</td>
<td>Between-group multivariate</td>
<td>Semantic &gt; intentional encoding</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Morcom et al. (2003)</td>
<td>Between-group multivariate</td>
<td>Levels of processing effect</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Rosen et al. (2002)</td>
<td>Between-group univariate</td>
<td>Encoding &gt; baseline</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td>Schiavetto et al. (2002)</td>
<td>Between-group ANOVA</td>
<td>Encoding &gt; Retrieval main effect and interaction</td>
<td></td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Episodic memory retrieval studies</td>
<td></td>
<td></td>
<td></td>
<td>YY</td>
<td>Y</td>
</tr>
<tr>
<td>Anderson et al. (2000)</td>
<td>Between-group multivariate</td>
<td>Retrieval &gt; encoding</td>
<td>Left</td>
<td>YY</td>
<td>YY</td>
</tr>
<tr>
<td>Cabeza et al. (2004)</td>
<td>Conjunction analysis</td>
<td>Retrieval &gt; baseline</td>
<td>Right</td>
<td>Y</td>
<td>O</td>
</tr>
<tr>
<td>Cabeza et al. (2002)</td>
<td>Within-group univariate</td>
<td>Source memory &gt; cued recall</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Cabeza et al. (2000)</td>
<td>Between-group ANOVA</td>
<td>Temporal order &gt; item retrieval</td>
<td></td>
<td>YY</td>
<td></td>
</tr>
<tr>
<td>Madden et al. (1999)</td>
<td>Between-group multivariate</td>
<td>Retrieval &gt; encoding</td>
<td></td>
<td>YY</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td>Within-group univariate</td>
<td>Retrieval &gt; baseline</td>
<td></td>
<td>YY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between-group univariate</td>
<td>Retrieval &gt; baseline</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Total sum of reported age-related increases</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

This table presents reviewed studies that reported anterior PFC activity. Reports of anterior PFC activity are listed first by study type (first column; WM, for working memory anterior PFC activations are presented in columns two and three, respectively. The activations are organized by cerebral hemisphere (Left versus Right) and by age group (Young versus Old). Y’s and O’s are used to notate the activations reported in Young and Old subject groups across studies, respectively. Y, anterior PFC activity in young subjects; O, anterior PFC activity in old subjects; YY, the authors reported young only or young greater than old activity (Y > O) in this region for a specific task effect. OO, the authors reported old only or old greater than young (O > Y) activity in this region for a specific task effect. The bottom row of the table represents the total weighted sum of reported left/right anterior PFC activation in young or old subjects across the studies presented (refer to the Methods section to see how the sum was calculated).
subjects. Brain activity differences were then examined between these groups.

Results
The results of this review are presented in two sections. First, we summarize the age-related differences in regional PFC activations. Second, we examine hemispheric differences in age-related deficits in PFC function.

Region-specific changes in PFC activity

Ventral PFC

WM studies. The majority of the WM studies reviewed used variations of traditional delay tasks. However, the number of studies that focused on any single cognitive operation were few. Thus, we do not differentiate between age-related differences in PFC activity within a particular WM operation or manipulation in this review.

In general, both young and elderly show similar patterns of PFC activation across WM studies. In a few studies, older subjects exhibited less left ventral PFC activity [3/9 studies; Grady et al., 1998; Jonides et al., 2000; Smith et al., 2001] and less right ventral PFC activity [2/9 studies; Grady et al., 1998; Grossman et al., 2002] compared to young subjects. In three studies ventral PFC was over-recruited in older subjects (Reuter-Lorenz et al., 2000; Smith et al., 2001; Park et al., 2003).

EM encoding studies. Both age groups exhibit left-biased ventral PFC activity during encoding but older subjects exhibited less left ventral PFC activity compared to young subjects (6/12 studies; see Table 2). In addition, in three of these studies the elderly also exhibited less right ventral PFC activity compared to young subjects (Anderson et al., 2000; Grady et al., 2002; Logan et al., 2002). However, in the Logan et al. (2002) study, the elderly activated the contralateral ventral PFC region to a greater extent during word encoding (right > left in elderly) and face encoding (left > right in elderly), compared to the young subjects.

The elderly over-recruited the ventral PFC in three studies (Madden et al., 1999; Rosen et al., 2002; Schiavetto et al., 2002). In two of these studies this over-recruitment was left lateralized (Madden et al., 1999; Schiavetto et al., 2002) and in the other it was right lateralized (Rosen et al., 2002). Overall, the studies show that both age groups activate the bilateral ventral PFC during EM encoding; however, there is greater activity in the left ventral PFC compared to the right ventral PFC and young subjects activate the left ventral PFC to a greater degree than older subjects.

EM retrieval studies. Older subjects consistently exhibit greater left ventral PFC during retrieval as compared to young subjects (6/8 studies; see Table 2). In contrast, Cabeza et al. (1997) report greater right ventral PFC activity in young versus older subjects.

Summary. Across task domains both age groups activate the ventral PFC. More specifically, during WM and EM encoding, older subjects do not engage ventral PFC to the same degree as young subjects. In contrast, during EM retrieval, older subjects over-recruit the ventral PFC, especially in the left hemisphere. Combined, these results suggest reduced task-specificity in ventral PFC function with age.

Dorsal PFC

WM studies. Older subjects exhibited greater dorsal PFC activity, especially in the left hemisphere, compared to young subjects (5/7 studies; see Table 3).

EM encoding studies. Overall, young subjects exhibited greater dorsal PFC activity compared to older subjects (5/9 studies; see Table 3). In two of these studies the effect was bilateral. However, in one study the elderly activated right dorsal PFC when young subjects did not in a between-group comparison (Anderson et al., 2000) and in another study the elderly activated the left dorsal PFC when young subjects did not in within-group comparisons (Madden et al., 1999).

EM retrieval studies. Young subjects exhibited greater dorsal PFC activity compared to older subjects (4/9 studies; see Table 3), particularly in the right dorsal PFC. However, in three studies the elderly activated right dorsal PFC when young subjects did not (at the thresholds specified; Madden et al., 1999; Grady et al., 2002; Dase laar et al., 2003).

Summary. Across task domains both age groups activate the dorsal PFC. During WM tasks, older subjects exhibit greater left dorsal PFC activity compared to young. During EM encoding and retrieval young subjects recruited the bilateral dorsal PFC to a greater degree than older subjects; though this effect was stronger for EM encoding. The tabulated weighted sums of dorsal PFC activity across task domains demonstrates more reports of greater left dorsal PFC activity in older subjects compared to young (9 for young and 15 for older) and more reports of greater right dorsal PFC activity in the young compared to the older subjects (19 for young and 11 for the older). These results suggest that older subjects may under-recruit the right dorsal PFC and over-recruit the left dorsal PFC across tasks.

Anterior PFC

WM studies. Anterior PFC activity was reported during WM tasks in only four studies. Grady et al. (1998) found greater left anterior PFC activity in young subjects, but greater right anterior PFC activity in older subjects. Grossman et al. (2002) found greater bilateral anterior PFC in older subjects.
Region-specific changes in PFC function with age

compared to young subjects. Smith et al. (2001) reported greater left anterior PFC activity in older versus younger subjects in the contrast comparing WM to control task activation. However, Smith et al. (2001) and Mitchell et al. (2000) reported greater right anterior PFC activity in young subjects. Thus, across experiments there was no consistent pattern in anterior PFC activity by age group.

EM encoding studies. In six studies reporting anterior PFC activity, three found greater left anterior PFC activity (Daselaar et al., 2003), and one found greater right anterior PFC activity (Grady et al., 1999), in the young versus the older subjects. However, Grady et al. (1999) reported greater left anterior PFC activity in older versus younger subjects for the level of processing contrast. In addition, another study (Morcom et al., 2002) reported greater bilateral anterior PFC activity in older versus young subjects during encoding.

EM retrieval studies. Overall, studies reported greater right versus left anterior PFC activity in young subjects during EM retrieval. In four of these studies older subjects under-recruited right anterior PFC compared to young subjects, for some of the task contrasts specified (Cabeza et al., 1997, 2000; Madden et al., 1999; Anderson et al., 2000).

However, Cabeza et al. (2002) reported greater bilateral anterior PFC activity in the elderly versus younger subjects during source memory retrieval versus cued recall, based on qualitative comparisons of within group analysis results. Two additional studies reported greater left anterior PFC activity in older subjects during EM retrieval (Madden et al., 1999; Cabeza et al., 2000).

Summary. Across task domains both age groups activate anterior PFC. The weighted total sums of reported age-related increases in left and right anterior activity indicate that there were greater reports of increased left anterior PFC activity, across task domains, in the older versus young subjects (8 for young and 12 for older). In contrast, there was greater right anterior PFC activity in the young versus the older subjects, across domains (10 for young and 7 for older).

Hemispheric differences in age-related deficits in PFC function

The weighted sum of the reported age-related increases tabulated for the bilateral ventral, dorsal and anterior PFC regions indicates that for all three regions there are fewer reports of right-lateralized activity for the elderly subjects compared to young subjects in the studies reviewed when one collapses across task domain (see bottom row of Tables 2–4). However, this effect is most evident in reports of dorsal PFC activations across task domains. In addition, the weighted sums of the reported age-related increases (tabulated for each PFC region) indicate that for all three subregions there are more reports of left-lateralized activity for the older compared to young subjects in the studies reviewed (see bottom row of Tables 2–4).

Discussion

The goal of this review was to determine whether there are region-specific changes in PFC function with age. A comprehensive review of published human functional neuroimaging studies revealed activation foci in the bilateral ventral, dorsal and anterior PFC regions across WM, EM encoding and EM retrieval tasks, in both age groups. By examining age-related differences within each task domain, we found that overall both age groups engage the similar brain regions while performing WM and EM tasks. This suggests that in general PFC function remains intact with age. However, by tabulating age-related differences in PFC activity across task domains we found that there were region-specific changes in PFC function with age. Thus, we argue that strict adherence to either the traditional functional compensation or dedifferentiation perspectives cannot adequately account for the complex patterns of age-related changes observed, since neither of these perspectives takes into account the differential patterns of region-specific, age-related change in prefrontal function (Nielsen-Bohlman and Knight, 1995; Li et al., 2001; Braver and Barch, 2002; Cabeza, 2002; Grady, 2002; Reuter-Lorenz, 2002).

In the following sections, we discuss how the age-related changes in functional activation in the ventral, dorsal and anterior PFC support the hypothesis that there are region-specific changes in PFC function with age. In addition, we present hypotheses of what these distinct region-specific changes in function may reflect on a neural level: dedifferentiation of cortical function, deficits in cortical function or functional compensation, respectively. However, to dissociate these underlying neural changes we must first present criteria for distinguishing between them.

Primary deficits in function refers to age-related neural dysfunction and would result in region-specific decreases in activity across all tasks with concomitant decreases in behavioural performance and brain-behaviour relationships in only older subjects. For example, Cabeza et al. (2000) observed right anterior PFC activity in young subjects, but not older subjects, during a PET study of temporal order memory. Older subjects also exhibited performance deficits during temporal order memory tasks. These results suggest that there is a primary deficit in right anterior PFC function with age.

Age-related functional compensation refers to increases in non-task-related brain regions, which results in better behavioural performance in older subjects. Task-related brain regions are those that are engaged during task performance in young subjects and non-task-related brain regions are those areas that are uniquely engaged in older subjects. Functional compensation would result in activity in both task-related and non-task-related brain regions in older subjects; however, activity in task-related brain regions may be reduced in older subjects compared to young subjects. In addition, activity in both task-related and non-task-related brain regions should produce concomitant increases in behavioural performance.
and brain-behaviour relationships in older subjects, though these effects may be lower in task-related brain regions.

It should, however, be noted that age-related increases in PFC activity that reflect functional compensation may not always produce performance benefits and could be interpreted as reflecting attempted functional compensation. In fact, one could argue that all increases in brain activity with age reflect the ageing brain’s attempts to functionally compensate for primary deficits in function in the other PFC and posterior cortical regions. However, such an extreme argument ignores the equally plausible idea that the ageing brain is a functionally noisier system (Huettel et al., 2001; Li et al., 2001; D’Esposito et al., 2003), and hence increases in the PFC may reflect spurious non-task related activity, perhaps due to dedifferentiation in function (see below). These non-task related increases in brain activity with age would not reflect attempted/successful compensation and thus would not be related to task performance. Due to this latter alternate explanation for age-related increases in activity that are not related to task performance, in the current review we only classify age-related activity increases in non-task-related PFC regions as reflecting functional compensation if there was a concomitant performance benefit in the elderly.

Age-related dedifferentiation of function refers to decreases in signal-to-noise ratio in cortical processing resulting in reduced regional process-specificity and increases in non-specific cortical activation across tasks, with age (Li et al., 2001). This would result in: (i) reduced activity in task-related brain regions with possible reductions in brain-behaviour correlations in older subjects, compared to young subjects and (ii) generalized activity of cortical regions in a non-selective manner, across tasks, which does not correlate well with behaviour, in older subjects alone (Logan et al., 2002). Thus, in this review of the published literature, by examining regional activations across task domains and their correlations with the respective behavioural output, we present hypotheses as to whether age-related changes in cortical function reflect dysfunction, functional compensation, or dedifferentiation. We hope that investigators attempt to test these hypotheses directly in the future.

Region-specific changes in PFC function with age

Ventral PFC activity: dedifferentiation or failed attempt at compensation?

We found that there were differences in ventral PFC activity with age. Similar to young subjects, older subjects activate the ventral PFC, particularly in the left hemisphere, during WM and EM encoding tasks. However, the elderly activate this region to a lesser degree than young subjects during these tasks. In contrast, the elderly over-recruit this region during EM retrieval compared to young subjects. Therefore, elderly subjects tend to activate the ventral PFC across task domains, in a less task-specific manner, compared to young subjects.

In studies that performed brain-behaviour analyses during WM and EM encoding tasks, different relationships for young versus older subjects were found. For example, in a WM task, Grady et al. (1998) found that better WM performance was related to increased right ventral PFC activity in young subjects, but not older subjects. During EM tasks, both Grady et al. (2002) and Morcom et al. (2003) found that left ventral PFC activity during encoding was related to higher subsequent memory effects in both age groups. These results together, particularly the EM encoding brain-behaviour results, show that ventral PFC activity is positively related to task performance in both age groups indicating that the reduced left ventral PFC activity in the elderly is not reflective of a primary deficit in function.

Logan et al. (2002) have shown that the age-related under-recruitment of left ventral PFC during EM encoding is related to failure of the elderly to spontaneously engage effective encoding strategies; however, when effective strategies are given to them, the elderly do not under-recruit this region. This finding also supports the view that reduced left ventral PFC activity in the elderly is not indicative of a primary deficit, but reflects inadequate automatic use of encoding strategies under normal conditions possibly due to reduced availability of processing resources (Craik, 1982; Craik and Byrd, 1982; Li et al., 2001; Lindenberger et al., 2001). We hypothesize that on a neural level this may be due to increased noise in the system (dedifferentiation) with age.

In some conditions, such as EM retrieval, older subjects activate the ventral PFC, particularly the left ventral PFC, to a greater degree than younger subjects (see Table 2) and this over-recruitment has been interpreted as reflecting functional compensation at a neural level (Cabeza, 2002; Park et al., 2003). However, this over-recruitment does not correlate well with retrieval behaviour (Cabeza et al., 1997, 2002). Also, in the three EM retrieval studies that reported greater left ventral PFC activity in the older versus younger subjects (Madden et al., 1999; Anderson et al., 2000; Cabeza, 2002), the elderly still performed worse at retrieval compared to young subjects. Together these results suggest that over-recruitment of the left ventral PFC at retrieval may not be compensatory in nature but may reflect non-selective activity.

Alternatively, the increased EM retrieval-related activity in the ventral PFC with age may reflect a failed attempt of the ageing brain to compensate for deficits in other PFC regions during retrieval. In the study by Logan et al. (2002) when encoding strategies were given to the elderly, they activate the left ventral PFC during encoding in a similar way to young subjects. Perhaps under intentional encoding and subsequent retrieval conditions, the elderly fail to use appropriate strategies at encoding and try to compensate by using these strategies at retrieval and thus activate the left ventral PFC at retrieval. However, given that current evidence does not suggest that neither the EM encoding related under-recruitment nor the EM retrieval related over-recruit of the left ventral PFC were directly detrimental or beneficial to behaviour, respectively, it is unclear how the neural mechanisms of
primary deficit and/or functional compensation could underlie this pattern of ventral PFC activity in the elderly.

Instead, this pattern could be reflective of dedifferentiation of function with age, which thus results in non-selective activation of the left ventral PFC across task domains due to reduced representational specialization on a cortical level (Li et al., 2001; Lindenberger et al., 2001; Logan et al., 2002; Park et al., 2004). In a recent fMRI study by Park et al. (2004) an age-related reduction in neural specialization in ventral visual regions dedicated to processing faces, places and words, was observed, and taken to support the differentiation hypothesis for ventral visual cortical function with age. Considering that information from the ventral visual cortex projects to the ventral PFC provides additional support for the hypothesis that age-related changes in ventral PFC function may be reflective of neural dedifferentiation (Ungerleider and Mishkin, 1982; Haxby et al., 1988, 1993; Ungerleider et al., 1989).

Support for the dedifferentiation hypothesis of ventral PFC function also comes from recent in vivo volumetric studies by Tisserand et al. (2002, 2004), which report that the strongest age-related grey matter volume reduction in the PFC was in the bilateral ventral PFC (i.e. inferior frontal gyrus); moreover, volume loss in this region was greater in older subjects who exhibited poorer performance during neuropsychological assessments (Tisserand et al., 2004). Greater age-related atrophy in inferior frontal gyrus was also observed by Good et al. (2001) using voxel-based morphometry. Therefore, this age-related decrease in bilateral ventral PFC grey matter may result in, or, be the result of, neural dedifferentiation of function within this region with age.

Together, these observations present a strong argument for dedifferentiation of the ventral PFC, particularly in the left hemisphere. However, it is still possible that this pattern of activity is reflective of compensation, albeit failed compensation. One of the future challenges for researchers is to test these competing hypotheses.

**Left dorsal and anterior PFC: functional compensation?**

In this review we found greater age-related increases in left versus right activation in the PFC, across task domains (Cabeza et al., 1997, 2004; Grady et al., 1998, 2002; Madden et al., 1999; Anderson et al., 2000; Smith et al., 2001; Grossman et al., 2002; Schiavetto et al., 2002; Daselaar et al., 2003). Most of these increases were observed in left dorsal and anterior PFC.

The left dorsal PFC was recruited by older subjects to a greater degree across task domains compared to young subjects, suggesting that left dorsal activity in older subjects may reflect functional compensation. However, the brain-behaviour analyses conducted to date, do not present strong evidence for this interpretation. For example, Daselaar et al. (2003) report similar left dorsal PFC activity in young, high and low-performing older subjects during EM retrieval whereas Cabeza et al. (2002) report greater left dorsal PFC activity in young versus high and low-performing older subjects. Also, Grady et al. (1998) reported that increased left dorsal PFC activity in older subjects was correlated with longer reaction times during a WM task. Thus, it is unclear whether age-related increases in the left dorsal PFC reflect functional compensation. Perhaps, these age-related increases reflect the attempt of ageing brains to compensate for functional deficits in the right PFC, which at times is effective.

There is stronger support that the age-related increase in the left anterior PFC is reflective of functional compensation. First, studies have shown increased left anterior PFC in older subjects compared to young subjects, across task domains (Madden et al., 1999; Cabeza et al., 2000, 2002; Smith et al., 2001; Grossman et al., 2002; Morcom et al., 2003). Second, studies have also found that this increase is related to better task performance in the older subjects. For example, Morcom et al. (2003) and Cabeza et al. (2002) reported increased left anterior PFC activity only in older subjects and this activity was related to better task performance at EM retrieval. Also, Cabeza et al. (2002) found that during EM retrieval, young and high and low-performing older subjects activate the right anterior PFC, but only high-performing older subjects activate the left anterior PFC.

A recent neuroimaging study in young subjects (Koechlin, 2003) and connectionist models (O’Reilly et al., 2002) have posited a model of hierarchical PFC organization. In the fMRI study (Koechlin, 2003), manipulation of the number of responses in the task affected premotor cortex activity, manipulation of the number of relevant stimulus dimensions affected dorsal PFC activity and manipulation of the across-block frequency of cue-to-response or cue-to-dimension mappings affected anterior PFC activity. Interestingly, structural equation modelling of the fMRI data revealed path coefficients from anterior PFC to dorsal PFC to premotor cortex, which is broadly consistent with a hierarchical organization. Though this model does not directly test, nor support, the ventral-to-dorsal-to-anterior PFC hierarchy, the results still suggest that there is a hierarchical pattern of information flow, from posterior to anterior regions within the PFC, which in turn places anterior PFC at the top of the hierarchy, and in a position to be recruited when ‘lower level’ systems fail. Therefore, one possible interpretation of the current review results is that with age there may be dedifferentiation of function in the left ventral PFC resulting in compensatory recruitment of the left dorsal and anterior PFC. Such a hypothesis of left PFC changes with age is consistent with the hierarchical model proposed by Koechlin et al. (2003) and can be easily tested in future studies.

**Changes in right dorsal and anterior PFC: deficits in function?**

Previous neuroimaging studies of cognitive ageing have consistently reported age-related decreases in right dorsal and anterior PFC activity (Cabeza, 1997, 2002; Grady et al., 1999,
subjects (Madden et al., 1988; Cermak et al., 1978; Smith et al., 2001). Across WM and EM studies, older subjects either fail to engage these regions at the threshold specified or do not engage these areas to the same degree as young subjects. Additionally, the weighted total sums of activations across task domains indicate that studies have reported less right dorsal and anterior PFC activity in older versus younger subjects. Brain-behaviour analyses indicate that when the elderly do activate the right dorsal PFC it does not aid task-performance. For example, studies have shown that increased right dorsal PFC activity is directly related to poorer task-performance. For example, studies have shown that increased right dorsal PFC activity is directly related to poorer behavioural performance in older subjects but not younger subjects (Madden et al., 1999; Rypma and D'Esposito, 2000). Moreover, right dorsal PFC activity was observed in both young and low performing-older subjects, but not high-performing older subjects (Cabeza, 2002). This suggests that ageing disrupts the normal functioning of these brain regions.

Together these results support the right hemi-ageing hypothesis which proposes that there is greater right- versus left-lateralized functional decline in the cerebral hemispheres with age (Brown and Jaffe, 1975; Lapidot, 1987; Albert and Moss, 1988; Cermak et al., 1989; Ellis and Oscar-Berman, 1989; McDowell et al., 1994; Gerhardstein et al., 1998; Dolcos et al., 2002). This hypothesis is supported by a variety of behavioural studies of verbal versus spatial processing, dichotic listening, object processing of tachistoscopically presented stimuli, sensorimotor processing and emotional processing (see Dolcos et al., 2002 for a review). For example, Gerhardstein et al. (1998) examined age differences in judgements of similarity between two objects presented sequentially to either the left visual field (right hemisphere) or right visual field (left hemisphere) and found that older subjects exhibited greater deficits in similarity judgements for stimuli presented in the left visual field. Moreover, neuropsychological studies have shown that older subjects perform similarly to patients with right, but not left, hemispheric damage during prosodic perception (Orbelo et al., 2003), strategy application (Levine et al., 1998) and word-list learning (Stuss et al., 1996; Mangels, 1997).

Importantly, the right hemi-ageing hypothesis does not explicitly propose a region-specific right hemisphere decline in the PFC. However, our review suggests that there is a region-specific change within the right dorsal and anterior PFC during WM and EM tasks. Thus, the results of this review and that of previous studies supporting the right hemi-ageing hypothesis raise the following question: why would the right cerebral hemisphere, and the right dorsal and anterior PFC particularly, be more vulnerable to age-related decline? To date, there has not been a single study, to our knowledge, that has directly examined possible underlying causes for the lateralised age-related decline of right versus left frontal cortex. However, volumetric and psychopharmacological studies have indirectly found that right frontal hemi-ageing may result from hemispheric differences in the maturational trajectories of the cerebral hemispheres, grey/white matter ratios, and the lateralization of various neurotransmitter systems, especially of dopamine (Oke et al., 1978; Slopsema et al., 1982; Mann, 1983; Arnsten and Goldman-Rakic, 1987; Morgan, 1987; van Dyck et al., 1995, 2002; Riekkinen et al., 1996; Barili et al., 1998; Larisch et al., 1998; Baltes et al., 1999; Miguez et al., 1999; Mohr et al., 2003; Raz et al., 2004; Sowell et al., 2004). For example, volumetric studies have shown that the right hemisphere exhibits a steeper maturational slope and by adulthood the right hemisphere has greater volume than the left hemisphere, particularly in the frontal lobes (Watkins et al., 2001; Lee et al., 2004; Raz et al., 2004; Sowell et al., 2004). In contrast, there is an age-related increase in grey matter density within the left hemisphere between adolescence and adulthood compared to the right hemisphere and studies have reported a larger grey-to-white matter ratio in specific left hemispheric regions compared to the right (Watkins et al., 2001; Sowell et al., 2004). Therefore, these volumetric studies indicate that there is basic structural difference between hemispheres, which may underlie the right hemispheric deficits observed in the dorsal and anterior PFC with age; however, more research is required to clarify this relationship.

Age-related changes in the neurotransmitter systems may also underlie the lateralized decline of the right versus left PFC that has been observed across neuroimaging, neuropsychological and behavioural studies. Pharmacological studies have found hemispheric localization of dopamine, serotonin, and norepinephrine neurotransmitter systems in distinct brain regions (Oke et al., 1978; Nowak, 1989; Rodriguez et al., 1994; Larisch et al., 1998; Andersen and Teicher, 1999; de la Fuente-Fernandez et al., 2000; Mohr et al., 2003). Lateralisation effects within the dopamine system are of particular interest when investigating potential causes for right hemi-ageing of the PFC since there is age-related decline in pre-synaptic markers and post-synaptic D1 and D2 receptor subtypes within the striatum and frontal cortex; moreover, an age-related decline in D2 receptor binding has been related to associated deficits in cognitive and motor task performance (McGeer, 1981; Morgan, 1987; Volkow et al., 1998a, 1998b, 2000; Miguez et al., 1999; de la Fuente-Fernandez et al., 2000; Braver and Barch, 2002; van Dyck et al., 2002). Larisch et al. (1998) have reported greater right versus left D2 receptor binding within the striatum of rats. Clearly further investigation is required to confirm the possibility that there is a lateralization of the dopamine system within the frontal cortex, however the current data suggest that right hemi-ageing of the dorsal and anterior PFC may be due to hemispheric asymmetries in dopamine receptor subtypes and concomitant age-related declines in dopamine function.

Conclusions

By reviewing age-related differences in PFC activity across WM and EM studies, and collapsing across tasks, we found that there were region-specific changes in PFC function with age. There were both age-related decreases and increases in specific PFC regions. We hypothesize from the activation
patterns of these distinct PFC regions in young versus older subjects and the brain-behaviour relationships reported across studies, that with age there are deficits in function, dedifferentiation of function, and functional compensation co-occurring in distinct PFC regions. It is possible that dedifferentiation leads to primary deficits in function and that these two functional changes may reflect different points on a continuum of age-related neural degeneration due to grey and white matter loss, dendritic regression and neurotransmitter deficits (Raz, 2000; Cabeza et al., 2005). Alternatively, dedifferentiation and deficits in function may be symptomatic of different types of underlying structural and/or neurotransmitter changes with age. Within this framework, region-specific functional decline, due to either dedifferentiation or deficits in function, in turn causes the ageing brain to attempt to compensate in a region-specific manner (Buckner, 2004; Cabeza et al., 2005).

Building upon this framework, we propose the following region-specific model of ageing that we hope will stimulate future research: due to neural degeneration and changes in neurotransmitter systems, with normal ageing, there results dedifferentiation of cortical function in the bilateral ventral PFC and deficits in function in the right dorsal and anterior PFC. These changes in turn result in functional compensation within the left dorsal and anterior PFC. We hope that future studies in the cognitive neuroscience of ageing examine regional changes in PFC sub-regions across task domains, and correlate these regional changes with behavioural performance. By doing so, these studies will be able to corroborate, modify or refute the hypotheses drawn from the current review.

Acknowledgements
Thank you to C. Lehrer and L. Mason for help in preparation of this manuscript and to A. Gazzaley and J. Rissman for their feedback. This work was supported by the National Institutes of Health and the American Federation for Aging Research.

References
Brodmann K. Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig; Barth JA; 1909.


Region-specific changes in PFC function with age


Peters A, Rosene DL. In aging, is it gray or white? J Comp Neurol 2003; 462: 139–43.
Rugg MD, Henson RN, Robb WG. Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. Neuropsychologia 2003; 41: 40–52.
Region-specific changes in PFC function with age

gray matter density associated with age and cognitive change over time. Cerebral Cortex 2004; 14: 966–73.