Memory and Executive Function in Aging and AD: Multiple Factors that Cause Decline and Reserve Factors that Compensate

Review

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Memory decline in aging results from multiple factors that influence both executive function and the medial temporal lobe memory system. In advanced aging, frontal-striatal systems are preferentially vulnerable to white matter change, atrophy, and certain forms of neurotransmitter depletion. Frontal-striatal change may underlie mild memory difficulties in aging that are most apparent on tasks demanding high levels of attention and controlled processing. Through separate mechanisms, Alzheimer's disease preferentially affects the medial temporal lobe and cortical networks, including posterior cingulate and retrosplenial cortex early in its progression, often before clinical symptoms are recognized. Disruption of the medial temporal lobe memory system leads directly to memory impairment. Recent findings further suggest that age-associated change is not received passively. Reliance on reserve is emerging as an important factor that determines who ages gracefully and who declines rapidly. Functional imaging studies, in particular, suggest increased recruitment of brain areas in older adults that may reflect a form of compensation.

Older adults always differ from their younger selves but vary considerably in their level of maintained cognitive ability (Figure 1). Some individuals show high functioning into their ninth and tenth decades with the only detectable changes being cognitive slowing and slight difficulties on the most attention-demanding tasks. Other older adults show severe memory impairment and dementia early in senescence. Beyond individual differences, aging influences certain cognitive domains and memory forms more than others. For example, long-term memory and working memory are commonly impaired while rote retrieval of word meaning (vocabulary) and priming remain relatively intact (Nyberg et al., 1996; Park et al., 1996; Schaie, 1996; Figure 2).

A central issue in cognitive aging research is to understand the physiological changes that cause memory decline and also to explain why retained memory abilities vary so greatly across individuals and cognitive domains. In the present review, a small portion of the aging literature is discussed, with an emphasis on factors that influence executive processes that are important to memory and also factors that directly disrupt the medial temporal lobe memory system. In later sections, functional consequences of disruption are examined, including the emerging possibility that medial temporal influ-

ences on memory decline arise, in part, from a disturbance of cortical networks involving precuneus extending into retrosplenial and posterior cingulate cortex. Table 1 defines terms that will be used throughout the review.

Multiple Factors Contribute to Memory Decline in Aging

Two frameworks have been proposed to understand cognitive aging that differ as to whether they hypothesize single or multiple factors to account for cognitive decline (see Figure 3). Within a *unitary factor* framework, cognitive decline (including memory) falls along a single continuum. Severe memory impairment, such as experienced in Alzheimer's disease, represents the acceleration of the same processes that lead to more subtle cognitive change in nondemented aging (e.g., Brayne and Calloway, 1988; Huppert, 1994; Huppert and Brayne, 1994). Diagnostic labels are applied when a certain threshold of disability is reached. By contrast, a *multiple factor* framework proposes distinct age-associated cascades that target different brain systems and may independently vary in their level of progression across individuals (e.g., Albert, 1997; Gabrieli, 1996). Within a multiple factor framework, cognitive decline in nondemented aging may be mild because some individuals, while being influenced by certain aging processes, are spared from the most devastating changes caused by Alzheimer's disease and other rapidly progressing dementias.

Considerable evidence, from both behavioral and neurobiological sources, suggests that multiple, distinct factors cause memory decline in aging. In particular, there is a recurring distinction between (1) disruption of executive functions that influence memory and (2) decline in long-term (declarative) memory (for a recent review, see Hedden and Gabrieli, 2004). From the outset, it is important to note that these two factors, while useful as heuristics, capture only the broadest separation among causes of memory decline. Multiple cognitive observations dissociate across these two factors, making them a good starting point for discussion. For example, older adults free from symptoms of dementia often show difficulties on tasks that stress attention and executive abilities (Hasher and Zacks, 1988; Craik et al., 1990; Jennings and Jacoby, 1993; Moscovitch and Winocur, 1995; West, 1996; Balota et al., 2000). By contrast, early stages of Alzheimer's disease are hallmarked by deficits in declarative memory, such as difficulty in remembering short lists of words or objects (Huppert, 1994), although effects on executive function can be detected (Balota and Faust, 2001). Analyses that seek factors to account for age-related changes in cognition converge on global factors that include executive function and separate factors that directly influence declarative memory (Glisky et al., 1995; Salthouse and Ferrer-Caja, 2003). These differential effects may arise from separate age-associated influences on frontal-striatal circuits and on the medial temporal lobe memory system.

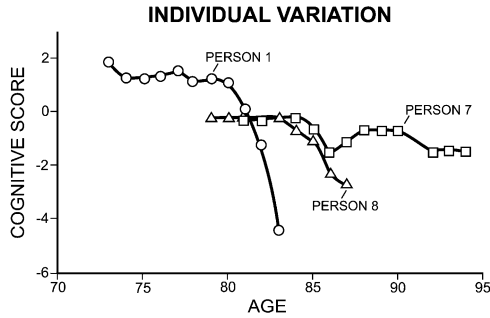*Correspondence: rbuckner@artsci.wustl.edu

INDIVIDUAL VARIATION

Figure 1. Cognition Varies Considerably across Older Individuals

Illustrated are three representative people who were each tested yearly on a cognitive task battery. The plot displays each individual's longitudinal progression. Person 1, while beginning with a high cognitive baseline, became impaired rapidly at a relatively young age. Person 7 and person 8 showed similar cognitive performance into their 80s but then diverged. A central goal in cognitive aging research is to understand the causes of cognitive decline and why some individuals age gracefully into their ninth and tenth decades while other become demented. Adapted from Rubin et al. (1998).

Frontal-Striatal Influences on Executive Function

Change in frontal-striatal circuits is the most likely significant cause of reduced executive function in nondemented older adults. Reduced executive function influences memory because acts of remembering often rely on controlled processing, such as strategic elaboration during memorization and guiding search at retrieval. Remembering source information and temporal details of past episodes appears to be particularly dependent on executive processes that are disrupted in aging (see Schacter et al., 1991; Johnson et al., 1993; West, 1996; for relevant discussion). Executive difficulties in aging are not limited to memory tasks but nonetheless may be central to why older adults experience memory difficulties.

A number of pathophysiological changes occur in aging that preferentially influence brain structures and are *candidates* for causing age-associated executive difficulties. One class of change that may influence executive function arises from damage to white matter. Ylikoski et al. (1995), in a study of nondemented older adults, conservatively estimate that 65% of individuals over 75 years of age show white matter abnormalities. Diffuse change in white matter is the most common observation, but small infarcts are also prevalent. For example, Longstreth et al. (2002) reported that 18% of older adults acquired an infarct within 5 years of an infarct-free baseline image. Even though cognitive effects could be detected on sensitive neuropsychological

tests, only 11% of those individuals acquiring infarcts experienced symptoms leading to a clinical diagnosis. Population-based estimates suggest nearly 30% of neurologically normal adults reaching their ninth decade have at least one brain infarct (DeCarli et al., 2004).

Figure 4 displays diffuse white matter lesions in an older adult. This common form of white matter change is referred to as "white matter hyperintensities" because of its bright spotty appearance. The pathophysiological origins of white matter hyperintensities and relation to infarcts are unclear, with likely contributions from non-vascular as well as vascular causes. Vascular compromise (small vessel disease) is common in aging and is accompanied by damage to white matter pathways (Pantoni and Garcia, 1997; DeCarli and Scheltens, 2002; Pugh and Lipsitz, 2002; see also Soderlund et al., 2003). Hypertension has been among the most salient predictors of white matter damage in these studies (e.g., Longstreth et al., 1996) and persists as a factor even when treated (Raz et al., 2003b).

Frontal white matter may be preferentially vulnerable to changes in aging. Anatomic patterns of white matter change have been explored using diffusion tensor imaging (DTI). DTI uses the uneven water diffusion along axons to measure white matter tissue integrity (LeBihan et al., 2001; Neil et al., 2002). Water diffuses rapidly along the length of healthy white matter but slowly across its fibers. As white matter degrades, diffusion becomes more even (isotropic) and increases across the fibers. Several DTI studies note age-associated differences in white matter that are present in nondemented aging and sometimes, but not always, preferential for anterior brain regions, including frontal lobar and anterior callosal regions (Pfefferbaum et al., 2000; O'Sullivan et al., 2001; Head et al., 2004; Madden et al., 2004; see Moseley, 2002, for review). O'Sullivan et al. (2001), for example, used DTI to measure white matter integrity within subregions of the corpus callosum. Significant age differences were noted in anterior callosal regions that were greater than those observed in posterior regions, a finding recently replicated in Head et al. (2004) (Figure 5). Bartzokis et al. (2004), using a related MRI method based on measurement of transverse relaxation rates, showed a 3-fold difference between age-associated decline in anterior in contrast to posterior callosal regions. It is presently not known whether DTI measures of white matter differences reflect demyelination, axonal loss, or other form of white matter disruption.

Evidence for an influence on cognition, including executive function and memory, comes from studies of white matter lesions on structural MRI images that link their severity to cognition (for reviews, see Gunning-
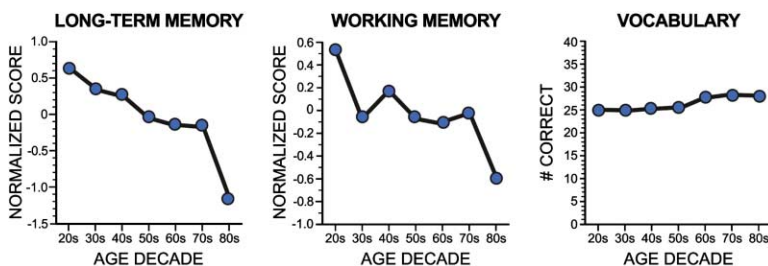

Figure 2. Aging Preferentially Influences Some Cognitive Domains More than Others

In particular, long-term (declarative) memory and working memory decline throughout life and more so in advanced aging, while some abilities, such as knowledge of vocabulary, are relatively maintained into senescence. Priming, a form of nondeclarative memory, can be relatively preserved (data not shown). Plotted data represent a subset of tasks from Park et al., 1996.

Table 1. Definitions

Long-Term Memory

Retains information over extended periods of time. Relies on brain systems that support the ability to form enduring memories, to maintain them for periods ranging from minutes to years, and to gain access to them for subsequent use.

Working (Short-Term) Memory

Maintains and allows manipulation of immediately available information. Relies on brain systems that represent memories in an active, online form. Interacts with long-term memory in that information from the past is often retrieved from long-term memory and manipulated within working memory.

Declarative Memory

Forms of long-term memory able to relate diverse information that can be used flexibly and (in humans) are available to conscious awareness and verbal report. These are to be contrasted to nondeclarative (procedural) forms of memory, such as skill learning and priming, that are less flexible and less relational and can operate outside awareness.

Executive Function

General cognitive processes that support strategic organization and control other processes important to complex, goal-oriented tasks. Long-term and working memory often depend on executive functions because strategic processes are required for task performance.

Amnesia

Partial or total loss of declarative memory, usually as a result of brain injury. Most often, distant memories are retained but new declarative learning is severely impaired.

Dementia

The loss of intellectual functions (such as executive or memory function) of sufficient severity to interfere with a person's daily functioning.

Alzheimer's Disease

A progressive, neurodegenerative disease characterized by loss of function and death of neurons in several brain areas, leading to decline of mental functions prominently including memory. Alzheimer's disease is the most common cause of dementia in aging.

Dixon and Raz, 2000; DeCarli and Scheltens, 2002). For example, in a large population-based study of 1077 non-demented older adults, cognitive test scores in older adults were found to be worse when severe white matter hyperintensities were observed, even after removal of direct influences of age, gender, and education (Figure 4) (de Groot et al., 2000; see also de Groot et al., 2002). DTI measures of white matter integrity have also corre-

UNITARY FACTOR

Young → Aging → Dementia

MULTIPLE FACTOR

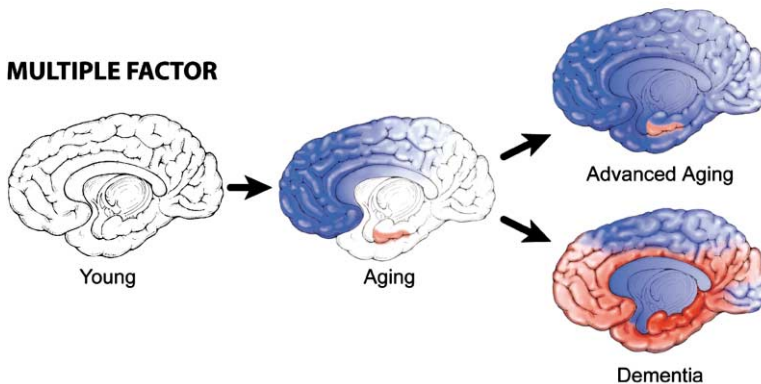Young → Aging → Advanced Aging / Dementia
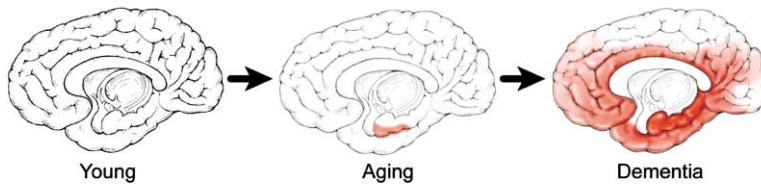
Figure 3. Unitary and Multiple Factor Frameworks of Aging Are Schematically Represented as Heuristics for Discussion

Within a unitary factor framework, mild memory decline common in aging exists along a single continuum with memory impairment associated with dementia. Dementia is considered as an acceleration of the same processes that affect cognition in all individuals. Within a multiple factor framework, separate factors are hypothesized to affect cognition in aging, each with distinct causes, risk factors, anatomic targets, and cognitive sequelae.
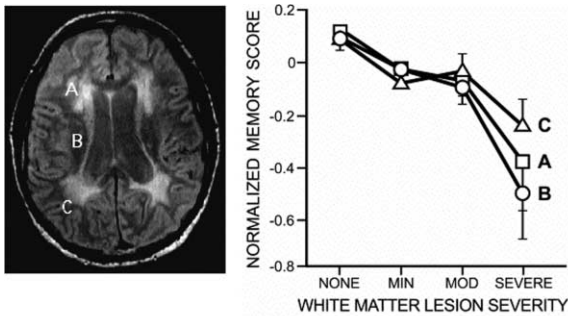
Figure 4. White Matter Lesions Correlate with Memory Decline in Older Adults

(Left) A typical example of white matter hyperintensities observed in an older adult on a T2-weighted MRI image. The displayed image represents an axial (horizontal) section through the brain. Anterior (A), lateral (B), and posterior (C) regions of hyperintensity can be observed. Image courtesy of W. Jagust. (Right) Memory performance degrades as a function of white matter lesion severity. This plot was constructed after removing effects of age, gender, and education in a population-based sample of 1077 older adults. The letters next to the lines indicate which general anatomic region they correspond to, as depicted in the left panel. Adapted from de Groot et al. (2000).

lated with executive function (e.g., O'Sullivan et al., 2001; see also Madden et al., 2004). However, it is important to note that executive function and memory are often not selectively impaired. de Groot et al. (2000) observed influences on executive tasks, such as the Stroop interference task, delayed memory recall, global tests of cognition, and even simple cognitive tests that measure response speed. When cognitive differences are noted in relation to white matter lesions, multiple domains of cognition are usually affected, often including executive and memory abilities.

Atrophy of frontal gray matter may also be an important related factor (e.g., Raz et al., 1997; Salat et al., 1999) as well as striatal volume loss (Raz et al., 2003a;
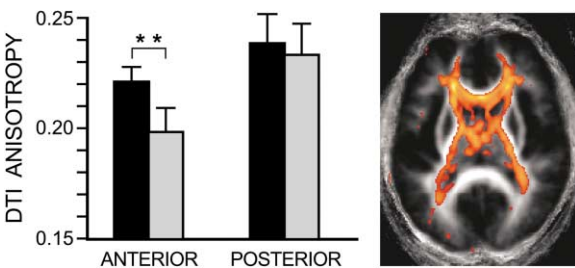

Figure 5. Anterior (Frontal) White Matter Shows Preferential Vulnerability to Degradation in Aging

(Left) Regional diffusion tensor imaging (DTI) measures of anterior and posterior callosal tracts are plotted for young (black bars) and nondemented old (gray bars) adults. The measure of white matter integrity is DTI anisotropy (see text). Significant effects are noted in anterior but not posterior regions. Adapted from O'Sullivan et al. (2001). (Right) A map of DTI-measured white matter integrity is plotted as a direct comparison of young and old adults. The displayed image represents an axial (horizontal) section through the brain. Brighter colors illustrate areas of greatest difference between age groups. Preferential deterioration of anterior white matter is clearly observed. Adapted from Head et al. (2004).

Table 2. Effect of Age on Regional Volume	
Frontal	−0.47
Temporal	−0.27
Parietal	−0.29
Caudate	−0.47
Putamen	−0.44
Globus Pallidus	−0.14
Hippocampus	−0.31
Parahippocampal Gyrus	−0.25
Amygdala	−0.26

Effect sizes represent the median (product-moment) correlation of age and structural measure across multiple studies in the literature (volume loss is head-size corrected). These values come from the comprehensive literature review reported by Raz (2000) (see also Raz, in press).

see Rubin, 1999, for discussion). Studies that measure volume through manual measurement of MRI sections observe age-associated volume loss in the frontal cortex that is greater than across other cortical and subcortical regions. Table 2 presents median effect sizes for age-related volume loss across multiple brain structures (adapted from Raz, 2000; see also Raz, 2004). Two observations are notable. First, all cortical and subcortical volumes show some level of reduction with age. Second, frontal and striatal regions show quantitatively greater volume reductions, suggesting preferential vulnerability. Recent studies examining age-associated differences in cortical thickness similarly note widespread regional effects, with some of the most robust effects observed in frontal regions (Salat et al., 2004). Direct associations between frontal atrophy and cognitive decline are also observed (Raz et al., 1998).

In addition to macroscopically visible changes, age differences in neurochemical properties are a further class of candidates for affecting executive function and memory. In particular, brain dopamine declines with age (e.g., Antonini et al., 1993; Rinne et al., 1993) and associates with performance on executive tasks (Volkow et al., 1998; Bäckman et al., 2000b). Monkey models have documented prefrontal dopamine depletion in aging (Goldman-Rakic and Brown, 1981; Wenk et al., 1989) that contributes to age-related cognitive decline (Arnsten et al., 1995). Goldman-Rakic and Brown (1981), for example, noted that aged monkeys experience 50% loss of dopamine in prefrontal and premotor cortex that is not present for norepinephrine or serotonin (see their Figure 1). Considering cortical volume loss may contribute to an underestimation of neurotransmitter depletion in some of these studies, the levels of loss are likely substantial. Moreover, dopamine antagonist injections into monkey prefrontal cortex affect working memory in a dose-dependent manner, directly implicating dopamine as an important neurotransmitter participating in frontal executive function (Sawaguchi and Goldman-Rakic, 1991). These results suggest a relation between neurochemical changes and age-associated cognitive deficits and also raise important avenues for further research (e.g., Braver and Barch, 2002). Structural change at the gross anatomic level, as described above, has been extensively studied in cognitive aging research, likely because such methods are readily accessible to many investigators. The increasing availability

of molecular methods and selective ligands that can target neurochemical processes in aging humans will expand the ability to measure underlying cellular processes affected by age that, in turn, lead to structural and cognitive change.

In summary, age-associated change in anterior brain regions correlates with executive dysfunction. Important to memory, decline in executive function impairs strategic, controlled processing at encoding and retrieval. An unresolved issue surrounds how the multiple forms of deterioration, such as white matter lesions and neurotransmitter depletion, relate to one another and ultimately to executive impairment. Converging results suggest that a prominent mechanism may arise from age-associated decline in vascular function that preferentially affects anterior white matter structures serving frontal-striatal circuits important to executive function.

Medial Temporal Influences on Memory

Medial temporal cortex, including the hippocampus and adjacent cortical areas, is critical for long-term, declarative memory (Squire, 1992; Cohen and Eichenbaum, 1993). Atrophy, cellular pathology, and cell loss are observed prominently in medial temporal structures in Alzheimer's disease leading to profound memory impairment (for review, see Albert, 1997). Symptoms advance to eventual global compromise as the disease progresses. The high baseline incidence of Alzheimer's disease and difficulty in early stage diagnosis make Alzheimer's disease an important factor that affects memory in aging, even when the disease is not clinically apparent.

At a cellular level, Alzheimer's disease is associated with build up of amyloid (extracellularly) and tau (intracellularly) in a pathological form (Golde et al., 2000; Mattson, 2004; Walsh and Selkoe, 2004 [this issue of *Neuron*]). One prominent hypothesis is that amyloid deposits (plaques) and soluble forms of amyloid lead to neuronal dysfunction and cell death. Pathology, in particular neurofibrillary tangles, is prominent in the medial temporal lobe early in the disease and spreads outward to association cortex over time (Braak and Braak, 1991; 1997; Price et al., 2001). Entorhinal cortex appears to be especially vulnerable to cell loss early in the progression of the disease (Hyman et al., 1984; Price et al., 1991; Gómez-Isla et al., 1996). Structural MRI studies consistently find medial temporal atrophy in patients with Alzheimer's disease (e.g., Jack et al., 1992; Killiany et al., 1993; see Jack and Petersen, 2000, for review; Figure 6) as well as hippocampal shape deformation (Csernansky et al., 2000). The vulnerability of medial temporal structures in the early stages of the disease likely explains why prominent initial symptoms include memory impairment. Neocortical association regions are also affected early in Alzheimer's disease, in particular by amyloid deposition. The topic of cortical involvement in early Alzheimer's disease will be discussed in a later section.

The presence of Alzheimer's disease in many older adults raises challenges to aging research and also an important conceptual question about whether Alzheimer's disease represents the acceleration of normal aging processes or a distinct disease entity. Specifically, it is difficult to obtain a sample of older adults free from the disease. For many studies, participants are assumed to be spared from Alzheimer's disease if they achieve a certain level of performance on a global cognitive
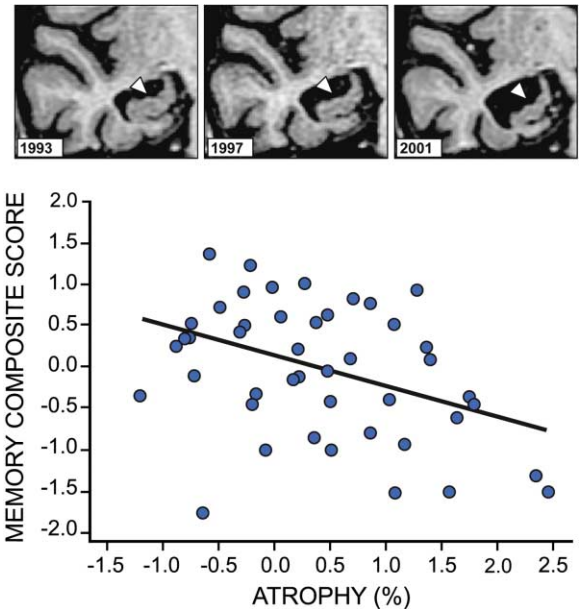

Figure 6. Hippocampal Volume Change Associates with Memory Performance

(Top) The hippocampus of an older adult imaged repeatedly with MRI is shown through a coronal section of the hippocampus. The arrow points to marked atrophy. This individual, who presented with mild cognitive impairment (MCI) initially, progressed to a diagnosis of probable Alzheimer's disease. Image courtesy of C.R Jack. (Bottom) Annualized atrophy (in percent change) in a group of older adults is plotted against memory decline (normalized by Z score). The two show significant correlation. Adapted from Rodrigue and Raz (2003).

screening test (e.g., the Mini-Mental State Examination). Such methods eliminate severely impaired individuals but lead to the inclusion of older adults in the early stages of the disease who, because of high baseline functioning and other mitigating factors, retain average global cognition during the initial progression of the disease. The relevance of this issue is that several studies of nondemented aging have found correlations between atrophy of the medial temporal lobe, or substructures within the medial temporal lobe, and memory performance (Rodrigue and Raz, 2003; Golomb et al., 1996) although others have not (see Van Petten, 2004, for review). A likely, partial explanation for these varied results is that some studies of aging, in particular when longitudinal clinical progression is not considered, include older adults in the beginning stages of Alzheimer's disease. Other factors that complicate studying the relation between medial temporal cortex and age-associated memory decline are whether cross-sectional differences or longitudinal change are being explored, as well as whether subregions, such as entorhinal cortex, are studied (e.g., Small et al., 2000; Killiany et al., 2002; Jack et al., 2004). Nonetheless, it remains a possibility that significant, progressive memory loss associated with medial temporal lobe dysfunction in aging predominently arises from antecedent Alzheimer's disease (see Morris et al., 1996, 2001, for relevant discussion and Small et al., 2002, 2004, for an alternative perspective).

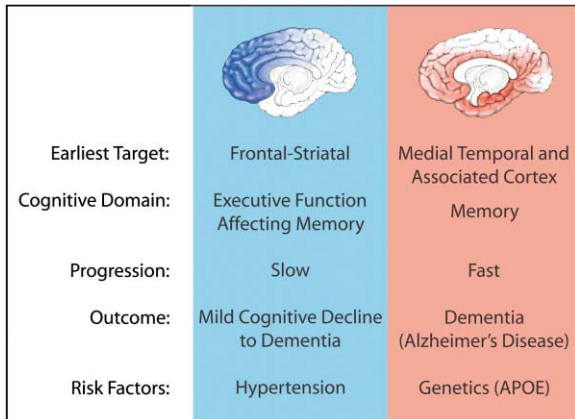Is memory impairment associated with Alzheimer's

Figure 7. Separate Frontal-Striatal and Medial Temporal Factors Are Schematically Illustrated

These two factors, while likely representing only a subset of the factors that influence cognitive decline in aging, have emerged as prominent candidates that directly or indirectly influence executive function and memory in aging. Both may combine in some individuals.
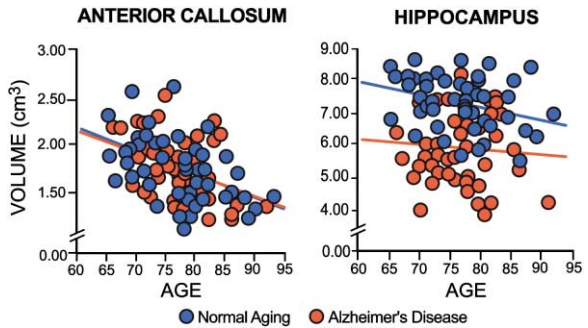

Figure 8. Anatomic Evidence for Dissociation between Frontal and Medial Temporal Factors in Aging

(Left) Volume of the anterior callosum, which receives fibers from the frontal lobe, is plotted for 100 older adults. Half are diagnosed with very early stages of Alzheimer's disease (red) and half are nondemented (blue). Note that all show similar age-related volume decline, indicating an aging process that is not accelerated by Alzheimer's disease. (Right) Hippocampal volume is plotted for the same individuals revealing marked volume loss in Alzheimer's disease. The slope of the hippocampal line for Alzheimer's disease should not be interpreted as demented individuals continue to decline at a markedly accelerated rate. Thus, a 65-year-old demented individual will not progress to become a mildly demented 80 year old. Adapted from Head et al. (2005).

disease accelerated aging? The common occurrence of Alzheimer's disease in older adults and its increasing prevalence with advanced aging raise the question of whether the disease is simply accelerated aging (Brayne and Calloway, 1988). In other words, is medial temporal dysfunction associated with Alzheimer's disease an inevitable consequence of aging? While a clear answer to this question has not emerged, it is notable that many older adults who experience normal signs of aging do not show pathology or memory dysfunction associated with Alzheimer's disease. For example, in the earliest stages of diagnosed Alzheimer's disease, entorhinal cortex shows between 30% to 60% neuron loss dependent on lamina; neuron loss in these regions is absent in individuals as old as 90 who do not show Alzheimer pathology (Gómez-Isla et al., 1996). Moreover, as will be described in the next section, influences on frontal-striatal systems can be dissociated from those linked to medial temporal dysfunction, further suggesting that some age-associated causes of memory impairment are not the initial stages of a progression that leads to Alzheimer's disease.

Independence and Interdependence of Frontal-Striatal and Medial Temporal Factors

Change in frontal-striatal and medial temporal systems both associate with age and commonly occur together, raising questions about whether they arise from a single factor or reflect multiple, dissociated factors that contribute to memory impairment in aging (Figure 7). One source of evidence for mechanistic separation comes from rare genetic mutations. Certain mutations have preferential effects on white matter and anterior brain regions while others parallel late-onset forms of Alzheimer's disease. Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal-dominant dementia that often associates with severe executive dysfunction (Joutel et al., 1996; see Kalimo et al., 2002 for review). In CADASIL, smooth muscles surrounding vessels degener-

ate with age, resulting in vascular compromise. White matter damage and, eventually, focal infarcts and stroke result. Frontal and subcortical regions, including the basal ganglia and thalamus, are preferentially vulnerable. By direct contrast, other genetic mutations cause early-onset forms of Alzheimer's disease with degeneration of the medial temporal lobe (e.g., Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995; see Price and Sisodia, 1998, for review). The existence of separate genetic mutations that preferentially target frontal-striatal and medial temporal structures indicates that they are *in principle* susceptible to different age-associated vulnerabilities.

Dissociation between frontal-striatal and medial temporal changes is also observed in common forms of aging. For example, the risk for medial temporal dysfunction associated with late-onset Alzheimer's disease is significantly influenced by variation in the APOE genotype (Strittmatter and Roses, 1995). By contrast, certain forms of white matter damage are linked to hypertension (DeCarli and Scheltens, 2002). Direct dissociations have also been observed structurally. In a whole-brain survey of age- and dementia-associated structural MRI differences, Ohnishi et al. (2001) identified widespread cortical changes that were characteristic of aging and medial temporal changes selective to Alzheimer's disease. Head et al. (2005) (see also Meguro et al., 2003) recently noted that anterior (frontal) white matter differences, while prominently associated with aging, are not accelerated in age-matched individuals with Alzheimer's disease, even though clinically significant memory impairment has begun (Figure 8). The implication is that changes in anterior structures present in aging are caused by independent mechanisms from those that lead to Alzheimer's disease (see also Petkov et al., 2004). While still preliminary, these combined results argue against models of aging that suggest that white matter

damage forms a continuum between aging and Alzheimer's disease (Bartzokis, 2004). Wu et al. (2002) offer evidence for dissociation between frontal-striatal and medial temporal factors and also an indication that the two factors act in a synergistic fashion. They explored the influence of only white matter damage, only hippocampal volume loss, or their co-occurrence on cognitive dysfunction. Each predicted impairment; when they occurred together, more severe cognitive decline was observed than either would be expected to elicit in isolation. Specifically, individuals with white matter damage *and* hippocampal volume loss had an greater likelihood of exhibiting severe cognitive symptoms than predicted by their individual risk levels.

Functional Dysfunction and Compensation
Physiological factors associated with aging, as described above, presumably cause disruption of brain networks that influence memory. Positron emission tomography (PET) and functional MRI (fMRI) have suggested possible functional consequences of age-associated frontal-striatal and medial temporal disruption. Both PET and fMRI measure local blood flow changes that correlate with neuronal activity (Raichle, 1987; Heeger and Ress, 2002; Logothetis, 2003). In addition to revealing patterns likely reflecting disruption, a number of studies have suggested cortical recruitment patterns in older adults that may reflect a form of compensation. Below is a review of data that suggest two forms of age-associated dysfunction relevant to executive function and declarative memory as well as evidence for functional compensation.

Context-Dependent Frontal Underrecruitment
Grady and colleagues (1995) report one possible cause of memory impairment in aging. In their seminal PET study, nondemented older adults were imaged while intentionally memorizing faces. During intentional memorization, young adults typically recruit (activate) multiple regions, including left prefrontal regions along the inferior frontal gyrus (near Broca's area) that play a role in verbal elaboration (e.g., Kapur et al., 1996; for reviews, see Buckner et al., 1999; Fletcher and Henson, 2001). Young adults thus appear to be able to spontaneously engage the appropriate networks that include prefrontal regions to form an effective memory encoding strategy. In contrast, Grady et al. observed that older adults showed reduced recruitment relative to young adults in the specific frontal regions associated with memory encoding—a phenomenon here termed *underrecruitment*. Activity levels in other cortical regions were maintained. Underrecruitment during intentional encoding has been replicated in multiple studies that have explored both verbal and nonverbal materials (Cabeza et al., 1997; Logan et al., 2002; Sperling et al., 2003; Nyberg et al., 2003; see Park and Gutchess, 2004, for review).

One interpretational concern is that underrecruitment might be an artifact of sample characteristics that confound measurement using imaging methods. Vascular compromise may impair the blood flow response in some older adults that is the basis of PET and fMRI (D'Esposito et al., 2003). The anatomic selectivity of underrecruitment in aging mitigates such concerns. Moreover, studies that explore fMRI-measured responses

during simple sensory and motor paradigms suggest that a hemodynamic confound is unlikely to account for the observed differences between younger and older adults (Buckner et al., 2000; D'Esposito et al., 1999; Huettel and McCarthy, 2001). Another possibility is that structural or physiological changes have impaired frontal function to the point that the maximal level of recruitment in older adults is significantly diminished relative to young adults. Despite the intuitive appeal of such an explanation, mounting evidence suggests that reduced frontal recruitment in aging is context dependent and can be ameliorated, to a large degree, under conditions where environmental cues and situational guidance aid memory.

Logan et al. (2002) provide direct evidence that frontal underrecruitment is context dependent in older adults (see also Rypma and D'Esposito, 2000). Their study was motivated by a long-standing theory of cognitive aging that focuses on reduced attentional and working memory capacity (Craik and Byrd, 1982; Craik 1986; see Zacks et al., 2000). Within this framework, advanced aging leads to capacity limitations that prevent older adults from flexibly producing memory encoding and retrieval strategies. When guidance is provided in the form of specific strategies or particularly useful memory cues (often referred to as environmental support) older adults improve performance. Using a contrast among multiple memory encoding conditions that varied the level of support provided, Logan et al. demonstrated that the same older adults who failed to recruit appropriate frontal regions under intentional memory encoding conditions, where strategies were spontaneously initiated, nonetheless recruited the regions to nearly the same degree as younger adults when a supportive memory encoding task was provided. This result suggests that some degree of frontal resources are available and that structured tasks provide the context (environmental support) to maximize older adults' ability to utilize available frontal resources. A speculative possibility is that the structural and physiological disruptions affecting frontal-striatal circuits, as described extensively in the previously sections, cause a reduction in the ability of older adults to flexibly produce memory encoding and retrieval strategies, which is manifest as context-dependent frontal underrecruitment.

Not all studies have observed comparable frontal recruitment in comparisons of young and older adults under supportive encoding conditions (e.g., Stebbins et al., 2002) or during other forms of tasks, such as during memory retrieval (e.g., Schacter et al., 1996) and rudimentary cognitive operations (Johnson et al., 2004). The reasons for variability remain unclear (see Park and Gutchess, 2004, for discussion). Nonetheless, the presence of similar recruitment levels in young and old adults in several studies of well-supported memory encoding (Logan et al., 2002; Morcom et al., 2003; Lustig and Buckner, 2004) tentatively suggests that frontal recruitment can occur under certain task conditions. As will be discussed in a later section, a common observation has been age-associated increase in frontal recruitment, perhaps as a form of compensation.

Disruption of Posterior Cortical Memory Networks
In contrast to the pathophysiological and structural studies of Alzheimer's disease that emphasize early

HEALTHY CORRELATES OF
RETRIEVAL SUCCESS

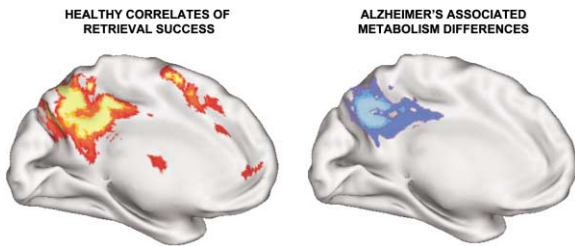ALZHEIMER'S ASSOCIATED
METABOLISM DIFFERENCES

Figure 9. Correlates of Memory Retrieval in Young Adults Converge with the Same Regions that Show Metabolic Change in Alzheimer's Disease

(Left) fMRI retrieval success effects are plotted for the medial surface of the cortex, showing regions more active when healthy, young adults correctly remember items from their past. Adapted from Wheeler and Buckner (2004). (Right) The correlation between Alzheimer's disease severity and FDG-PET resting glucose metabolism is plotted for a sample of nearly 400 patients. Brighter colors represent regions showing reduced metabolism as the disease becomes more severe. Note the strong correlation between impairment and hypometabolism near precuneus extending into posterior cingulate and retrosplenial cortex. Adapted from Herholz et al. (2002). The correspondence is notable, as retrosplenial cortex has dense reciprocal projections to the hippocampus and parahippocampal gyrus. Retrieval success effects and metabolism differences may thus be reflecting function (Left) and dysfunction (Right) of cortical networks subserving memory.

CONTROL   ALZHEIMER'S DISEASE

Figure 10. Amyloid Deposition in Alzheimer's Disease

PET images of the medial surface show retention of Pittsburg Compund-B (PIB), an amyloid-imaging tracer, in a normal control subject (Left) and an individual with Alzheimer's disease (Right). PIB retention is prominent in posterior parietal regions near posterior cingulate and retrosplenial cortex (A) and in frontal cortex (B). The presence of substantial amyloid burden in posterior regions that overlap memory networks, as shown in Figure 9, suggests a mechanism by which amyloid toxicity might disrupt memory. Data from Klunk et al. (2004). Image courtesy of W. Klunk, C. Mathis, and J. Price, University of Pittsburgh. The image has been reoriented from its original form to be comparable to Figure 9. Correspondence among regions showing retrieval success effects, metabolism difference in Alzheimer's disease, and amyloid burden extends to lateral parietal regions (data not shown) as well as to measures of cortical atrophy (e.g., see Scahill et al., 2002).

involvement of medial temporal regions, the most common functional observation in Alzheimer's disease has been disruption of metabolism and activity patterns in cortical regions, implicating an influence of the disease on a distributed network that is important to memory. PET studies of resting metabolism, using methods tailored to measure the metabolic rate of glucose, consistently observe reductions in temporoparietal association cortex and retrosplenial cortex, among other regions (e.g., Benson et al., 1983; Kumar et al., 1991; Herholz, 1995; Loessner et al., 1995; de Leon et al., 2001). Patients genetically at risk for the disease also present with similar metabolism differences (Reiman et al., 1996). As one example, Figure 9 shows the correlation between global cognitive function and resting metabolism in an analysis of nearly 400 participants with probable Alzheimer's disease (Herholz et al., 2002). Prominent correlation is noted in precuneus extending into posterior cingulate and retrosplenial cortex. Suggesting a direct link with memory, resting glucose metabolism in retrosplenial cortex correlates with memory recall performance (Desgranges et al., 2002).

An important, open question has been to understand how posterior cortical dysfunction in aging links to medial temporal systems and memory function. Insight comes from studies of long-term memory retrieval in healthy, young adults. Event-related fMRI studies of memory, which isolate neural correlates of memory retrieval, reliably observe increased posterior parietal activity when individuals correctly recognize items as compared to when they reject new items—a phenomenon referred to as the *retrieval success* effect (for reviews, see Buckner and Wheeler, 2001; Rugg et al., 2002). Items vividly retrieved, such that participants claim to distinctly remember their past occurrence, correlate with
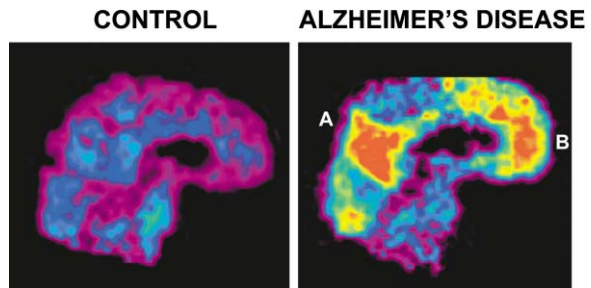
the greatest retrieval success effects (Henson et al., 1999; Wheeler and Buckner, 2004). Moreover, activity levels in cortical regions demonstrating retrieval success effects decrease when old items are forgotten and increase when new items are erroneously endorsed as remembered (Wheeler and Buckner, 2003; Kahn et al., 2004). Of relevance to understanding causes of memory impairment in aging, the regions demonstrating retrieval success effects in young adults with intact memory function overlap considerably with those showing resting metabolism differences in Alzheimer's disease. Figure 9 displays this anatomic relation for posterior regions on the midline. Anatomic overlap extends to lateral posterior parietal regions (data not shown).

Generalizing from monkey anatomy, posterior cingulate and retrosplenial cortex are at, or near, major cortical connections to the medial temporal memory system (Insausti et al., 1987; Vogt et al., 1992; Suzuki and Amaral, 1994; Morris et al., 1999; Kobayashi and Amaral, 2003). Retrosplenial cortex provides nearly one-fifth of the inputs to entorhinal and parahippocampal cortex. Afferent connections to retrosplenial cortex are also dominated by medial temporal projections. Kobayashi and Amaral (2003) speculate, based on this anatomy, that retrosplenial cortex acts as an interface zone between working memory (executive) functions enabled by prefrontal cortex and long-term memory functions subserved by the medial temporal lobe memory system (see also Valenstein et al., 1987). This set of convergent results provides intriguing evidence for how memory dysfunction might arise in aging associated with Alzheimer's disease. One possibility is that as medial temporal dysfunction progresses, the functioning of connected cortical networks including retrosplenial cortex are disrupted, leading to change in baseline metabolic activity and memory impairment. Early and significant neuron

loss in entorhinal cortex in Alzheimer's disease (Gómez-Isla et al., 1996) may be particularly relevant given its dense connectivity to retrosplenial cortex.

Alternatively, direct loss of neurons or other forms of pathology may occur within distributed cortical regions early in the disease concurrent with disruption in reciprocally connected medial temporal structures. Consistent with a direct pathological influence, initial in vivo images of amyloid in humans suggest marked deposition in posterior parietal cortex extending into cingulate and retrosplenial cortex (Klunk et al., 2004; Figure 10). Providing preliminary data for direct mechanism of cortical disruption, Klunk and colleagues further observed that amyloid deposition in parietal cortex correlates negatively with glucose metabolism (Klunk et al., 2004). Moreover, initial studies that survey gray matter loss in Alzheimer's disease note clear atrophy in posterior parietal cortex, in addition to medial temporal atrophy (Scahill et al., 2002; Thompson et al., 2003). For example, Scahill et al. (2002) (see also Fox et al., 2001), using a measure of longitudinal atrophy, observed prominent change in precuneus extending into cingulate and retrosplenial cortex in individuals with moderate Alzheimer's disease as well as presymptomatic individuals at the earliest stage of clinical conversion (see their Figures 4 and 5).

Further support for a network-based explanation comes from fMRI studies of Alzheimer's patients. Lustig et al. (2003) observed marked differences in posterior parietal activation, near posterior cingulate and retrosplenial cortex, in Alzheimer's patients that may be related to resting metabolism (see Gusnard and Raichle, 2001, for background). Similarly, differences in resting functional connectivity between posterior cortical regions and the medial temporal lobe have also been directly observed in Alzheimer's disease (Greicius et al., 2004; see also Greicius et al., 2003). Taken together, these data point toward a disrupted network that includes the medial temporal lobe and precuneus extending into posterior cingulate and retrosplenial cortex as being important to memory impairment in Alzheimer's disease.

Future investigations will be required to reconcile traditional pathological and volumetric analyses, which emphasize medial temporal structures at early stages of Alzheimer's disease, and the newer imaging methods, which converge on posterior cortical networks. Differential sensitivities of the methods may be an important factor. In addition, the anatomic topographies of the effects described above and their overlap are only provisionally specified at the present time. More detailed characterization may add important constraints given the known differences in connectivity patterns between posterior cingulate and retrosplenial cortex (Kobayashi and Amaral, 2003) and the complexities in making precise linkage between functional and anatomic data (e.g., see Vogt et al., 2000). Nonetheless, the anatomic similarity between fMRI-measured retrieval success effects, baseline metabolic patterns, cortical atrophy patterns, and in vivo amyloid deposition in Alzheimer's disease encourages consideration of how they relate and cause memory impairment in aging.
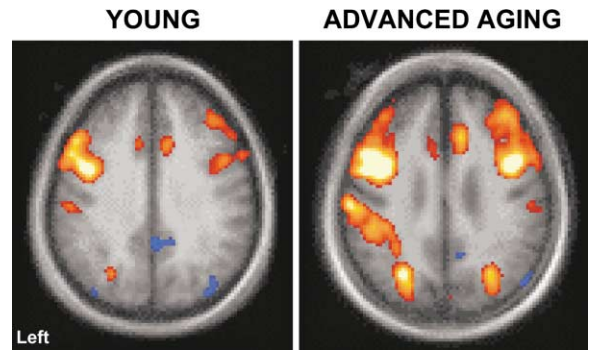

YOUNG   ADVANCED AGING

Figure 11. Older Adults Show Increased Activation in Frontal and Other Brain Regions as Compared to Young Adults, Possibly as a Form of Compensation

Both functional MRI images show activation during a language task. (Left) Young adults show strongly left-lateralized activation, while (Right) older adults show strong bilateral activation. Adapted from Logan et al. (2002).

Cognitive Reserve and Compensatory Recruitment

Cognitive reserve refers to the observation that factors associated with brain decline do not fully predict cognitive performance across individuals (Stern, 2002, 2003). Some individuals perform markedly better than a given level of brain damage might predict, while others are devastated. The concept of cognitive reserve posits that compensatory or other forms of reserve factors, such as education level and intelligence, mitigate cognitive decline. An important topic for aging research is to understand how these variables, which likely serve as proxies for innate or learned flexibility in responding to change, are instantiated in brain systems. Imaging studies are well suited for demonstrating direct neural responses that may be the mechanisms of reserve. In particular, reorganization of brain pathways and recruitment of atypical brain pathways may represent significant factors in understanding memory performance and variability in aging.

Paradoxical activation increases, particularly in frontal regions, have been repeatedly observed in PET and fMRI aging studies. For example, on language and verbal memory encoding tasks that are strongly left lateralized in young adults, older adults tend to show bilateral recruitment patterns (for discussion, see Grady and Craik, 2000; Langley and Madden, 2000; Park et al., 2001; Reuter-Lorenz, 2002; Cabeza, 2002; Buckner, 2003). Increased recruitment has been demonstrated in older adults without symptoms of dementia (Cabeza et al., 1997; Madden et al., 1999; Reuter-Lorenz et al., 2000; Logan et al., 2002; Park et al., 2003), individuals with Alzheimer's disease (Becker et al., 1996; Bäckman et al., 1999; Grady et al., 2003), nondemented individuals genetically at risk for Alzheimer's disease (Bookheimer et al., 2000), and following stroke (Buckner et al., 1996; Rosen et al., 2000). Morcom et al. (2003) recently noted that activation levels in bilateral frontal regions predicted verbal memory encoding in older adults in contrast to left-lateralized regions in young adults. Figure 11 illustrates one example of age-associated increased recruitment as measured by fMRI.

Accumulating data further suggest that increased recruitment may be a compensatory response in aging (Cabeza et al., 2002; Rosen et al., 2002; Grady et al., 2003), although alternative possibilities have not been fully explored. Cabeza and colleagues, for example, selected two groups of older adults—those who performed similarly to younger adults on a battery of memory tests and those who performed worse. Bilateral frontal activation was observed in those older adults who performed well as compared to unilateral activation in those who performed poorly, suggesting that activation increases were compensatory. Rosen et al. (2002) similarly noted that older adults with high memory scores showed significant recruitment of frontal regions, including atypically increased right frontal activation, as compared to low-scoring older adults. Finally, normal individuals at genetic risk for developing Alzheimer's disease show increased left frontal recruitment relative to control subjects (Bookheimer et al., 2000). A possible interpretation, which needs further exploration, is that dysfunction is already present and that increased recruitment is acting as a compensatory response to maintain memory performance during the initial stages of disease progression.

Are there specific age-associated factors that elicit increased recruitment? One possibility is that increased recruitment is a response to certain forms of age-associated dysfunction, such as the frontal-striatal or medial temporal changes discussed earlier in this review. Such specificity seems unlikely. The presence of increased recruitment in many different populations suggests that it is a response that generalizes across specific age-associated brain changes and even beyond older adult populations (e.g., see Casey et al., 2000). In discussions of cognitive reserve, a distinction is sometimes made between a compensatory response to known origins of brain damage, such as observed in stroke or Alzheimer's disease, and responses that occur in typical aging (Stern, 2002). Increased recruitment, if it does indeed reflect a general, productive form of response, blurs this distinction; it may represent a *general* response to increasing task difficulty conveyed by any number of global factors that affect aging. Increased recruitment may operate to maintain a high level of performance in older adults in the presence of detrimental physiological changes. As task demands are increased or the pathological burden becomes severe (e.g., in Alzheimer's disease), cognitive differences may nonetheless emerge despite compensatory processes.

Conclusions

Memory decline in aging arises from multiple, distinct age-associated processes. While the constellation of factors that influence memory in advanced aging eludes a simple, parsimonious explanation (e.g., see Light, 1991; West, 1996; Bäckman et al., 2000a; Greenwood, 2000; Raz, 2000; Park et al., 2001; Della-Maggiore et al., 2002; Hedden and Gabrieli, 2004), there is a recurring distinction between cognitive decline associated with executive and attention difficulties and that associated with long-term, declarative memory. Paralleling these cognitive factors, functional disruption is observed in frontal-striatal systems as well as medial temporal and associated cortical networks that are important to memory. Candidate causes are vascular change linked to hypertension, neurotransmitter depletion, and pathology arising from Alzheimer's disease. These causes, while all strongly associated with age, may progress at different rates across individuals and combine their influence to affect memory. An important further factor in cognitive aging is how an individual responds to change. Growing evidence suggests that compensation for brain decline in aging may partly account for why some older adults age gracefully and others decline rapidly.

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