Functional Neuroimaging of Memory: Implications for Cognitive Aging

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KEY WORDS PET; fMRI; brain function; activation; learning; information processing

ABSTRACT Our understanding of the ways in which changes in specific neural systems mediate adult age differences in memory is rapidly increasing, due in no small part to the advent of functional neuroimaging techniques. This article reviews age-related changes in memory performance obtained with behavioral measures, describes models of the neural mechanisms of memory, and derives predictions from these models regarding age-related changes in brain activation patterns. The neuroimaging findings obtained to date support models emphasizing the role of prefrontal cortex in age-related changes in memory functioning, especially for episodic memory retrieval. In general, neural activation associated with episodic memory encoding is regionally similar for younger and older adults but relatively lower in magnitude for older adults. During retrieval, activation that is restricted to the right prefrontal cortex for younger adults is more likely to be bilateral for older adults. Prefrontal activation exhibits an age-related increase when working memory tasks require simple storage and an age-related decrease when working memory requires higher-level executive processes. Although the evidence is limited, behavioral performance and activation patterns appear to be similar among younger and older adults on tests of semantic (context-independent) and implicit memory. We conclude that several methodological issues, such as defining the relation between brain structure and function, and determining the relationship between performance and activation, are particularly important for understanding age-related changes. Future directions for aging research include further investigation of the relation between encoding and retrieval and the identification of both spared and impaired neural systems. *Microsc. Res. Tech. 51:75–84, 2000.*

FUNCTIONAL NEUROIMAGING OF MEMORY: IMPLICATIONS FOR COGNITIVE AGING

The emergence of functional neuroimaging technology has significantly advanced current knowledge of the neural systems mediating human memory. With such technology, cerebral metabolic activity is measured "on-line" as a cognitive task is being performed, and, in this way, the brain regions recruited for specific memory processes can be identified. Beyond informing theories of memory, the availability of these neuroimaging techniques has provided an additional avenue for studying the functional neuroanatomy of age-related changes in memory. Declines in some aspects of memory functioning during aging have been widely documented, as have age-associated structural brain changes, but until recently, few studies have explored the associations between these memory deficits and structural changes (e.g., Golomb et al., 1994; Raz et al., 1998, 1999). Functional neuroimaging measures will facilitate such research.

Just as the strength of theories of memory based on behavioral measures is tested by their ability to explain the memory changes that accompany normal aging, neuroimaging investigations of memory must be able to account for the age-related changes in brain function that potentially mediate changes in memory performance. In a reciprocal fashion, findings regarding patterns of impaired and spared memory with aging, and the neural underpinnings of these changes, contribute to stronger models of memory. In this vein, this article (1) summarizes present knowledge of age-related changes in memory; (2) outlines neural models of memory, which were developed from neuropsychological studies with patient populations and neuroimaging studies with younger adults; (3) derives predictions from these models regarding patterns of brain activation in older adults; (4) discusses initial findings from functional neuroimaging studies in the context of these predictions; (5) reviews the ability of these models to explain the age patterns found in the neuroimaging data; and (6) suggests future directions for this emerging field.

The present review is necessarily selective. We focus primarily on findings from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) technologies; event-related potentials (ERPs) are discussed by Friedman and Johnson (pages 6–28, this issue) and by Friedman and Fabiani (1995). In addition, we focus on the changes in memory perfor-

Contract grant sponsor: National Institute on Aging; Contract grant numbers: R01 AG11622, R37 AG021163.

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Received 12 January 2000; accepted in revised form 19 March 2000

mance that are associated with normal aging. Research using functional neuroimaging to distinguish normal from pathological age-related changes (e.g., Alzheimer's disease) is reviewed by Eustache et al. (pages 94–100, this issue) and by Hoffman (1997).

AGE-RELATED CHANGES IN MEMORY

Aging is accompanied by spared and impaired memory functions. In the present context, we mention only the highlights of an extensive research literature (Anderson and Craik, 2000; Balota et al., 2000; Craik and Jennings, 1992; Smith, 1996). First, we briefly discuss the theoretical perspectives on the causes of age-related memory changes, which range from general to process-specific. Cognitive slowing is a general perspective, according to which aging is accompanied by slowing in all components of cognitive processing (e.g., Birren et al., 1980; Cerella, 1985; Salthouse, 1996b). By this account, age-related memory impairments are mediated by age-related effects in a general speed factor, as reflected in measures of the speed of elementary cognitive operations (Salthouse, 1996a). This account has received considerable empirical support. Across a wide range of cognitive tasks, older adults' mean response latencies are a monotonic function of those of younger adults, and this function is often resistant to influence from the processing demands of specific task conditions (e.g., Brinley, 1965; Myerson et al., 1992; Salthouse, 1985). Salthouse (1994a, 1996b) has shown that slowing of elementary perceptual processes accounts for a significant portion of the age-related variance in performance on cognitive tasks. In contrast, proponents of process-specific theories advocate that concepts referring to specific and isolatable cognitive processes, such as the depth of semantic encoding (Craik and Jennings, 1992), cue accessibility (West and Craik, 1999), and inhibition of irrelevant information (Hasher and Zacks, 1988), are necessary to account for age-related memory changes.

The role of functional neuroimaging in the debate between general and process-specific theories is still evolving. For example, generalized slowing is a characterization of behavioral data that is consistent with different patterns of neural activation. Both a widespread change in neural activation and a localized change in a region associated with many cortical pathways (e.g., the thalamus) could lead to performance consistent with generalized slowing. Only models that specify the neural mechanisms of cognitive performance can be tested with neuroimaging data. For example, a version of the generalized slowing model that defines slowing as the result of a diffuse change in the central nervous system would predict an age-related decline in the magnitude of cortical activation without a change in the regional pattern. To the extent that characterizations of age-related changes in memory performance include concepts that refer to central nervous system mechanisms, neuroimaging will provide relevant data.

Episodic Memory

Episodic memory is the acquisition, storage, and retrieval of information that refers to a specific context and is consciously and intentionally recollected (Tulving, 1983). It is well established that prominent age differences exist on tests of episodic memory (Craik and Jennings, 1992; Smith, 1996). Older adults have difficulty in both the initial storage of memories (encoding) and the later utilization of memories (retrieval), and they are less likely to spontaneously use elaborative and organizational strategies to store and retrieve information. Age differences are greatest on tests of free recall and are relatively reduced on tests of cued recall and recognition. Episodic memory for contextual information (such as the source of memorized information or the time at which the information was encoded) is particularly vulnerable to age effects (Spencer and Raz, 1995).

Semantic Memory

Semantic memory refers to a person's general knowledge about the world (Tulving, 1983) including facts, concepts, and vocabulary. It differs from episodic memory in that it is not associated with specific learning contexts or events. Many aspects of the retrieval and use of semantic information, such as the meaning of individual words and facts, show relatively little change with age, even when tested with speeded responses (e.g., Balota and Duchek, 1988; Laver and Burke, 1993; Madden et al., 1993). Burke and colleagues, however, have reported that "tip of the tongue" experiences (a feeling of knowing the correct word but an inability to produce it from memory) are more frequent at older ages (Burke et al., 1991; Rastle and Burke, 1996).

Implicit Memory

Implicit memory is the non-conscious influence of past experience on current performance or behavior (Schacter, 1992). It is assessed by means of indirect tests on which no reference is made to the learning episode or context. For example, when participants are asked to complete word fragments (e.g., _A_LE) with the first word that comes to mind, they complete the fragments with previously studied words (e.g., maple) at greater-than-chance levels. This implicit memory effect, termed "priming," occurs in older adults as well as younger adults, on a variety of tasks using both word and nonword stimuli (e.g., Light et al., 1995; Maki et al., 1999). Implicit priming effects are occasionally smaller for older adults than for younger adults, but these age differences are not as pronounced as those obtained with tests of explicit memory (La Voie and Light, 1994). Procedural memory is another aspect of implicit memory that is relatively spared by aging. It is measured empirically by improved speed or accuracy across trials of a repeated challenging task. Although older adults may be slower or less accurate on procedural tasks overall, they often show similar levels of improvement with practice (e.g., Howard and Howard, 1992, 1997).

Working Memory

Working memory is the temporary storage and manipulation of episodic information (Baddeley, 1986). Age differences are relatively small on tasks that require simple short-term storage of information (e.g., Gregoire and Van der Linden, 1997), but when manipulation of the contents of storage is required (i.e., executive functions), age-related declines are more ap-

parent (e.g., Brebion et al., 1997; Shimamura et al., 1995). Current research suggests that age differences in working memory may be mediated by a reduced ability to inhibit irrelevant information from entering working memory storage (Hasher and Zacks, 1988; Zacks and Hasher, 1997; but see Burke, 1997) or by age differences in perceptual speed (e.g., Fisk and Warr, 1996; Salthouse, 1994b; Salthouse and Meinz, 1995).

MODELS OF THE NEURAL INSTANTIATION OF MEMORY AND PREDICTIONS FOR AGE-RELATED MEMORY CHANGES

The research reviewed in the previous section suggests that certain memory processes (e.g., episodic memory, executive components of working memory) are more prone to the effects of aging than others (e.g., semantic or implicit memory, storage components of working memory). One potential means by which to explain the differential effects of aging on memory is to turn to models that attempt to specify the neural instantiations of memory. These models have been developed based on neuropsychological studies of brain-damaged patients and functional neuroimaging studies of neurologically healthy younger adults.

HERA Model

Neuroimaging studies with younger adults have consistently documented engagement of the prefrontal cortex during episodic memory performance (Desgranges et al., 1998; Gabrieli, 1998). The two hemispheres of the prefrontal cortex appear to have different roles in the processes of encoding and retrieval. Encoding is associated with preferential activation of the left prefrontal cortex, whereas retrieval is associated with preferential activation of the right prefrontal cortex. This pattern of findings led Tulving et al. (1994) to propose a hemispheric encoding/retrieval asymmetry (HERA) model that maintains that left prefrontal cortex is differentially more involved in encoding of episodic information and processing of semantic information, whereas the right prefrontal cortex is differentially more involved in retrieval of episodic memories. For tasks in which increased activation represents the mediation of task performance, the HERA model suggests that observed age differences in episodic memory should be accounted for by an age-related reduction in activation of left prefrontal cortex during encoding and a similar reduction of activation of right prefrontal cortex during retrieval.

CARA Model

Buckner (1996) has argued that the HERA model underestimates the role of the left prefrontal cortex in the retrieval of episodic information. Left prefrontal cortex is commonly activated during both encoding and retrieval, and several studies have reported bilateral prefrontal activation during retrieval tasks (e.g., Backman et al., 1997; Buckner et al., 1995; Schacter et al., 1996). Such observations led Nolde et al. (1998) to propose the cortical asymmetry of reflective activity (CARA) model. In this model, the processes involved in encoding and retrieval are drawn from the same set of underlying reflective processes (e.g., processes that sustain, manipulate, and evaluate activation generated by perceptual processes). Right prefrontal cortex may subserve reflective component processes that are sufficient for simple memory tasks (e.g., temporary storage of activated information or the comparison of two stimuli on some dimension), but more complex tasks (e.g., deliberate analysis of activated information or the initiation of self-cueing to retrieve information) may require additional component processes mediated by left prefrontal cortex. From this model, assuming that some tasks that are relatively simple for younger adults are more demanding for older adults, the CARA model would predict an age-related increase in left prefrontal activation during operations of retrieval.

Moscovitch's Component Process Model

Moscovitch (1992) proposed a model of memory based on neuropsychological studies of brain-damaged patients. In this model, the frontal lobes play a specific role in strategic recollections that rely on effortful encoding and retrieval. The hippocampus, in contrast, forms explicit associative memories that are automatically retrieved with the appropriate cues. Because the frontal system shows more structural change with age than the hippocampal formation (Raz, 2000), Moscovitch and Winocur (1992) predicted that age-related declines in performance would be greater on episodic memory tasks that require strategic encoding or retrieval (e.g., free recall or source retrieval) than on tasks that require simple associative memories (e.g., forced-choice recognition). These relatively greater deficits should be correlated with activation changes primarily in the frontal lobe and less so with activation changes in the temporal lobe. Implicit memory as depicted in the Moscovitch model is mediated by primary sensory and subcortical structures (e.g., the posterior and mid-lateral neocortex). An age-related preservation of primary sensory and subcortical areas predicts preserved performance on implicit memory tasks as well as preserved activation of these brain areas during performance.

Other Predictions Based on Neuroimaging Findings from Younger Adults

The above models do not address all aspects of memory in which age-related changes have been studied (e.g., semantic, working, and procedural forms of memory). For these areas of memory, age predictions can be derived from neuroimaging data collected with younger adults. Studies of semantic memory have found that the left prefrontal cortex is consistently activated across a variety of semantic tasks (e.g., Demb et al., 1995; Gabrieli et al., 1996; Wagner et al., 1997). Although prominent age-related changes in prefrontal activation are predicted during episodic tasks, whether similar prefrontal changes will be noted on semantic memory tasks remains to be seen, given older adults' relatively intact performance on semantic memory tasks.

Neuroimaging research with younger adults has revealed that prefrontal activations also predominate during working memory tasks (e.g., MacLeod et al., 1998; McIntosh et al., 1996b; Smith and Jonides, 1999). In contrast to semantic memory, age effects are prominent in working memory, so age differences in prefrontal activation would be expected during working memory tasks, particularly on tasks with high executive

demands. Research with younger adults suggests that different areas of the prefrontal cortex specialize in storage and executive components of working memory (Hartley and Speer, pages 45–53, this issue), so age differences in activation patterns may be greatest for dorsolateral prefrontal cortex, associated with executive processing, and less prominent for ventrolateral prefrontal cortex, associated with simple storage and maintenance processes. Of further interest is whether aging is associated with a reduction in lateralization of activation for spatial vs. nonspatial stimuli (D'Esposito et al., 1998; McCarthy et al., 1996; Smith et al., 1996).

Turning to implicit memory, visual repetition priming in younger adults leads to de-activations in posterior visual areas including extrastriate occipital cortex (Buckner et al., 1995, 1998a; James et al., 1999; Squire et al., 1992), suggesting that exposure to a stimulus facilitates subsequent processing of that stimulus. Because age-related structural changes are less pronounced in occipital cortex than in other cortical regions (Madden and Hoffman, 1997; Raz, 2000), and because age-related impairments on priming tasks are minimal, older adults would be expected to exhibit the same patterns of cortical deactivation as younger adults during priming tasks. Procedural memory appears to depend on the integrity of the cerebellum, primary motor cortex, supplementary motor areas, and basal ganglia (Grafton et al., 1995, 1998). We would expect older adults to exhibit task-appropriate activations of these areas, based on little evidence of structural changes in these areas and unimpaired learning on procedural memory tasks (but see Raz et al., pages 85–93, this issue).

FUNCTIONAL NEUROIMAGING OF AGE-RELATED CHANGES IN MEMORY

Functional neuroimaging research has only recently addressed the impact of aging on the neural basis of memory (Anderson and Grady, in press; Cabeza, in press; Grady, 1998; Madden and Hoffman, 1997; Raz, 2000). Structural imaging and autopsy studies have demonstrated that age-related volumetric reductions are greater in the frontal and temporal lobes (areas associated with memory functions) than in the parietal and occipital lobes (Madden and Hoffman, 1997; Raz, 2000). The advent of functional imaging has allowed examination of the association between these structural changes and the functional changes in the mechanisms underlying memory processes. Aging research to date has been conducted almost exclusively with PET, although current endeavors are increasingly relying on fMRI techniques.

Episodic Memory

Prefrontal Cortex. In younger participants, studies addressing age-related changes in encoding activation have for the most part replicated the HERA pattern of differential activation of left prefrontal cortex during encoding (Anderson et al., in press, Cabeza et al., 1997; Grady et al., 1995). However, the HERA pattern does not seem to hold for older adults. Prefrontal activation for older adults either is not specific to encoding (Cabeza et al., 1997; Grady et al., 1995) or occurs in the form of left prefrontal activation that is reduced in magnitude compared to younger adults (Anderson et al., in press). Grady et al. (1999) compared activations across different types of encoding tasks (words vs. pictures, incidental vs. intentional encoding) and found that younger adults demonstrated greater left prefrontal activation for word encoding than for picture encoding. Activation was also relatively more left lateralized for incidental encoding than for intentional encoding when the incidental encoding involved deep processing of stimuli. Older adults showed this differential activation pattern for stimulus features and encoding strategies to a significantly lesser degree than younger adults.

During retrieval, younger adults show preferential right over left prefrontal activation, in accord with the HERA model (Backman et al., 1997; Cabeza et al., 1997, 2000; Grady et al., 1995; Madden et al., 1999b). Older adults likewise exhibit right prefrontal activation during retrieval. Some studies have found this activation to be of a magnitude that is equal (Backman et al., 1997; Grady et al., 1995; Schacter et al., 1996) or greater (Madden et al., 1999b) than that of younger adults; other studies report group interactions that are consistent with an age-related reduction in right prefrontal activation (Anderson et al., in press; Cabeza et al., 1997, 2000). In contrast to the activation patterns of younger adults, older adults tend to exhibit left as well as right prefrontal activation during retrieval, and this left prefrontal activation is significantly greater than that of younger adults (Backman et al., 1997; Cabeza et al., 1997; Madden et al., 1999b). Figure 1 illustrates the age-related increase in the spatial extent of prefrontal activation that has been observed for some retrieval tasks.

Two studies have employed retrieval tasks that are thought to be particularly demanding on frontal processes (Cabeza et al., 2000; Schacter et al., 1996). Under conditions of high retrieval effort, both younger adults and older adults exhibited bilateral frontal activation, although for younger adults this activation was located in anterior regions of the frontal lobe, and for older adults it was located in posterior regions (Schacter et al., 1996). Frontal activation was not found under conditions of low retrieval effort and high retrieval success, suggesting that other brain areas mediate relatively automatic recall for both younger and older adults. On a temporal-order retrieval task ("Which word was presented more recently?"), which assesses context memory, both younger adults and older adults activated bilateral prefrontal cortex. Younger adults engaged right prefrontal cortex more during temporal-order retrieval than during item retrieval, but older adults did not.

To summarize the findings regarding prefrontal activation during episodic memory tasks, younger adults show predominantly left prefrontal activity during encoding and predominantly right prefrontal activity during retrieval. Older adults, on the other hand, show either no prefrontal activity specific to encoding, or left prefrontal activity that is reduced in magnitude compared to younger adults. During retrieval, older adults' prefrontal activation tends to be bilateral, with mixed findings regarding whether there is an age-related reduction in right prefrontal activation. Both younger and older adults show a more bilateral pattern of retrieval activation during demanding tasks, although

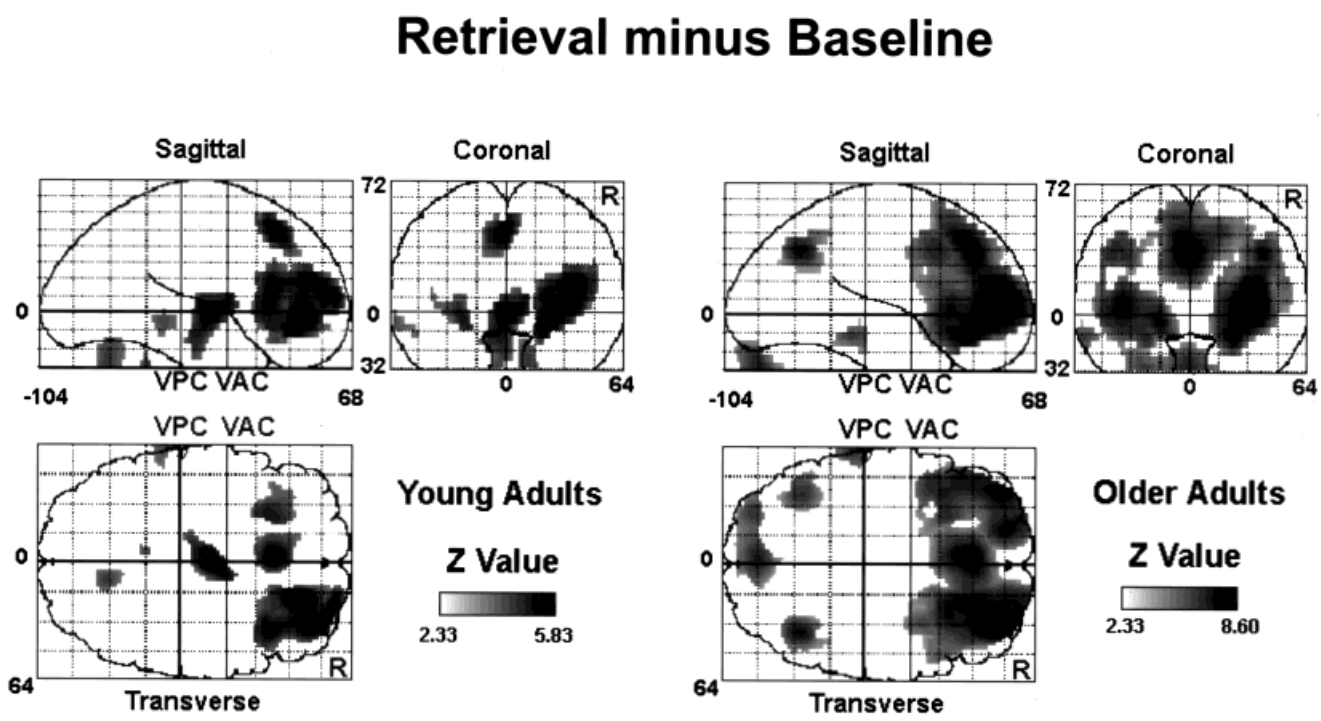

Fig. 1. Areas of increased rCBF between retrieval and baseline conditions, as a function of age group, from Madden et al. (1999b). The Retrieval minus Baseline subtraction represents the processes involved in making a yes/no decision regarding whether each of a series of words was presented previously (during an Encoding condition). The Baseline condition required participants to make a series of uppercase/lowercase decisions (without a memory requirement) regarding a separate series of words. The rCBF measurement was obtained with PET and analyzed with Statistical Parametric Mapping (Friston et al., 1995). The results are presented as averaged images in the sagittal, coronal, and transverse planes, using the stereotaxic space of Talairach and Tournoux (1988). The right half of the coronal image and the lower half of the transverse image correspond to the participant's right hemisphere. Within each age group, voxels for which rCBF increased significantly are presented in gray scale values, thresholded at $P < .001$ (uncorrected). To view a color version of this figure, which includes a color scale for the subset of voxels that differed significantly between age groups, visit the website: www.interscience.wiley.com

younger adults may be better at modulating this activity in accord with task demands.

Mediotemporal Cortex. Evidence to date suggests that there are few age differences in medial temporal activations during episodic encoding and retrieval. Grady et al. (1995) found age-related reductions in hippocampal and parahippocampal activations during encoding of faces. Madden et al. (1999b), in contrast, did not observe significant age differences in activation associated with word encoding. Some studies have failed to observe mediotemporal activations that are specific to encoding processes (Anderson et al., in press; Cabeza et al., 1997) or retrieval processes (Anderson et al., in press; Grady et al., 1995). This may be associated with the finding by Schacter et al. (1996) that only retrieval conditions that involve low effort and high success lead to hippocampal activation, and this activation is equivalent for younger and older adults. Other studies have similarly found that when younger adults produce hippocampal activation during retrieval, older adults produce this activation in similar (Cabeza et al., 2000) or greater magnitudes (Backman et al., 1997).

Semantic Memory

Preliminary research suggests that the prefrontal activation that is associated with semantic memory is preserved in older adults. During retrieval of semantic information that is sufficient for word-nonword decisions, younger and older adults display similar patterns of prefrontal activation, although older adults exhibit less activation in occipitotemporal areas associated with visual identity processing (Madden et al., 1996).

Implicit Memory

As found in younger adults (Buckner et al., 1995, 1998a; James et al., 1999; Squire et al., 1992), visual repetition priming is associated with reduced activation of the right occipital cortex in older adults (Backman et al., 1997). This suggests that younger and older adults exhibit similar priming at the neural and behavioral levels. Raz et al. (pages 85–93, this issue) report that age-related changes in regional brain volume, as obtained from MRI, mediate age differences in performance in a procedural (motor learning) task.

Working Memory

Two neuroimaging studies have examined age-related changes in the neural correlates of storage processes involved in working memory. Grady et al. (1998) assessed short-term storage of face stimuli over a variable delay and found that older adults exhibited greater dorsolateral prefrontal and dorsal occipital activation than younger adults. An increase in the delay

period resulted in greater left prefrontal activation and reduced extrastriatal activation for both younger and older adults, but right prefrontal activation was less modulated across the delay for older adults. Reuter-Lorenz et al. (2000) examined age differences in the lateralization of verbal and spatial working memory. On both verbal and spatial tasks, activation patterns in the posterior areas of the brain (e.g., parietal and temporal cortices) were similar for younger and older adults. However, in anterior areas, younger adults exhibited left-lateralized activity during short-term storage of letters and right-lateralized activity during short-term storage of locations, whereas older adults exhibited bilateral activation during both tasks. Closer inspection indicated that this bilaterality was most prominent in frontal areas associated with verbal and spatial rehearsal (Broca's area and lateral supplementary motor areas, respectively). Older adults exhibited paradoxical activity in dorsolateral prefrontal cortex: greater right than left activation on the verbal task and greater left than right activation on the spatial task.

These two studies suggest that older adults may rely more heavily on dorsolateral prefrontal cortex (usually associated with executive components of working memory) than younger adults when completing simple storage tasks. This finding, plus the observed increase in bilateral activation, indicates that compensatory neural recruitment (Cabeza et al., 1997; Grady, 1998; Grady and Haxby, 1995) accounts for the relative maintenance of the storage component of working memory with age. Whether this neural compensation would be similarly observed on working memory tasks with greater executive demands is yet to be determined. Initial evidence suggests that such compensation is not maintained. Jonides et al. (2000) reported that interference from previously stored verbal information during working memory led to greater activation of left prefrontal cortex for younger adults than for older adults. Rypma and D'Esposito (2000) measured activation during encoding, storage, and retrieval components of working memory and found that age differences were evident only during retrieval of high memory loads. Activation of dorsolateral prefrontal cortex was greater for younger adults than for older adults, whereas ventrolateral activation was comparable for the two groups. Retrieval-related activation, however, was associated with slower responses for younger adults and with faster responses for older adults, suggesting that with aging, optimal response discriminability requires a higher level of neural activation.

NEUROIMAGING OF AGE-RELATED MEMORY CHANGES: INTERPRETATION OF FINDINGS

HERA Model

Consistent with the HERA model, there appears to be an age-related reduction in the magnitude of left prefrontal activation during encoding (Anderson et al., in press; Cabeza et al., 1997; Grady et al., 1995). Older adults demonstrate either no prefrontal activation specific to encoding (Cabeza et al., 1997; Grady et al., 1995) or equivalent bilateral prefrontal activation (Madden et al., 1999b). Only one study has reported a pattern of prefrontal activation for older adults similar to that typically found with younger adults in terms of greater activity in the left hemisphere than in the right (Anderson et al., in press). On retrieval tasks, the data is not clearly supportive of the HERA model. Whereas some findings suggest there is an age-related reduction in right prefrontal activation (Anderson et al., in press; Cabeza et al., 1997, 2000), other findings suggest age-equivalency or even increased activation in right prefrontal cortex during retrieval (Backman et al., 1997; Grady et al., 1995; Madden et al., 1999b; Schacter et al., 1996). Additionally, right prefrontal activation is usually accompanied by left prefrontal activation that is of greater magnitude in older adults than in younger adults (Anderson et al., in press; Backman et al., 1997; Cabeza et al., 1997; Madden et al., 1999b).

CARA Model

The CARA model posits that complex retrieval tasks are more likely than simple retrieval tasks to activate left prefrontal cortex. Both younger and older adults exhibit a bilateral pattern of retrieval activation during demanding memory tasks such as retrieval of contextual information (Cabeza et al., 2000; Schacter et al., 1996). On less demanding retrieval tasks, younger and older adults both tend to exhibit right prefrontal activation, but older adults also exhibit accompanying left prefrontal activation (Backman et al., 1997; Cabeza et al., 1997; Madden et al., 1999b). Consistent with the CARA model, these results suggest that retrieval cues are less likely to activate the previously studied information in older adults, and as a result there is an age-related increase in the need to engage in strategic retrieval processes mediated by the left prefrontal cortex (Anderson and Grady, in press). Cabeza et al. (1997) suggest that the involvement of the left prefrontal cortex during recall in older adults reflects compensatory recruitment of brain regions (see Grady and Craik, 2000, for further discussion of the role of the left prefrontal cortex in the memory performance of older adults).

Moscovitch's Component Process Model

Moscovitch's model (1992) specifies that prefrontal regions contribute to performance on strategic, explicit tests of memory by selecting and implementing encoding strategies and determining the correct temporal and spatial context of encoded information. Medial temporal regions, in contrast, process associative memories that are automatically retrieved with the appropriate cues. Moscovitch and Winocur (1992) proposed that age-related deficits in strategic episodic memory processes will be accompanied by compromised prefrontal functioning, whereas simpler associative memory processes mediated by the mediotemporal lobes and implicit memory processes mediated by primary sensory areas will show little or no age effects.

Several findings support the idea that age-related changes in prefrontal activation are most prominent on episodic tasks that require greater self-initiated processing than on relatively automatic tasks. As noted previously, age-related reductions in prefrontal activity during encoding occur when the task requires self-initiated encoding processes (Anderson et al., in press; Cabeza et al., 1997; Grady et al., 1995). Furthermore, under conditions in which frontal activation occurs only with high retrieval effort and low retrieval suc-

cess, older adults exhibit bilateral frontal activations that are more posterior to those of younger adults (Schacter et al., 1996). Younger adults engage right prefrontal cortex more during temporal-order retrieval than during item retrieval (Cabeza et al., 2000), which is consistent with the idea that order retrieval requires retrieval of contextual information and is therefore more effortful than item retrieval. Older adults fail to show differential prefrontal activation patterns for these tasks. Finally, in an analysis of practice effects on retrieval, both younger and older adults exhibited diminished retrieval-related activation in the prefrontal cortex as performance improved across the session (Madden et al., 1999b). This reduction appeared to be greater for younger adults (practice effects were assessed within each age group), suggesting that the older adults were relatively less efficient at reducing the strategic demands of the memory task.

Consistent with the Moscovitch and Winocur's (1992) prediction of relatively small age differences in mediotemporal activation during episodic memory, several neuroimaging studies have found similar patterns of mediotemporal activation among younger and older adults during encoding and retrieval (Backman et al., 1997; Cabeza et al., 2000; Madden et al., 1999b; Schacter et al., 1996), although Grady et al. (1995) found an age-related decline in encoding-related activation. Mediotemporal activations were found on tasks that promoted automatic associative retrieval by providing word stems to recall semantically encoded words (Backman et al., 1997; Schacter et al., 1996). Tasks that used less elaborate encoding or less facilitative retrieval failed to show mediotemporal activations in either younger or older adults (Anderson et al., in press; Cabeza et al., 1997; Grady et al., 1995; Schacter et al., 1996). Cabeza et al. (2000) found mediotemporal activation during item retrieval but not during temporal order retrieval, with no differences between age groups. Together, these data are consistent with the idea that medial temporal regions are involved in relatively automatic retrieval operations.

Finally, as predicted by the Moscovitch (1992) model, on an implicit memory task in which no effortful retrieval was involved, older and younger adults' priming performance was associated with similar reductions in blood flow in visual processing areas (Backman et al., 1997). This finding is consistent with the activation patterns found among younger adults in other priming studies (Buckner et al., 1995, 1998a; James et al., 1999; Squire et al., 1992).

METHODOLOGICAL CONSIDERATIONS AND FUTURE DIRECTIONS

To review, age-related changes in neural activation patterns are most prominent during episodic memory performance, during both encoding and retrieval. The regions associated with age-related change are located primarily in the prefrontal cortex, with few age differences occurring in mediotemporal activations. In general, activations associated with memory encoding are relatively lower in magnitude for older adults. During retrieval, activations that are restricted to right prefrontal cortex for younger adults are more likely to be bilateral for older adults. Age effects on prefrontal activation have appeared in the context of working memory tasks, although the pattern of age differences varies as a function of the processing stage of the task. During storage operations, older adults again show greater bilateral activation than younger adults, along with increased dorsolateral prefrontal activation. Executive operations are associated with an age-related reduction of dorsolateral prefrontal activation. Evidence regarding semantic and implicit memory is limited, but behavioral performance and activation patterns for these types of memory tests appear to be similar among younger and older adults.

Age differences in the patterns of prefrontal activation across hemispheres during episodic encoding and retrieval provide support for both the HERA and CARA models, although the results may be more consistent with the CARA model. There is also considerable support for the Moscovitch components of processing model. Age-related activation changes are most prominent in the prefrontal lobes during episodic tasks that have high strategic demands. Mediotemporal activations (thought to be associated with simple associative episodic memory) are largely intact with age, as are posterior de-activations associated with implicit priming tasks.

The three neural models of memory discussed here share among them the derived predictions that the prefrontal cortex plays a prominent role in age-related memory changes. This prediction is not new, as several psychological theories have proposed variants of the "frontal hypothesis of cognitive aging" (West, 1996). These theories predict that age-related deficits in complex cognitive processes (e.g., those that require retrieval of contextual information or inhibition of prepotent responses) are mediated by prefrontal deficits. As detailed here, functional neuroimaging data offer further evidence to support these prefrontal models, although the contribution of other cortical and subcortical structures (e.g., frontal-striatal circuits) should also be investigated (Bashore, 1993; Rubin, 1999).

Methodological Considerations

Interpretation of Age-Related Declines in Activation. The interpretation of age-related differences in activation patterns is challenging for a variety of reasons. We mention three here: (1) As noted previously, even with a homogeneous group of research participants, careful design and interpretation of tasks is necessary to determine whether improved task performance is associated with either increasing or decreasing activation. The interpretation is further complicated when testing individuals of different ages, who are likely to differ in their level of performance on the cognitive task of interest. (2) Even in the absence of significant disease, aging is associated with a decline in cortical volume and other structural changes (Madden and Hoffman, 1997; Raz, 2000). The influence of these structural changes on functional measures is not well understood. When comparing participants of different ages it is consequently helpful to report brain volume measures as well as functional measures (Madden et al., 1996, 1997, 1999a). (3) There is evidence that the coupling between neural activity and the hemodynamic response may change as a function of age (D'Esposito et al., 1999), which would also be problematic for the interpretation of age differences in neural activation as inferred from functional imaging.

Relationship Between Performance and Activation. As discussed by Cabeza (in press), the interpretation of functional neuroimaging results may depend on the cognitive performance displayed by the older sample investigated. When older adults perform more poorly than younger adults on behavioral tasks, it is unclear whether activation changes reflect age differences or performance differences. One approach to this issue is to adjust the task parameters for each participant so that performance is equated for younger and older adults (as in Cabeza et al., 1997). Another approach is to allow performance to vary with age (as it does outside the laboratory) but to examine the relationship between task performance and neural activation within each age group. Madden et al. (1999a, b), for example, demonstrated that the time required for episodic retrieval (in a recognition test for previously studied words) was associated with different patterns of regional activation for younger and older adults. Under some conditions, the underlying relation between cortical activation and performance (i.e., whether more activation is associated with better performance), and not just the regional pattern, may change with age (Rypma and D'Esposito, 2000). Recently developed statistical techniques, such as Partial Least Squares analysis (Grady et al., 1998; McIntosh et al., 1996a) focus prominently on the relation between performance and activation and will be of assistance in addressing this issue. It would also be valuable to examine individual differences within each age group (e.g., comparing brain activations of high-functioning vs. low-functioning older adults). In this way, test performance is introduced as a factor in the design.

Future Directions

Application of Neuroimaging Research With Younger Adults. Neuroimaging research with younger participants continues to pinpoint functional specializations of memory. Applying these methodologies and theoretical perspectives to the investigation of age-related changes may lead to exciting new developments. For example, present research suggests that specific areas of the right prefrontal cortex are involved in retrieval effort and retrieval success (Buckner et al., 1998b; McIntosh et al., 1997; Rugg et al., 1998; Wagner et al., 1998a). Furthermore, event-related fMRI, which characterizes the hemodynamic response to individual stimuli, now allows the examination of how neural activation differs for subsequently remembered and forgotten experiences. For example, Wagner et al. (1998b) have demonstrated that later retrieval of an experience was predicted by the magnitude of left prefrontal and temporal activation during encoding of that experience. By imaging older adults using these paradigms, we can begin to further understand the neural basis for increased forgetting with age, whether it is the result of impairment in initial encoding, retrieval effort, or retrieval success.

Neuroimaging Age-Preserved Memory Areas. An adequate model of the neural instantiations of memory must explain the basis for preserved memory functions as well as impaired memory functions with age. Therefore, aspects of memory that are relatively resistant to age effects, such as semantic memory and procedural memory, deserve further examination. It will be important to establish whether these aspects of memory are preserved because processing in the underlying brain areas is preserved or because other brain areas are compensatorily recruited to aid performance. As was noted previously, performance on working memory tasks that emphasize storage of information may be relatively maintained with age because of older adults' ability to activate additional brain areas to aid performance (Grady et al., 1998; Reuter-Lorenz et al., 2000). It would be useful to explore age-related patterns of activation on semantic and procedural tasks with high "top-down" processing demands, such as self-initiated word retrieval and planned movement sequences, to determine whether these demands lead to age-related functional compensation. Further research in these areas will offer a more complete account of memory-related neural preservation and disruption with age.

REFERENCES

Anderson ND, Craik FIM. 2000. Memory in the aging brain. In: Tulving E, Craik FIM, editors. The Oxford handbook of memory. Oxford: Oxford University Press, p 411–425.

Anderson ND, Grady CL. in press. Functional imaging in cognitively intact aged people. In: Hof PR, Mobbs CV, editors. Functional neurobiology of aging. San Diego: Academic Press.

Anderson ND, Iidaka T, Cabeza R, Kapur S, McIntosh AR, Craik FIM. in press. The effects of divided attention on encoding- and retrieval-related brain activity: A PET study of younger and older adults. J Cogn Neurosci

Backman L, Amskvist O, Anderson J, Nordberg A, Winblad B, Reineck R, Langstrom B. 1997. Brain activation in young and older adults during implicit and explicit retrieval. J Cogn Neurosci 9:378–391.

Baddeley A. 1986. Working memory. Oxford: Oxford University Press.

Balota DA, Duchek JM. 1988. Age-related differences in lexical access, spreading activation, and simple pronunciation. Psychol Aging 3:84–93.

Balota DA, Dolan PO, Duchek JM. 2000. Memory changes in healthy older adults. In: Tulving E, Craik FIM, editors. The Oxford handbook of memory. Oxford: Oxford University Press, p 395–409.

Bashore TR. 1993. Differential effects of aging on the neurocognitive functions subserving speeded mental processing. In: Cerella J, Rybash J, Hoyer W, Commons ML, editors. Adult information processing: Limits on loss. San Diego: Academic Press, p 37–76.

Birren JE, Woods AM, Williams MV. 1980. Behavioral slowing with age: Causes, organization, and consequences. In: Poon LW, editor. Aging in the 1980's. Washington, DC: American Psychological Association, p 293–308.

Brebion G, Smith MJ, Ehrlich M-F. 1997. Working memory and aging: Deficit or strategy differences. Aging Neuropsychol Cognit 4:58–73.

Brinley JF. 1965. Cognitive sets, speed and accuracy of performance in the elderly. In: Welford AT, Birren JE, editors. Behavior, aging and the nervous system. Springfield, IL: Charles C. Thomas, p 114–149.

Buckner RL. 1996. Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. Psychonomic Bull Rev 3:149–158.

Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME. 1995. Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci 15:12–29.

Buckner RL, Goodman J, Burock M, Rotte M, Koutstaal W, Schacter D, Rosen B, Dale AM. 1998a. Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron 20:285–296.

Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte M, Rosen BR. 1998b. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. NeuroImage 7:163–175.

Burke DM. 1997. Language, aging, and inhibitory deficits: Evaluation of a theory. J Gerontol [Psychol Sci] 52B:P254–P264.

Burke DM, MacKay DG, Worthley JS, Wade E. 1991. On the tip of the tongue: What causes word finding failures in young and older adults? J Memory Lang 30:542–579.

Cabeza R. in press. Functional neuroimaging of cognitive aging. In: Cabeza R, Kingstone A, editors. Handbook of functional neuroimaging of cognition. Cambridge, MA: MIT Press.

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, Jennings JM, Houle S, Craik FIM. 1997. Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. J Neurosci 17:391–400.

Cabeza R, Anderson ND, Mangels JA, Nyberg L, Houle S. 2000. Age-related differences in neural activity during item and temporal-order memory retrieval: A positron emission tomography study. J Cogn Neurosci 12:197–206.
Cerella J. 1985. Information processing rates in the elderly. Psych Bull 98:67–83.
Craik FIM, Jennings JM. 1992. Human memory. In: Craik FIM, Salthouse TA, editors. The handbook of aging and cognition. Hillsdale, NJ: Erlbaum, p 51–110.
Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JDE. 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. J Neurosci 15:5870–5878.
Desgranges B, Baron J-C, Eustache F. 1998. The functional neuroanatomy of episodic memory: The role of the frontal lobes, the hippocampal formation, and other areas. NeuroImage 8:198–213.
D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. 1998. Functional MRI studies of spatial and nonspatial working memory. Cognit Brain Res 7:1–13.
D'Esposito M, Zarahn E, Aguirre GK, Rypma B. 1999. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. NeuroImage 10:6–14.
Fisk JE, Warr P. 1996. Age and working memory: The role of perceptual speed, the central executive, and the phonological loop. Psychol Aging 11:316–323.
Friedman D, Fabiani M. 1995. Memory and aging: An event-related potential perspective. In: Allen PA, Bashore TR, editors. Age differences in word and language processing. Amsterdam: Elsevier, p 345–389.
Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2:189–210.
Gabrieli JDE. 1998. Cognitive neuroscience of human memory. Ann Rev Psychol 49:87–115.
Gabrieli JDE, Desmond JE, Demb JB, Wagner AD, Stone MV, Vaidya CJ, Glover GH. 1996. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. Psychol Sci 7:278–283.
Golomb J, Kluger A, de Leon MJ, Ferris SH, Convit A, Mittelman M, Cohen J, Rusinek H, De Santi S, George AE. 1994. Hippocampal formation size in normal human aging: A correlate of delayed secondary memory performance. Learn Mem 1:45–54.
Grady CL. 1998. Brain imaging and age-related changes in cognition. Exp Geront 33:661–673.
Grady CL, Craik FIM. 2000. Changes in memory processing with age. Curr Opin Neurobiol 10:224–231.
Grady CL, Haxby JV. 1995. Functional neuroimaging of the aging brain. In: Boller F, Grafman J, editors. Handbook of neuropsychology, Vol 10. Amsterdam: Elsevier Sciences, p 467–481.
Grady CL, McIntosh AR, Horwitz B, Maisog JM, Ungerleider LG, Mentis MJ, Pietrini P, Schapiro MB, Haxby JV. 1995. Age-related reductions in human recognition memory due to impaired encoding. Science 269:218–221.
Grady CL, McIntosh AR, Bookstein F, Horwitz B, Rapoport SI, Haxby JV. 1998. Age-related changes in regional cerebral blood flow during working memory for faces. NeuroImage 8:400–425.
Grady CL, McIntosh AR, Rajah MN, Beig S, Craik FIM. 1999. The effects of age on the neural correlates of episodic encoding. Cereb Cortex 9:805–814.
Grafton ST, Hazeltine E, Ivry RB. 1995. Functional mapping of sequence learning in normal humans. J Cogn Neurosci 7:497–510.
Grafton ST, Hazeltine E, Ivry RB. 1998. Abstract and effector-specific representations of motor sequences identified with PET. J Neurosci 18:9420–9428.
Gregoire J, Van der Linden M. 1997. Effects of age on forward and backward digit spans. Aging Neuropsychol Cognit 4:140–149.
Hasher L, Zacks RT. 1988. Working memory, comprehension, and aging: A review and a new view. In: Bower GH, editor. The psychology of learning and motivation, Vol 22. New York: Academic Press, p 193–225.
Hoffman J. 1997. Positron emission tomography studies in dementia. In: Krishnan KRR, Doraiswamy PM, editors. Brain imaging in clinical psychiatry. New York: Marcel Dekker, p 533–573.
Howard DV, Howard JH. 1992. Adult age differences in the rate of learning serial patterns: Evidence from direct and indirect tests. Psychol Aging 7:232–241.
Howard JH, Howard DV. 1997. Age differences in implicit learning of higher order dependencies in serial patterns. Psychol Aging 12: 634–656.
James TW, Humphrey GK, Gati JS, Menon RS, Goodale MA. 1999. Repetition priming and the time course of object recognition: An fMRI study. NeuroReport 10:1019–1023.
Jonides J, Marshuetz C, Smith EE, Reuter-Lorenz PA, Koeppe RA. 2000. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. J Cogn Neurosci 12:188–196.
Laver GD, Burke DM. 1993. Why do semantic priming effects increase in old age? A meta-analysis. Psychol Aging 8:34–43.
La Voie D, Light LL. 1994. Adult age differences in repetition priming: A meta-analysis. Psychol Aging 9:539–553.
Light LL, La Voie D, Kennison R. 1995. Repetition priming of nonwords in young and older adults. J Exp Psychol [Learn Mem Cog] 21:327–346.
MacLeod AK, Buckner RL, Miezin FM, Petersen SE, Raichle ME. 1998. Right anterior prefrontal cortex activation during semantic monitoring and working memory. NeuroImage 7:41–48.
Madden DJ, Hoffman JM. 1997. Application of positron emission tomography to age-related cognitive changes. In: Krishnan KRR, Doraiswamy PM, editors. Brain imaging in clinical psychiatry. New York: Marcel Dekker, p 575–613.
Madden DJ, Pierce TW, Allen PA. 1993. Age-related slowing and the time course of semantic priming in visual word identification. Psychol Aging 8:490–507.
Madden DJ, Turkington TG, Coleman RE, Provenzale JM, DeGrado TR, Hoffman JM. 1996. Adult age differences in regional cerebral blood flow during visual word identification: Evidence from $H_2{}^{15}O$ PET. NeuroImage 3:127–142.
Madden DJ, Turkington TG, Provenzale JM, Hawk TC, Hoffman JM, Coleman RE. 1997. Selective and divided visual attention: Age-related changes in regional cerebral blood flow measured by $H_2{}^{15}O$ PET. Hum Brain Mapp 5:389–409.
Madden DJ, Gottlob LR, Denny LL, Turkington TG, Provenzale JM, Hawk TC, Coleman RE. 1999a. Aging and recognition memory: Changes in regional cerebral blood flow associated with components of reaction time distributions. J Cogn Neurosci 11:511–520.
Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, Coleman RE. 1999b. Adult age differences in the functional neuroanatomy of verbal recognition memory. Hum Brain Mapp 7:115–135.
Maki PM, Zonderman AB, Weingartner H. 1999. Age differences in implicit memory: Fragmented object identification and category exemplar generation. Psychol Aging 14:284–294.
McCarthy G, Puce A, Constable RT, Krystaal JH, Gore JC, Goldman-Rakic P. 1996. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. Cereb Cortex 6:600–611.
McIntosh AR, Bookstein FL, Haxby JV, Grady CL. 1996a. Spatial pattern analysis of functional brain images using partial least squares. NeuroImage 3:143–157.
McIntosh AR, Grady CL, Haxby JV, Ungerleider LG, Horwitz B. 1996b. Changes in limbic and prefrontal functional interactions in a working memory task for faces. Cereb Cortex 6:571–584.
McIntosh AR, Nyberg L, Bookstein FL, Tulving E. 1997. Differential functional connectivity of prefrontal and medial temporal cortices during episodic memory retrieval. Hum Brain Mapp 5:323–327.
Moscovitch M. 1992. Memory and working-with-memory: A component process model based on modules and central systems. J Cogn Neurosci 5:257–267.
Moscovitch M, Winocur G. 1992. The neuropsychology of memory and aging. In: Craik FIM, Salthouse TA, editors. The handbook of aging and cognition. Hillsdale, NJ: Erlbaum, p 315–372.
Myerson J, Ferraro FR, Hale S, Lima SD. 1992. General slowing in semantic priming and word recognition. Psychol Aging 7:257–270.
Nolde SF, Johnson MK, Raye CL. 1998. The role of prefrontal cortex during tests of episodic memory. Trends Cognit Sci 2:399–406.
Rastle KG, Burke DM. 1996. Priming the tip of the tongue: Effects of prior processing on word retrieval in young and older adults. J Mem Lang 35:585–605.
Raz N. 2000. Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In: Craik FIM, Salthouse TA, editors. The handbook of aging and cognition, 2nd ed. Mahwah, NJ: Erlbaum, p 1–90.
Raz N, Gunning-Dixon FM, Head D, Dupuis JH, Acker J. 1998. Neuroanatomical correlates of cognitive aging: Evidence from structural magnetic resonance imaging. Neuropsychology 12:95–114.
Raz N, Briggs SD, Marks W, Acker JD. 1999. Age-related deficits in generation and manipulation of mental images: II. The role of dorsolateral prefrontal cortex. Psychol Aging 14:436–444.

Reuter-Lorenz PA, Jonides J, Smith EE, Miller A, Marshuetz C, Koeppe RA, Hartley A. 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 12:174–187.

Rubin DC. 1999. Frontal-striatal circuits in cognitive aging: Evidence for caudate involvement. Aging Neuropsych Cognit 6:241–259.

Rugg MD, Fletcher PC, Allan K, Frith CD, Frackowiak RSJ, Dolan RJ. 1998. Neural correlates of memory retrieval during recognition memory and cued recall. NeuroImage 8:262–273.

Rypma B, D'Esposito M. 2000. Isolating the neural mechanisms of age-related changes in human working memory. Nature Neurosci 3:509–515.

Salthouse TA. 1985. Speed of behavior and its implications for cognition. In: Birren JE, Schaie KW, editors. Handbook of the psychology of aging, 2nd ed. New York: Van Nostrand Reinhold, p 400–426.

Salthouse TA. 1994a. How many causes are there of aging-related decrements in cognitive functioning? Dev Rev 14:413–437.

Salthouse TA. 1994b. The aging of working memory. Neuropsychology 8:535–543.

Salthouse TA. 1996a. General and specific mediation of adult age differences in memory. J Gerontol [Psychol Sci] 51B:P30–P42.

Salthouse TA. 1996b. The processing-speed theory of adult age differences in cognition. Psychol Rev 103:403–428.

Salthouse TA, Meinz EJ. 1995. Aging, inhibition, working memory, and speed. J Gerontol [Psychol Sci] 50B:P297–P306.

Schacter DL. 1992. Understanding implicit memory: A cognitive neuroscience approach. Am Psychol 47:559–569.

Schacter DL, Savage CR, Alpert NM, Rauch SL, Albert MS. 1996. The role of hippocampus and frontal cortex in age-related memory changes: A PET study. NeuroReport 7:1165–1169.

Shimamura AP, Berry JM, Mangels JA, Rusting CL, Jurica PJ. 1995. Memory and cognitive abilities in university professors: Evidence for successful aging. Psychol Sci 6:271–277.

Smith AD. 1996. Memory. In: Birren JE, Schaie KW, editors. Handbook of the psychology of aging. San Diego: Academic Press, p 236–250.

Smith EE, Jonides J. 1999. Storage and executive processes in the frontal lobes. Science 283:1657–1661.

Smith EE, Jonides J, Koeppe RA. 1996. Dissociating verbal and spatial working memory using PET. Cereb Cortex 6:11–20.

Spencer WD, Raz N. 1995. Differential effects of aging on memory for content and context: A meta-analysis. Psychol Aging 10:527–539.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. 1992. Activation of the hippocampus in normal humans: A functional anatomical study of memory. Proc Natl Acad Sci USA 89:1837–1841.

Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme.

Tulving E. 1983. Elements of episodic memory. Oxford: Clarendon Press.

Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S. 1994. Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. Proc Natl Acad Sci USA 91:2016–2020.

Wagner AD, Desmond JE, Demb JB, Glover GH, Gabrieli JDE. 1997. Semantic repetition priming for verbal and pictorial knowledge: A functional MRI study of left inferior prefrontal cortex. J Cogn Neurosci 9:714–726.

Wagner AD, Desmond JE, Glover GH, Gabrieli JDE. 1998a. Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. Brain 121:1985–2002.

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. 1998b. Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. Science 281:1188–1191.

West RL. 1996. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 120: 272–292.

West R, Craik FIM. 1999. Age-related decline in prospective memory: The roles of cue accessibility and cue retrievability. Psychol Aging 14:264–272.

Zacks R, Hasher L. 1997. Cognitive gerontology and attentional inhibition: A reply to Burke and McDowd. J Gerontol [Psychol Sci] 52B:P274–P283.