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## *Neuroimaging of Healthy Cognitive Aging*

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Cognitive aging research and theory has, until recently, been based upon behavioral measures of cognitive performance such as response time and accuracy. Results from behavioral methodologies have indicated a general age-related decline in cognitive functions such as speed of processing, attention, perception, working memory, and cued and free recall—and age invariance when assessing cognitive processes associated with vocabulary and semantic memory. Recently, advances in the area of neuroimaging have allowed for the examination of the relationship between cognitive and neural differences in the aging brain. Given that cognitive processes depend on brain anatomy and physiology, it is natural to expect that previously observed behavioral differences in aging are intimately linked to age-related changes in the integrity of cerebral architecture and function.

By using *in vivo* neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI), researchers can tap into the neural substrates of cognitive aging linking behavior and function. As this technology has improved over the last two decades, significant advances have been made in the field of functional neuroimaging of cognitive aging. Research has shown us that, despite a common notion that everything declines in aging, neural activity associated with cognitive aging is characterized by both age-related *increases* as well as age-related *decreases* in brain activity. Failure on the part of older adults to activate brain regions typically recruited by younger adults during cognitive tasks is usually characterized as neurocognitive decline. However,

additional neural recruitment by older adults during task performance, beyond that seen in younger adults, is typically characterized as functional compensation. Examination of both types of neural activity is necessary for developing a better understanding of the plasticity of both the aging brain and cognitive aging in general.

There are two basic neuroimaging approaches to link the effects of aging on the brain and on behavior. The first is to correlate a *resting neuroimaging* measure, such as an MRI measure of brain volume or a PET measure of resting blood flow, to a behavioral measure obtained outside the scanner, such as performance in a memory test. The second is to use a *task-related neuroimaging* technique, such as functional MRI (fMRI), to measure activity in the scanner while participants are performing a cognitive task. Both approaches have strengths and weaknesses and complement each other. In the first major section of this chapter, we provide a brief overview of resting neuroimaging studies of aging, and in the second major section, which is the core of the chapter, we review functional neuroimaging studies of aging in various cognitive domains. The chapter ends with a section linking consistent neuroimaging findings to major theories of cognitive aging.

## RESTING NEUROIMAGING STUDIES OF AGING

Resting neuroimaging measures include measures of brain volume, white matter integrity, resting blood flow and metabolism, and neurotransmitter function. These different measures are considered in separate sections below.

### Measures of Brain Volume

Understanding age-related atrophy is essential to the understanding of functional differences between age groups. However, as it is not the main focus of this chapter, only a very brief overview of volumetric MRI studies of healthy aging is presented here (for a more complete review of age-related structural decline see Raz, 2005). While earlier studies of structural differences in aging have used a cross-sectional approach, more recent studies have used a longitudinal design. Despite this inherent bias towards healthier and more stable samples, longitudinal estimates of decline usually exceed those of cross-sectional studies. One explanation is that in cross-sectional analyses, intrapersonal change is masked to some degree by the noise associated with age-independent individual differences, whereas longitudinal studies are able to exclude both individual differences and cohort effects (Raz et al., 2005). The current section will

focus on these more recent assessments of gray matter change across time.

Changes in whole brain volume as a function of aging have been examined in over 14 studies to date (Raz, 2005). In general, these changes are not linear, but become steeper in old age. For example, the cerebral cortex as a whole declines at a rate 0.12% per year in younger adults but at a rate of 0.35% per year in adults over 52 years of age. Similarly, ventricles expand at a rate of 0.43% in younger adults but at a rate of 4.25% after the age of 70.

From a cognitive neuroscience perspective, the most interesting finding is that age-related atrophy differs across regions. With an average decline rate of between 0.9% and 1.5% per year, the frontal lobes show the steepest rate of atrophy (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Moreover, frontal atrophy has been shown to correspond with cognitive deficits mediated by frontal regions. For example, Gunning-Dixon and Raz (2003) found that in a large group of older adults perseveration errors on the Wisconsin Card Sorting Task, a measure of executive functioning, negatively correlated with prefrontal volume.

The parietal lobes show the second steepest decline function (Pfefferbaum et al., 1998; Raz, 2005; Resnick et al., 2003), with an annual rate between 0.34 and 0.90%. Compared to frontal and parietal lobes, the occipital lobe shows small or nonsignificant age-related atrophy. Additionally, atrophy rates differ also among subregions of each lobe. For example, there is evidence that within frontal and parietal cortex, more inferior subregions show the steepest rates of decline (Resnick et al., 2003).

Due to their role in memory function, the medial temporal lobes (MTL) have elicited more focal examinations over the years. Like other brain regions, longitudinal estimates of temporal lobe shrinkage exceed those of cross-sectional data (Scahill, Frost, Jenkins, Whitwell, Rossor, & Fox, 2003). Additionally, subregions of the temporal lobes (e.g., entorhinal cortex, hippocampus, parahippocampal gyrus) exhibit differential rates of decline. For example, a recent longitudinal study found that in healthy older adults, the hippocampus showed substantial atrophy whereas the entorhinal cortex did not (Raz et al., 2005). Furthermore, studies have shown that the rate of hippocampal atrophy increases with age (Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Scahill et al., 2003). In one study, for example, this rate was an average of 0.86% per year in the whole sample (26–82 years) but 1.18% when considering only individuals over 50 years of age (Raz et al., 2004). A review of 12 studies estimated that after the age of 70 this rate may be as high as 1.85% per year (see Raz, 2005). These findings are very interesting because the entorhinal cortex is one of the regions first affected by Alzheimer's Disease (AD; Braak, Braak, & Bohl, 1993). As discussed later, together with recent fMRI evidence of

dissociations between hippocampal and rhinal functions in aging (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006), these findings have implications for the early diagnosis of AD. (See Fig. 1.1.)

Correlating structure with function, Rodrigue and Raz (2004) acquired both volumetric measures of the prefrontal cortex (PFC), hippocampus, and entorhinal cortex and measures of episodic memory across a 5-year interval in a large group spanning 26–83 years of age. While the volume of hippocampus and PFC correlated with age at baseline and follow-up, once the effects of age were controlled for, neither predicted memory performance. However, increased shrinkage of entorhinal cortex was associated with poorer memory performance at follow-up. Results support previous work showing a correlation between entorhinal cortex shrinkage and memory performance in the very old (Du et al., 2003). Additionally, Persson and colleagues (2006) found reduced hippocampal

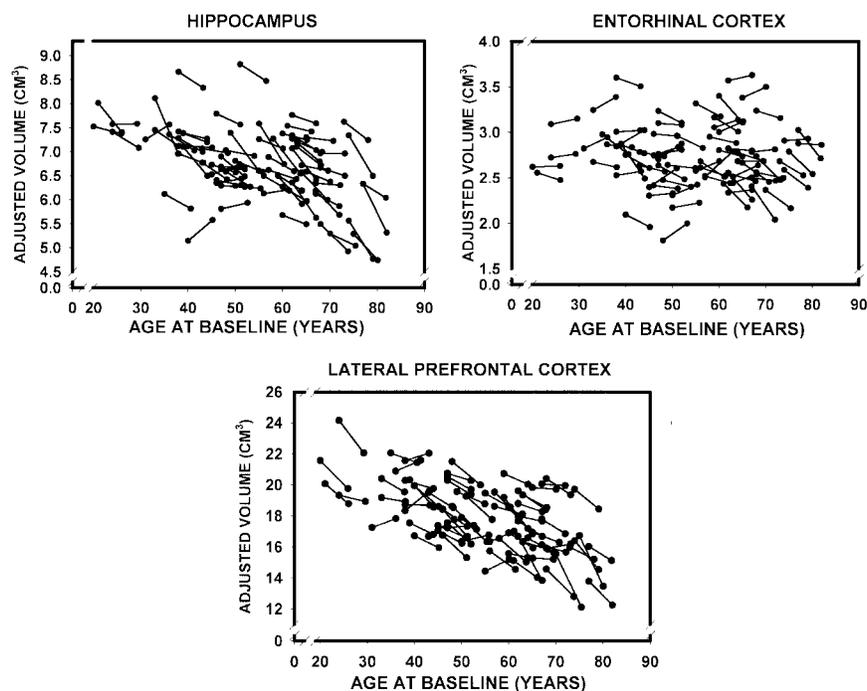


FIG. 1.1. Longitudinal changes in adjusted volumes of the hippocampus, entorhinal cortex, and lateral prefrontal cortex as a function of baseline age. Reproduced by permission of Oxford University Press from Raz et al. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, 15(11), 1676–1689.

volume in a group of older adults whose episodic memory performance declined across a decade compared to that of a group whose memory performance remained stable.

Subcortical atrophy in healthy aging is also prevalent, with longitudinal studies showing age-related striatal decline beginning in early adulthood. Four studies assessing decline in younger adults (average age = 29 yrs) showed caudate shrinkage that exceeds 1% per year (Chakos et al., 1994; Lang et al., 2001; Lieberman et al., 2001; Tauscher-Wisniewski, Tauscher, Logan, Christensen, Mikulis, & Zipursky, 2002) (but see DeLisi, Sakuma, Tew, Kushner, Hoff, & Grimson, 1997). Only one study to date has assessed striatal shrinkage in a group that included older adults. Following 53 adults (ranging in age from 26–82 at time 2) over five years, researchers see a more modest 0.83% decline in caudate volume per year (Raz et al., 2003). However, caudate decline is not representative of decline in other striatal nuclei. When assessed separately, the caudate exhibits a steeper rate of decline compared to the putamen, which shows less decline than the globus pallidus (Lang et al., 2001; Raz, Rodrigue, Kennedy, Head, Gunning-Dixon, & Acker, 2003). When correlating motor speed and striatal atrophy in a large sample of older adults (129 older adults ranging in age from 64 and 74 years), Soderlund, Nyberg, and Nilsson (2004) concluded that atrophy in the caudate nucleus predicted poorer performance in women, but not men.

Several metencephalic structures (e.g., cerebellum, vermis, pons) also show decline with age (Raz, 2005). While most longitudinal studies in this area have been conducted within a small age range (e.g., either younger or older adults), they generally show significant age-related shrinkage across all metencephalic structures. On average the cerebellum shows the greatest shrinkage, followed by the vermis, with the pons showing the smallest decline.

Finally, age-related decline has also been seen within the corpus callosum. Though cross-sectional studies show only modest shrinkage in the corpus callosum (Driesen & Raz, 1995), longitudinal studies show more significant age-related reductions (e.g., Sullivan, Pfefferbaum, Adalsteinsson, Swan, & Carmelli, 2002; Teipel et al., 2002), around 0.90% per annum. Furthermore, thinning of the corpus callosum over a 4-year period has been shown to correlate with performance on the Stroop task (Sullivan, Pfefferbaum et al., 2002) in older adults. A later study by Sullivan, Adalsteinsson, and Pfefferbaum (2006) found that fronto-callosal fibers showed a steeper rate of age-related decline than posterior fibers. Results support the view that age-related callosal degradation contributes to functional decline and that anterior regions are more vulnerable than other regions.

Interestingly, gender differences in volumetric decline across time

appear nonexistent (Raz et al., 2005; Resnick et al., 2003), except perhaps in the caudate (Raz et al., 2005) which may show greater decline in women compared to men. There is also some evidence that volume loss is attenuated (though not absent) in the healthiest of individuals (Resnick et al., 2003). Overall, results support differential aging of individual cortical and subcortical regions.

### Measures of White Matter Integrity

Postmortem studies suggest that age-related white matter loss occurs throughout the brain, and in particular in the frontal lobes, with white matter loss more extensive than gray matter loss (Double et al., 1996; Esiri, 1994; Kemper, 1994). In contrast, *in vivo* studies find no significant loss in healthy aging (Raz, 1996; Raz et al., 1997; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995), albeit some evidence suggests loss restricted to frontal regions (Raz et al., 1997; Salat, Kaye, & Janowsky, 1999). Several studies examining white matter differences across the entire lifespan (Courchesne et al., 2000; Pfefferbaum, Mathalon, Sullivan, Rawles, Zipursky, & Lim, 1994; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004) show decline beginning only in the seventh decade (but see Liu & Cooper, 2003).

Beyond overall volume measurements, it is also possible to measure white matter integrity. One method is to assess the number of white matter hyperintensities (WMHs) in the aging brain. While the exact cause of WMHs is unknown, they are posited to arise both from neural and vascular pathologies (for a review see Pantoni & Garcia, 1997). A review of 49 studies of healthy aging found the mean correlation between age and severity of WMHs to be .37 (Gunning-Dixon & Raz, 2000). Other risk factors for WMHs include hypertension (Gunning-Dixon & Raz, 2000), elevated systolic blood pressure (DeCarli et al., 1995), and apolipoprotein E-4 (e.g., Kuller et al., 1998; but see Schmidt et al., 1996).

In addition to correlating prefrontal volume with executive functioning, Gunning-Dixon and Raz (2003) also found that WMHs in the prefrontal cortex are independently associated with perseveration errors on the Wisconsin Card Sorting Task. Additionally, in an extensive study including 1254 participants ranging in age from 64 to 76 years, Soderlund, Nyberg, Adolfsson, Nilsson, and Launer (2003) found that periventricular WMHs and subcortical atrophy predicted lower performance on both motor speed and the Stroop task. Results remained stable after controlling for demographic factors (e.g., age, gender, education).

An advent of recent years, diffusion tensor imaging (DTI) has been employed to identify the structural integrity of white matter tracts in the brain. DTI measures assess changes in the MR signal due to the

movement of water molecules. In healthy myelinated fiber tracts, water molecules travel along the internal membrane, not across the fiber walls. With degradation of myelin sheath in normal aging, the probability and speed of diffusion along the fiber walls diminishes. Two measures, fractional anisotropy (FA) and apparent diffusion coefficient (ADC), quantify these changes and in turn, white matter integrity. Reduced FA and increased ADC are indicative of degraded micro-structural tissue integrity.

Several studies have investigated age-related differences in FA and ADC in numerous brain regions (Abe et al., 2002; Madden, Whiting, Huettel, White, MacFall, & Provenzale, 2004; Madden et al., 2007; Pfefferbaum, Sullivan, Hedehus, Lim, Adalsteinsson, & Moseley, 2000; Salat et al., 2005; Sullivan et al., 2001). Significant age-related decline in white matter integrity was found in the centrum semiovale (white matter in the medial 55% of the left and right hemispheres), frontal white matter tracts, the posterior limb of the internal capsule, and the genu of the corpus callosum. Furthermore, evidence suggests that age-related decline in anisotropy and diffusivity is more pronounced in anterior, as opposed to posterior regions. Correspondingly, two studies focusing specifically on alternations of prefrontal white matter (Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat et al., 2005) showed that prefrontal FA was reduced in older adults compared to younger adults. Furthermore, Salat et al. (2005) found that prefrontal FA values were significantly correlated with prefrontal volume measures in individuals over the age of 40. Within prefrontal regions, ventromedial and deep prefrontal regions showed a greater reduction compared to other regions. Similar to this finding, Pfefferbaum et al. (2005) also found significant age-related FA decline in restricted frontal regions, whereas posterior and inferior white matter was largely preserved. The authors suggest that this pattern of frontal dysfunction may account for age-related behavioral deficits in frontally based processes. Additionally, Head et al. (2004) found age differences in FA and ADC in anterior and posterior corpus callosum and all four cortical lobes. Age-related differences were greater in anterior compared to posterior callosal white matter as well as frontal vs. temporal, parietal, and occipital white matter. Results suggest an anterior–posterior gradient for decline in the structural integrity of white matter. (See Fig. 1.2.)

Like cortical atrophy, declines in white matter volume and integrity also exhibit correlations with cognitive performance in older adults. Following the aforementioned anterior–posterior gradient, these correlations are often more prevalent in anterior regions. Accordingly, declines in frontal white matter (e.g., FA values) have been associated with measures of processing speed (Symbol Digit Modalities Test) and reasoning (Raven's Progressive Matrices Test; Stebbins et al., 2001) and memory

performance (Persson et al., 2006). Taken together, results indicate that degradation of both white and gray matter within the frontal lobes contributes to decline in cognitive processes mediated by this region.

However, studies have found relationships between white matter integrity and performance in other brain regions as well. For example, Madden et al. (2004) found that FA in the splenium (most posterior portion of the corpus callosum) was a significant predictor of reaction time (RT) for younger adults, whereas FA in the anterior limb of the internal capsule predicted RT in older adults. Results not only suggest that slower responding is correlated with decline in FA values, but that performance in older adults is more dependent on the integrity of the fronto-striatal circuitry than on the frontal circuitry alone. Persson et al. (2006) found that word reading correlated with ADC and FA values in premotor/precentral callosal bundles, with FA and fiber length in postcentral bundles, and with number of fibers in posterior parietal and superior temporal bundles. The authors suggest that age-related degradation in the corpus callosum may impede bilateral recruitment—recruitment necessary for enhanced performance in older adults (Cabeza, 2002).

### Measures of Resting Blood Flow and Metabolism

In addition to age-related differences in both gray and white matter, research has examined differences in cerebral blood flow (CBF) and metabolic activity in aging. As suggested by the aforementioned volume data, age-related differences are observed in resting functional imaging as well. Early research using nontomographic methods (Kety, 1956) first indicated CBF and metabolic activity decline with age. Furthermore, this decrease paralleled decreases in cortical density. Kety suggested that age-related decreases in metabolic activity were indicative of neuronal loss.

More recent evidence from imaging methodologies suggests mixed results in regards to CBF and metabolic activity in healthy aging (for a review see Madden & Hoffman, 1997). However, when present, age differences indicated decline in both measures as a function of age. For example, assessing regional cerebral metabolic rate for glucose (rCMR-glc), several studies indicated no change across age (e.g., de Leon et al., 1983; Duara et al., 1983; Haxby et al., 1986), whereas others noted an age-related decline in rCMR-glc in frontal (e.g., Azari et al., 1992; Horwitz, Duara, & Rapoport, 1986; e.g., Kuhl, Metter, Riege, & Phelps, 1982; Riege, Metter, Kuhl, & Phelps, 1985) and parietal regions (e.g., Azari et al., 1992; Horwitz et al., 1986; e.g., Kuhl et al., 1982). When compared directly, greater decline was observed in frontal regions (de Leon et al., 1987; Kuhl et al., 1982). More recently, studies have shown that glucose regulation may have a significant impact on cognition in older adults (e.g., Kaplan,

Greenwood, Winocur, & Wolever, 2000; Messier & Gagnon, 2000). For example, Kaplan et al. (2000) found that glucose regulation was associated with both verbal declarative memory and visuomotor performance in healthy older adults.

Regional cerebral metabolic rate for oxygen (rCMRO<sub>2</sub>) also shows mixed results, with some studies finding no difference across age (e.g., Herscovitch, Auchus, Gado, Chi, & Raichle, 1986; Itoh et al., 1990) and others showing age-related decreases in multiple regions (e.g., Leenders et al., 1990; Pantano, Baron, Lebrun-Grandie, Duquesnoy, Bousser, & Comar, 1984; e.g., Yamaguchi et al., 1986). Like rCMRglc, rCMRO<sub>2</sub> decline was often observed in frontal and parietal regions (e.g., Pantano et al., 1984). Furthermore, most decreases in rCMRO<sub>2</sub> showed linear declines with age.

Finally, regional CBF (rCBF) also showed both stability (e.g., Herscovitch et al., 1986; Itoh et al., 1990; Yamaguchi et al., 1986) and decline (e.g., Frackowiak, Lenzi, Jones, & Heather, 1980; Leenders et al., 1990; Marchal et al., 1992) across early aging studies. This controversy has remained in more recent assessments. For example, Larsson et al. (2001) found an age-related decrease in rCBF across 28 gray and white matter regions when assessing middle-aged (40 yrs), young-old (75 yrs), and old-old (88 yrs), with the annual reduction in rCBF increasing from .10% from middle-aged to young-old to .13% from young-old to the old-old adults. However, a study by Meltzer and colleagues (2000) suggests that apparent age-related reductions in rCBF can be removed by correcting for partial-volume effects (see also Inoue et al., 2005). Thus, the authors suggest that age-related cerebral atrophy may confound interpretation of metabolic measurements in previous studies, and thus must be first corrected for when interpreting difference in rCBF among groups.

More recent PET and fMRI studies have also found age-related differences in the blood oxygen level dependent (BOLD) signal and hemodynamic response (HDR) amplitude. Assessing HDR in visual cortex during photic stimulation, Ross and colleagues (1997) observed a decrease in HDR amplitude, but not in the volume of cortical activation. Other studies have found mixed results in regards to age-related differences in HDR. For example, Brodtmann, Puce, Syngienotis, Darby, & Donnan (2003) did not observe age-related differences in the HDR until the ninth decade, suggesting that these age-related differences in HDR may be restricted to only the oldest-old. Buckner, Snyder, Sanders, Raichle, & Morris (2000) found age-related reductions in the amplitude of the HDR in visual cortex, but not in other brain regions (e.g., motor cortex). The authors concluded that the summation of the HDR overall was highly similar between age groups. Two other studies (D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Huettel, Singerman, & McCarthy, 2001) also observed age

equivalent HDR, but reductions in the number of activated voxels. The authors suggest reductions in activated voxels in older adults may be due to increased physiological noise in older adults. Despite the absolute differences in some resting measures mentioned above, recent work suggests that relative activation changes should be preserved with age and that functional neuroimaging designs that employ group comparisons between task conditions or parametric manipulations are valid and can be an effective means of assessing age-related differences in functional and anatomical measures (Buckner et al., 2000; Huettel et al., 2001).

### **Measures of Neurotransmitter Function: The Case of Dopamine**

Much of the research assessing neurotransmitter differences in aging has focused on the role of dopamine (DA). There are two main families of DA receptors,  $D_1$  and  $D_2$ . In the presynaptic terminal, the DA transporter protein regulates the synaptic DA concentration. Dopamine systems are critical for higher order cognitive functions. For example, patients with DA deficits (Huntington's and Parkinson's disease) often show cognitive deficits—which can be modulated by dopamine agonists and antagonists. The role of DA in cognition is also supported by computational models, and by ontogenetic and phylogenetic evidence.

Like the aforementioned structural decline, *in vivo* measurements of DA decline exceed those of *in vitro* studies. *In vivo* studies (Antonini & Leenders, 1993; Ichise et al., 1998; Suhara et al., 1991; Wang et al., 1998) using PET and single photon emission computerized tomography (SPECT) have found loss of striatal  $D_1$  and  $D_2$  receptor binding across adulthood, with age-related decreases ranging between 7–10% per decade. Additionally, age-related decreases in striatal DA transporter protein binding has been measured *in vivo* at a rate of 4.4 to 8% per decade (Rinne, Sahlberg, Ruottinen, Nagren, & Lehtikoinen, 1998; van Dyck et al., 1995).

The relationship between age-related changes in DA and age-related cognitive differences has been examined in only a small number of studies. Despite the paucity of data, findings are remarkably consistent. Age deficits in striatal DA have been associated with reduction in episodic memory (Bäckman et al., 2000; Erixon-Lindroth, Farde, Wahlin, Sovago, Halldin, & Bäckman, 2005), executive function (Erixon-Lindroth et al., 2005; Mozley, Gur, Mozley, & Gur, 2001; Volkow et al., 1998), and motor performance (Mozley et al., 2001; Wang et al., 1998). Furthermore, several studies have also found that striatal DA markers served as a significant predictor of cognitive performance, after controlling for the effects of age (Bäckman et al., 2000; Volkow et al., 1998), and also, that age-related cognitive deficits were completely mediated by reductions in striatal DA functioning (Erixon-Lindroth et al., 2005).

DA loss in aging has also been observed in frontal, temporal, and occipital cortices as well as in hippocampus and thalamus (Inoue et al., 2001; Kaasinen et al., 2000). The magnitude of extrastriatal DA decline mirrors that observed within the striatum itself. Given the cognitive role of fronto-striatal loops, age-related striatal DA deficits could also account for age-related cognitive deficits associated with PFC dysfunction. Moreover, age-related deficits in DA binding have been observed in PFC, as well as in posterior cortical and hippocampal regions.

Evidence is mixed as to whether these declines are linear (see Reeves, Bench, & Howard, 2002) or exponential (Antonini & Leenders, 1993; Bannon & Whitty, 1997; Rinne et al., 1998) across adulthood. The correlation between declines in DA receptor binding and DA transporter protein binding may reflect a common causal mechanism for age-related DA loss (e.g., DiGirolamo et al., 2001).

### Summary

Taken together, resting neuroimaging measures suggest significant age-related differences. Both white and gray matter decline show similar patterns in aging, with structural decline appearing most prominent in advanced aging and anterior regions showing greater decline compared to posterior regions. Age-related decline in both pre- and post-synaptic DA markers also tends to follow this anterior-posterior gradient of decline. Both patterns coincide with behavioral data findings that show greater age-related performance decrements in cognitive functions mediated by frontal functioning (see West, 1996) and greater cognitive decline in advanced aging (for a review see Park, 2002). Furthermore, resting blood flow and metabolism measures (i.e., in rCMR<sub>glc</sub>, rCMRO<sub>2</sub> and CBF) also show age-related decline in healthy adults. However, caution should be used when interpreting these findings, for they also may reflect changes caused by age differences in cerebral atrophy.

In addition to resting neuroimaging measures, several studies have also examined cognitive performance—finding significant correlations between structure and function. Thus, results underscore the need to not only consider age-related differences within a given measure, but also to assess its relationship with behavioral measures of cognition. One of the strongest approaches to understanding the neural mechanisms for age-related cognitive decline will be to consider the interaction of several methodologies in assessing age-related cognitive deficits.

### TASK-RELATED ACTIVATIONS IN NEUROIMAGING STUDIES OF AGING

Before reviewing the findings of studies in each cognitive domain, it is useful to describe first two patterns of age-related differences in brain activity that are consistently found in several domains. First, several studies, particularly in the visual perception domain, have found an age-related decrease in occipital activity coupled with an age-related increase in PFC activity. This pattern, which we call *posterior-anterior shift in aging* (PASA), can be easily identified in Table 1.1 (black circles in occipital lobe, white circles in frontal lobe). Grady et al. (1994) were the first to noticed this pattern, and they suggested that older adults compensated for visual processing deficits (occipital decrease) by recruiting higher order cognitive processes (PFC increase). In this study older and younger adults were matched in accuracy but differed in RTs, so the authors further suggested that additional recruitment of PFC functions allows older adults to maintain a good accuracy level at the expense of slower reaction times. Most subsequent studies that found PASA endorsed Grady et al.'s compensatory account of age-related PFC increases.

Second, in many studies across several different cognitive domains (perception, attention, working memory, episodic memory encoding, episodic memory retrieval, inhibitory control, etc.) older adults showed a more bilateral (less asymmetric) pattern of PFC activity than younger

TABLE 1.1  
PASA (Posterior–Anterior Shift in Aging)

			<i>Occipital</i>	<i>Frontal</i>
BP	Perception	Grady 94	–	+
BP	Perception	Grady 94	+/-	+
BP	Perception	Grady 00	–	+/-
BP	Perception	Levine 00	+/-	+
BF	Perception	GunningDixon 03	–	+
EF	Perception	lidaka 02	–	+/-
BP	Attention	Madden 97	–	+
EF	Attention	Cabeza 04	–	+
EF	Working Memory	Cabeza 04	–	+
BP	Problem Solving	Nagahama 97	–	+/-
EF	Encoding	Meulenbroek 04	–	+/-
EF	Encoding	Gutchess 05	–	+
EF	Retrieval	Cabeza 04	+/-	+
BP	Retrieval	Grady 02	–	+
BP	Retrieval	Anders 00	+/-	+/-
BP	Retrieval	Cabeza 00	–	+/-

TABLE 1.2  
HAROLD

			<i>Younger</i>		<i>Older</i>	
			<i>L</i>	<i>R</i>	<i>L</i>	<i>R</i>
BF	Encoding	Stebbins 02	++	+	+	+
BF	Encoding-inc	Logan 02	++	+	++	++
BF	Encoding-inc	Rosen 02	++	+	+	+
EF	Encoding-inc/Dm	Morcom 03	+	-	++	++
BF	Encoding-int	Logan 02	+	+	+	+
BP	Encoding-int	Cabeza 97	++	-	+	+
EF	Inhibitory Control	Nielson 02	-	+	+	+
EF	Language	Perrson 04	+	-	+	+
BP	Perception	Grady 94 exp 2	-	+	++	++
BP	Perception	Grady 00a	+	+++	++	++
BP	Retrieval	Cabeza 97	-	++	+	+
BP	Retrieval	Bäckman 97	-	+	+	+
BP	Retrieval	Madden 99	-	+	++	++
BP	Retrieval	Grady 00b	-	++	+	+
BP	Retrieval	Cabeza 02	-	+	+	+
EF	Retrieval	Maguire 03*	-	+	+	+
BP	Working Memory (letter)	Reuter-Lorenz 00	+	-	+	+
BP	Working Memory (location)	Reuter-Lorenz 00	-	+	+	+
BP	Working Memory	Dixit 00	+	+++	++	++
EF	Working Memory	Cabeza 04b	+	+	+	+
BP	Working Memory	Grady 98	+	++	+	+

adults. This pattern was conceptualized as a *Hemispheric Asymmetry Reduction in OLDER Adults* (HAROLD) model (Cabeza, 2002; see Table 1.2). The HAROLD pattern was originally described by Cabeza et al. (1997) and attributed to a compensatory mechanism. This *compensation account* is consistent with evidence that bilateral activity in older adults is positively correlated with successful cognitive performance (Reuter-Lorenz et al., 2000), and is found in high-performing rather than in low-performing older adults (Cabeza, 2002; Rosen et al., 2002). However, an alternative account is that a more widespread activation pattern reflects an age-related difficulty in engaging specialized neural mechanisms (e.g., Li & Lindenberger, 1999; Logan, Sanders, Snyder, Morris, & Buckner, 2002). This *dedifferentiation account* is consistent with an age-related increase in correlations across tasks (Lindenberger & Baltes, 1994). In general, the available evidence tends to be more consistent with the compensation than with the dedifferentiation account (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2005) but further research is certainly required.

### Visual Perception

Visual perception studies often find age-related reductions in activations in visual cortex regions, as well as in more anterior regions of the ventral pathway, such as the parahippocampal gyrus (Iidaka et al., 2002; Levine et al., 2000) and also the amygdala (Fischer et al., 2005; Gunning-Dixon et al., 2003; Iidaka et al., 2002). MTL decreases may reflect an extension of occipital decreases or specific deficits in memory or emotion-related processes. Additionally, other studies showed age-related increases in more anterior brain regions such as PFC (Grady et al., 1994; Grady, McIntosh, Horwitz, & Rapoport, 2000), anterior cingulate (Gunning-Dixon et al., 2003), and insula (Fischer, Sandblom, Gavazzeni, Fransson, Wright, & Bäckman, 2005) (see Table 1.3). Researchers suggest that that the frontal increases compensate for the occipital decrease. As noted earlier, a compensation hypothesis is common in explaining age-related shifts in neural activation. However, like other compensation theories, the specific cognitive operations recruited by older adults have yet to be identified.

### Attention

In general, attention studies also show age-related compensation in the form of the PASA pattern (Cabeza, Daselaar, Dolcos, Prince, Budde, & Nyberg, 2004; Madden & Hoffman, 1997) as well as other forms of compensation such as activation of deep gray matter regions (Madden et al., 2004; see Table 1.3). For example, when cueing selective attention, both spatial (Madden & Hoffman, 1997) and color (Madden et al., 2002) visual cues elicited weaker occipital activity in older adults, but stronger PFC activation. Similar results have been found for sustained attention (Cabeza et al., 2004). In this study, the PASA pattern was simultaneously found for visual attention, verbal working memory, and verbal episodic retrieval (see below), supporting the generality of this phenomenon.

However, not all attention studies show anterior increases. As noted, age-related increases in deep gray matter regions (striatum, thalamus, insula) were seen for an odd-ball task where activation in frontal regions showed no age-related differences (Madden, Whiting, Provenzale, & Huettel, 2004). In the single study to date focusing on the effects of aging on auditory attention using a dichotic listening task (Thomsen, Specht, Hammar, Nyttines, Erslund, & Hugdahl, 2004), older adults showed a reduction in left dorsal PFC (BA 8/9) activation. Cortical thickness in this region was also reduced in older adults, suggesting both functional and structural changes underlie age-related attentional deficits.

TABLE 1.3  
PET/fMRI Studies of Visual Perception/attention

			<i>Left Hemisphere</i>							<i>Right Hemisphere</i>						
			<i>Occipital</i>			<i>Left PFC</i>				<i>Right PFC</i>				<i>Occipital</i>		
			17	18	19	P	VL	DL	A	A	DL	VL	P	19	18	17
<b>Visual Perception</b>																
BP	Grady 94	face: matching – bl				○	○					○	○			●
BP	Grady 94	location: match – bl		●	○						○	○				●
BP	Grady 00	face-ndgr. match – bl		●		○	○	○	○	●		●				
BP	Levine 00	form perception – bl		○	●	○		○						●		
BF	GunningDixon 03	face expression: discrim. – bl	●	●	●	○		○				○		●	●	●
EF	Iidaka 02	face expression: perception – bl		●		●				○		●				●
EF	Fischer 05	face expression: angry v. neutral										○				
<b>Attention</b>																
BP	Madden 97	visual srch: divided – central		●					○				○			●
BP	Madden 02	visual srch: covariate w/ perform			●					●				●		●
EF	Cabeza 04	visual sustained attention – bl		●	●	○	○		○	○		○	○		●	
EF	Thomsen 04	dichot. listening: attend-left		●	○	●	●			●		●				

● only young/young > old; ○ only old/old>young; BP = blocked PET, BF = blocked fMRI; EF = event-related fMRI; bl = baseline; srch =search; dichot = dichotic; P = posterior, VL = ventroalteral, DL = dorsolateral, A = anterior.

### **Language/Semantic Processing**

To date, the majority of studies in this domain have investigated simple linguistic and semantic processes using words as stimuli. Two studies by Madden and collaborators investigating lexical decisions (word/nonword) found age-related reductions in ventral pathway activity (Madden et al., 1996, 2002). Unlike studies of perception and attention, these studies did not show compensatory increases in frontal regions. Johnson and Jusczyk (2001) also showed that simple auditory semantic and phonological decisions may not require compensatory PFC activity. Additionally, the work of Persson, Sylvester, Nelson, Welsh, Jonides, and Reuter-Lorenz (2004) and Grossman and colleagues (2002a, 2002b) suggest that age-related differences are minimal when the demands for mediating age-sensitive cognitive functions are low. For example, during a study of sentence comprehension across different working memory loads, both younger and older adults recruited a similar set of regions, independent of working memory demands, including the left temporal and ventrolateral PFC regions, and bilateral occipital cortex—and common activation in left ventrolateral PFC was associated with increased working memory load. However, overall, older adults showed weaker task-related activity in parietal cortex but greater activity in dorsal left PFC, right temporal, and bilateral anteromedial PFC regions. According to the authors, the latter age-related increases reflect up-regulation of portions of rehearsal (Broca's area) and material-specific (right temporoparietal cortex) aspects of a large-scale working memory network supporting complex sentence comprehension. The preservation of cortical regions mediating core language functions appears robust enough to posit that healthy aging is not associated with cortical reorganization or compensation related to language abilities. Rather, it is the increased demands of working memory and visual perceptual skills in aging that account for observed age-related differences.

### **Working Memory**

Working memory (WM) involves a composite of cognitive operations, including maintenance of information over a brief delay, manipulation and monitoring of information, and executive processes involved in problem solving and reasoning tasks. We will review each of these components separately.

*Maintenance and Manipulation*

Overall, maintenance and manipulation of information in WM results in age-related reductions in activity in PFC regions engaged by younger adults but greater activity in other PFC regions, such as contralateral PFC regions (i.e., the PFC hemisphere less engaged by younger adults). Typically referred to as HAROLD, these age-related increases in frontal bilaterality have been seen in both verbal (e.g., Cabeza et al., 2004; Reuter-Lorenz et al., 2000) and visuospatial WM tasks (Park et al., 2003; Reuter-Lorenz et al., 2000). See Table 1.4 for an overview of WM studies. For example, Reuter-Lorenz et al. (2000) examined simple maintenance operations in aging using both verbal and spatial stimuli. Whereas the verbal task resulted in reduced left and increased right PFC activity, the spatial task showed reduced right and increased left PFC activity in older adults. Thus, in both instances, older adults showed a more bilateral pattern of PFC activity consistent with the HAROLD model. Often, such contralateral recruitment in older adults is interpreted as compensatory, frequently cited as reflecting a response to increased task demands (Grady, McIntosh, Bookstein, Horwitz, Rapoport, & Haxby, 1998) or retrieval effort (Park et al., 2003), as well as decreased activation in other brain regions such as PFC and MTL (e.g., Cabeza et al., 2004; Haut, Kuwabara, Leach, & Callahan, 2000; Park et al., 2003; Rypma, Prabhakaran, Desmond, & Gabrieli, 2001).

Age-related reductions in MTL regions have been observed in three nonverbal WM studies (Grady et al., 1998; Mitchell, Johnson, Raye, & D'Esposito, 2000; Park et al., 2003) but never in verbal WM studies. For example, in a study by Mitchell et al. (2000) older adults showed equivalent performance to young in a single item WM task, but a marked decrease in performance for the combination (location plus object) condition. This performance deficit was accompanied by decreased activity in the left anterior hippocampus and anteromedial PFC (right BA 10) compared to younger adults. Suggesting that a disruption in hippocampal-PFC circuitry may underlie age-related deficits in the combination condition, the authors concluded that aging not only affects the overall magnitude of brain activity, but also can disrupt activations amongst regions (see also Della-Maggiore, Sekuler, Grady, Bennett, Sekuler, & McIntosh, 2000; McIntosh et al., 1999). Interpreting the lack of MTL decreases in verbal WM studies, it is possible that nonverbal tasks were more dependent on hippocampal-mediated relational memory processing, and hence, more sensitive to age-related deficits in these regions.

TABLE 1.4  
PET/fMRI Studies of Working Memory (WM) and Executive Functioning

			Left Hemisphere				Right Hemisphere			
			Left PFC				Right PFC			
			P	VL	DL	A	A	DL	VL	P
<b>Verbal WM</b>										
BP	Reuter-L. 00	letter: WM – bl (VOIs)					○			○
BF	Rypma 01	letter: WM: 6–1 letter load	●		○	●	●	●	●	●
BF	Rypma 00	letter: WM Enc, main, retr	●							●
EF	Cabeza 04	word: WM – bl	○			○	○		○	○
BP	Haut 00	number: self-ordering > ctrl								●
BP	Haut 00	number: ext.-ordered > ctrl	○							
EF	Johnson 04	word: refresh > repeat/read	●							
EF	Sun 05	fwd & bkwd digit span						○		
<b>Visuospatial WM</b>										
BP	Reuter-L. 00	locat: WM – bl (VOIs)	○			○				
BP	Grady 98	face: WM – bl	○ ●						●	
BP	Grady 98	incr w/long delays							●	●
EF	Mitchel 00	objects.: combo > obj / loc						●		
EF	Park 03	scenes: maint or probe		○		○	○		○	
BF	Lamar 04	DMTS – ctrl				●				●
BF	Lamar 04	DNMTS – ctrl	●			●	●		■	
<b>Executive Functioning</b>										
EF	Nielsen 02	no-go > base	○ ○			○	■			
BF	Milham 02	Stroop: incong > others	● ○			●				○
BF	Langenecker 04	Stroop: incong > neutral	○			○	○		○	○
BP	Nagahama 97	WCST – bl	●	●		●			○	○
BP	Esposito 99	WCST (corr w/ age)	●							○
BP	Esposito 99	RPM (corr w/ age)	○	○				○		

● only young/young > old; ○ only old/old > young; ■ young-old; BP = blocked PET; BF = blocked fMRI; EF = event-related fMRI; bl = baseline; DA = divided attention; Enc = Encoding; Ret = retrieval; fwd = forward; bkwd = backward; obj = object; loc = location; ctr = control; dscr = discrimination; incr = increasing; incong = incongruent; corr = correlation; WCST = Wisconsin Card Sorting Task; P = posterior; VL = ventrolateral; DL = dorsolateral; A = anterior.

### Executive Functions

The effects of aging on brain activity associated with executive functions have been measured with tasks that tap such processes as inhibitory control, task switching, dual-task performance, and reasoning. The most consistent finding across all studies to date has been age-related increases in PFC activation (Jonides, Marshuetz, Smith, Reuter-Lorenz, Koeppel, & Hartley, 2000a; Langenecker, Nielson, & Rao, 2004; Milham et al., 2002;

Nielson, Langenecker, & Garavan, 2002; Smith, Geva, Jonides, Miller, Reuter-Lorenz, & Koeppel, 2001). PFC increases in these executive tasks were more prevalent than those seen in simpler WM tasks, possibly reflecting greater cognitive demands for executive function tasks. This notion conforms to the compensation account suggested in several studies. Fittingly, in several of the studies, age-related PFC increases led to bilateral PFC activations in older adults (HAROLD). Also consistent with this account, PFC regions were differentially engaged by younger adults with limited cognitive resources (Smith et al., 2001). However, in some cases, age-related increases in PFC activity may indicate a failure to inhibit irrelevant information presented earlier (Milham et al., 2002). In regards to parietal activity, the results are mixed, with some studies finding age-related increases in parietal activity (Nielson et al., 2002) and other showing decreases (Esposito, Kirby, Van Horn, Ellmore, & Faith Berman, 1999; Milham et al., 2002; Nagahama et al., 1997).

### **Implicit Memory**

Several neuroimaging studies have investigated effects of aging on implicit memory using such task as word stem completion priming (Bäckman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997; Daselaar, et al., 2005), repetition priming (Lustig & Buckner, 2004), sequence learning (Aizenstein et al., 2005; Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003) and probabilistic categorical (Fera et al., 2005) learning. Overall, results indicate that memory functions in this domain are relatively preserved in older adults. Three studies found age equivalent activations (Bäckman et al., 1997; Daselaar et al., 2003; Lustig & Buckner, 2004) and two others found similar regions activated in young and older adults, but reduced activity within these region, in older adults (Daselaar et al., 2005; Fera et al., 2005). When present, age differences in activation during implicit tasks involve age-related decreases in frontal and striatal regions (Aizenstein et al., 2005; Fera et al., 2005). Whereas priming is known to be mediated by frontal and occipital regions (Buckner et al., 1995), sequence and categorical learning are attributed to activation in fronto-striatal circuitry (Daselaar et al., 2003; Grafton, Hazeltine, & Ivry, 1995). Thus, the aforementioned dissociation in preserved vs. impaired neural functioning may be a result of age differences in the neural circuitry supporting different types of implicit tasks.

### **Episodic Memory Encoding**

Episodic memory is one of the cognitive functions most affected by aging, and accordingly it is the focus of a large number of functional

neuroimaging studies. An important advantage of functional neuroimaging is that, unlike behavioral methods, it provides separate measures of encoding and retrieval processes. This section considers studies that measured brain activity during encoding, and the next section those that measured activity during retrieval.

Encoding studies typically fall into one of three groups: intentional encoding studies, incidental encoding studies (both using blocked designs), and subsequent memory studies. During intentional encoding studies, participants are scanned while attempting to memorize words, faces, objects, or spatial routes, whereas, during incidental encoding, participants are usually asked to make a judgment (i.e., semantic, size) concerning stimuli during encoding, with no overt attempts at memorizing. Finally, in subsequent memory studies, activity associated with successful encoding operations is identified by comparing activity for items that are subsequently remembered to items that are subsequently forgotten (for a review see Paller & Wagner, 2002). The most common results, spanning all three methods are discussed below. See Table 1.5 for an overview of all encoding studies.

The most consistent finding within blocked designs is an age-related reduction in left PFC activity (Anderson, Lidaka, Cabeza, Kapur, McIntosh, & Craik, 2000; Cabeza et al., 1997; Daselaar, et al., 2003b; Grady, Bernstein, Beig, & Siegenthaler, 2002; Grady et al., 1995; Logan et al., 2002; Morcom, Good, Frackowiak, & Rugg, 2003; Nyberg et al., 2003; Rosen et al., 2002; Stebbins et al., 2002). This finding was more prevalent in intentional compared to incidental encoding studies (see Table 1.5), suggesting that the environmental support provided by a deep encoding task may attenuate the age-related decrease in left PFC activity. This difference highlights a strategic component in age-related memory decline. However, recent subsequent memory studies using event-related fMRI show increased age-related activity in dorsolateral and orbito-prefrontal cortex (Dennis, Daselaar, & Cabeza, 2006; Gutchess et al., 2005; Morcom et al., 2003). One explanation for this difference in PFC activity may be accounted for by differences in blocked vs. event-related designs, which measure sustained and transient encoding-related activity, respectively. In support of this theory, Dennis et al. (2006) showed that while younger and older adults recruited a similar set of regions for transient successful encoding, they recruited qualitatively different regions supporting sustained successful encoding.

A second common finding within encoding studies is that of age-related increased activity in right PFC regions, resulting in a more bilateral pattern of PFC activity (i.e., HAROLD) (Anderson, Lidaka, Cabeza, Kapur, McIntosh, & Craik, 2000; Cabeza et al., 1997; Daselaar et al., 2003b; Grady, et al., 2002; Logan et al., 2002; Rosen et al., 2002; Stebbins

TABLE 1.5  
PET/fMRI Studies of Episodic Memory Encoding

			Left Hemisphere						Right Hemisphere					
			MTL		Left PFC				Right PFC			MTL		
			PHG	HC	P	VL	DL	A	A	DL	VL	P	HC	PHG
<b>Intentional encoding</b>														
BP	Grady 95	face: Enc – 2 bl				●						○	●	
BP	Cabeza 97	word pair: Enc – Rn/Rc			●			●						
BP	Anderson 00	word pairs: FA Enc – FA Rc			●	●		●	●	○		○		
BF	Logan 02 exp 1	words: intent enc – bl				●			○					
BP	Madden 99	words: Enc – bl												
BP	Schiavetto 02	obj ident Enc > obj loc Enc		●		●								
BF	Iidaka 01	object pairs: abstract Enc – bl												
BP	Nyberg 03	loci mnemonic: training – pretest						●						
<b>Incidental encoding</b>														
BP	Grady 02	face: Enc – Rn				●								
BF	Stebbins 02	word: deep – shallow			●	●		●						
BF	Logan 02 exp 2	word: deep – shallow							○					
BF	Daselaar 03b	word: deep – shallow		●							●			
BF	Rosen 02	Old-high, word: deep – shallow							○		○			
EF	Daselaar 03c	Old-low, word: rem – bl	●	●										
<b>Subsequent memory</b>														
EF	Morcom 03	word Dm: Y long delay – O short delay						○		○				
EF	Gutchess 05	picture Dm	●					○	○	○				●
EF	Dennis 06	word Dm: Transient activity	●	●	●		○	○	○					
EF	Dennis 06	word Dm: Sustained activity								●		●		

● only young/young > old; ○ only old/old > young; BP = blocked PET; BF = blocked fMRI; EF = event-related fMRI; bl = baseline; DA = divided attention; Enc = Encoding; Ret = retrieval; Shall = shallow; obj = object; P = posterior; VL = ventrolateral; DL = dorsolateral; A = anterior.

et al., 2002). While the aforementioned decreases were often interpreted as reflecting a disturbed encoding network (i.e., the typical set of regions associated with encoding in young adults) in older adults, increased contralateral recruitment was often interpreted as compensatory. Two studies that divided older adults into high- and low-performers found the HAROLD pattern only in the high-performing group (Daselaar et al., 2003b; Rosen et al., 2002), supporting a finding previously reported for retrieval (Cabeza, Anderson, Locantore, & McIntosh, 2002). These results provide direct support for the compensation account of HAROLD.

A third common finding is decreased MTL activity in older compared to younger adults (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003a, Daselaar et al., 2003b; Dennis, Daselaar, & Cabeza, 2006; Grady et al., 1995, 2002; Gutchess et al., 2005; Iidaka et al., 2002). Taken together, decreases in left PFC and MTL are often interpreted as reflecting a disturbed encoding network in older adults. For example, Grady and colleagues (1995) found that younger but not older adults showed a highly significant correlation between MTL and left PFC activity. Based on these results, the authors concluded that aging is accompanied by reduced neural activity and diminished connectivity between PFC and MTL areas. Supporting the aforementioned theory of age-related disruptions in the encoding network, Gutchess et al. (2005) found that older adults exhibited a significant negative correlation between inferior frontal and parahippocampal activity, whereas younger adults did not. These results suggest that older adults who engage less hippocampal activity conversely engage more frontal areas, suggesting that a selective recruitment of left PFC may compensate for MTL dysfunction. Furthermore, Daselaar and colleagues (2003b) were able to directly link reductions in MTL activity to reduced memory performance. Taken together, these findings indicate that reduced MTL function accompanies frontal differences and also contributes to age-related memory decline.

Finally, it should be noted that older adults also exhibit decreases in posterior parietal (Iidaka et al., 2001; Schiavetto, Kohler, Grady, Winocur, & Moscovitch, 2002) and visual regions (Iidaka et al., 2001; Meulenbroek, Petersson, Voermans, Weber, & Fernandez, 2004; Schiavetto et al., 2002) compared to younger adults. Studies by Schiavetto et al., Iidaka et al., and Meulenbroek et al. suggest age-related deficits in visuospatial processing associated with reduced activity in parietal regions. These studies suggest that age-related reductions in parietal activity were associated with deficits in encoding of visuospatial information; thus suggesting that attentional deficits may play a role in decline of visuospatial memory. Furthermore, decreased activation in posterior brain regions and increased PFC activity suggest a reduction in functional specialization with age.

### Episodic Memory Retrieval

As with encoding, the literature regarding aging and imaging in retrieval can also be broken down into three main categories of study: recognition, recall, and context memory. In recognition studies participants are shown items presented at encoding along with new items and asked to judge whether they recognize the item as old or new, whereas recall studies require participants to freely generate that which was presented during encoding. Finally, context memory involves remembering not just the individual item presented at encoding, but also in what context (i.e., temporal order, color, location) it was presented. Again, the most consistent findings from all three types of retrieval studies are discussed below (see Table 1.6).

Several studies report finding similarly activated regions for recognition across age groups (Daselaar et al., 2003b; Grady et al., 1995; Tisserand, McIntosh, van der Veen, Backes, & Jolles, 2005). Such results have led researchers to suggest that age effects are more pronounced for encoding than retrieval. However, despite this relative stability, age differences do arise. For example, in a recent study by Cabeza et al. (2004), older adults showed decreases in occipital and parietal regions coupled with increases in PFC regions (i.e., the PASA pattern). Several studies find age-related decreases in right PFC activity (Anderson et al., 2000; Bäckman et al., 1997; Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Cabeza, Dolcos, Graham, & Nyberg, 2002; Cabeza et al., 1997; Schacter, Savage, Alpert, Rauch, & Albert, 1996; Schiavetto et al., 2002). Overall, older adults show larger age deficits as task difficulty increases (i.e., context>recall>recognition tasks).

Reduced right PFC activity in older adults often resulted in a more bilateral pattern of PFC in older adults than in younger adults (i.e., HAROLD). This age-related bilaterality has also been observed in MTL regions during recall of words (Bäckman et al., 1997) and autobiographical memories (Maguire & Frith, 2003), suggesting that HAROLD may generalize to other brain regions outside of PFC. Like left PFC decreases, retrieval resulting in the HAROLD pattern has been found more frequently in studies using demanding recall and context memory tasks than during simpler item recognition. Overall, results suggest a three-way interaction between age, task difficulty, and frontal laterality. Importantly, distinguishing between old-high performing and old-low performing adults, the study by Cabeza et al. (2002) showed that only the old-high performers showed this frontal bilaterality, providing direct evidence for the compensation account of HAROLD.

Regarding MTL activity during retrieval, several studies reported increases in MTL activity with age (Bäckman et al., 1997; Cabeza et al.,

TABLE 1.6  
PET/fMRI Studies of Episodic Memory Retrieval

			<i>Left Hemisphere</i>						<i>Right Hemisphere</i>					
			<i>MTL</i>		<i>Left PFC</i>				<i>Right PFC</i>			<i>MTL</i>		
			<i>PHG</i>	<i>HC</i>	<i>P</i>	<i>VL</i>	<i>DL</i>	<i>A</i>	<i>A</i>	<i>DL</i>	<i>VL</i>	<i>P</i>	<i>HC</i>	<i>PHG</i>
<b>Recognition</b>														
BP	Cabeza 97	word pair: Rn – Enc								●				
BP	Madden 99	word: Rn – bl				○	○	○	○	○		○		
EF	Daselaar 03c	Old-high, word: Rn – bl				○								
EF	Cabeza 04	Rn – bl	○	●	○			○	○		○		●	
<b>Recall</b>														
BP	Schacter 96	stem Rc: low – high						●	○		●			
BP	Cabeza 97	pair Rc: Rc – Enc				○						●		
BP	Backman 97	stem Rc: Rc – bl		○	○		○						○	
EF	Maguire 03	autobio events – publ event												○
BP	Anderson 00	pair Rc: FA – FA Enc			○	○	●			●		●		
<b>Context memory</b>														
BP	Cabeza 00	word: Context – Rn								●		○		
BP	Cabeza 02	Old-high, word: Context – Recall					●			●	○	○		
BP	Schiavetto 02	object: loc Rn > obj Rn	○			●								

● only young/young > old; ○ only old/old > young; BP = blocked PET; BF = blocked fMRI; EF = event-related fMRI; bl = baseline; DA = divided attention; Enc = Encoding; Ret = retrieval; Rc = recall; obj = object; loc = location; FA = full attention; P = posterior; VL = ventrolateral; DL = dorsolateral; A = anterior.

2004; Maguire & Frith, 2003; Meulenbroek et al., 2004; Schiavetto et al., 2002). Consistent with behavioral findings, results reported by Cabeza and colleagues suggest that these increases may reflect a greater reliance on familiarity-based retrieval in aging (Cabeza et al., 2004; Daselaar et al., 2006). For example, Cabeza et al. (2004) found a dissociation between hippocampus, which showed weaker activity in older adults, and the parahippocampal gyrus, which showed greater activity in older adults. Given the evidence linking the hippocampus to recollection and cortical MTL regions to familiarity (see Yonelinas, 2001), these results fit with the hypothesis that older adults are more impaired in recollection than in familiarity (e.g., Jennings & Jacoby, 1993; Parkin & Walter, 1992) and suggest that they may compensate for recollection deficits by relying more on familiarity. Consistent with this speculation, older adults had a larger number of Know responses than did younger adults, and these responses were positively correlated with parahippocampal activation in older adults. The effects of aging on recollection vs. familiarity were further investigated in a study by Daselaar et al. (2006), which is described at the end of the chapter.

### Summary

In summary, our review of functional neuroimaging studies of cognitive aging has identified considerable age-related differences in activity during all cognitive tasks reviewed. Despite the abundance of age-related differences presented, several patterns emerge from these findings. First, several studies in visual perception (e.g., Grady et al., 1994), attention (e.g., Madden et al., 2002), and recognition memory (e.g., Cabeza et al., 2004) show age-related occipital decreases accompanied by frontal increases (PASA). Additionally, studies spanning the domains of WM (e.g., Reuter-Lorenz et al., 2000), attention (e.g., Cabeza et al., 2004), language (e.g., Persson et al., 2004), encoding (e.g., Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997), and retrieval (e.g., Cabeza et al., 1997) have showed age-related decreases in hemispheric asymmetry (HAROLD). Still others (e.g., Gutchess et al., 2005) show age-related reductions in MTL activity accompanied by increases in frontal activity.

Despite differences in the pattern of age-related differences in neural activity, one common thread prevails—the occurrence of both age-related decreases as well as *increases* in neural activity. For the most part these increases are viewed as beneficial to performance in older adults. This view postulates that older adults compensate for decreases in neuronal activity in one brain region by recruiting additional resources to perform a cognitive task (see Cabeza, 2002). However, as seen by the aforementioned patterns this compensation can occur in several forms. As in

the case of studies showing HAROLD, older adults compensate for declines in neural activity by recruiting cortical regions responsible for similar functioning as areas showing decline (e.g., the contralateral hemisphere). Older adults may also recruit cortical regions responsible for related cognitive operations (e.g. familiarity vs. recollection). Finally, in the case of subsequent memory studies and studies showing PASA, older adults can compensate for relatively automatic sensory and encoding processes with more strategic and elaborative processing associated with frontal functioning. One might wonder if recruitment of additional brain regions is compensatory, then why don't younger adults show such patterns of activation as well? One answer is that compensation or the recruitment of additional brain regions may come with a cost (Bäckman & Dixon, 1992; Cabeza, 2002). For example, recruitment of contralateral hemispheres may reduce the brain's ability to perform simultaneous tasks. Evidence supporting this view comes from studies showing age-related reductions in performance under dual task or divided attention conditions (e.g., Anderson, Craik, & Naveh-Benjamin, 1998). Given the nature of neural compensation in aging, it is not only important to evaluate activation associated with age-related cognitive decline in order to understand what brain areas/processes are most vulnerable to the effects of aging, but also to evaluate age-related increases in activity to assess how and when older adults are able to cope with these declines—and at what possible cost.

### LINKING BRAIN DATA AND COGNITIVE AGING THEORIES

Although the number of functional neuroimaging studies of cognitive aging has dramatically increased during the last decade, very few of these studies have made direct contact with cognitive aging theories. One reason is that cognitive aging theories were originally developed to account for age-related differences in behavior, and hence, they do not usually make predictions regarding the effects of aging on brain activity. A second reason is that these theories typically try to explain deficit in cognition and they rarely include hypotheses regarding compensatory mechanisms. In contrast, the notion of compensation is a central concept in the domain of functional neuroimaging of aging.

Thus, in order to link functional neuroimaging findings to cognitive aging theories one must “expand” these theories with additional assumptions regarding (a) the brain correlates of relevant cognitive processes, and (b) compensatory mechanisms. In this section, we illustrate this “theory expansion” using as examples five popular cognitive aging theories. The first four are general cognitive aging theories that apply to all

cognitive functions: the sensory deficit theory (Baltes & Lindenberger, 1994); the resources deficit theory (Craik, 1986); the speed deficit theory (Salthouse, 1996); and the inhibition deficit theory (Hasher & Zacks, 1988). The fifth theory is specific to the memory domain: the recollection deficit theory (Johnson, Hashtroudi, & Lindsay, 1993; Naveh-Benjamin, 2000; Parkin & Walter, 1992). For each theory, we describe how the theory may be expanded by incorporating assumptions regarding brain mechanisms and regarding functional compensation, and how the resulting “expanded theory” may account for the available functional neuroimaging evidence.

### **Sensory Deficit Theory**

According to the sensory deficit theory, age-related deficits in sensory processing play a major role in age-related cognitive decline (Lindenberger & Baltes, 1994). Consistent with this view, older adults show considerable deficits in basic sensory functioning, including simple vision and auditory processing (for a review, see Schneider & Pichora-Fuller, 2000). The main evidence for the sensory deficit theory comprises findings of strong correlations between age-related differences in sensory and cognitive measures (e.g., Baltes & Lindenberger, 1997; e.g., Lindenberger & Baltes, 1994).

#### ***Adding Assumptions regarding Brain Mechanisms and Compensation***

To link the sensory deficit theory to functional neuroimaging data, one must expand this theory with assumptions regarding neural mechanisms. In general, discussions regarding the sensory deficit theory have contrasted a *cascade view* (Figure 1.3-A), in which sensory organ degeneration leads to sensory deficits and eventually to cognitive decline, to a *common cause view* (Figure 1.3-B), in which sensory and cognitive deficits are both mediated by widespread neural degeneration (for a review, see Schneider & Pichora-Fuller, 2000). A third possibility is that age-related sensory decline reflects a decline in the function of sensory cortices (Cabeza, Dolcos, Prince, Budde, & Nyberg, 2004; Grady et al., 1994). This assumption leads the prediction of age-related reductions in sensory cortex function (e.g., visual cortex activity). As for compensation, given that perception reflects the interaction of bottom-up sensory processing and top-down cognitive processing, one may hypothesize that deficits in the former may be compensated by greater reliance on the latter. Assuming that top-down cognitive operations are partly mediated by PFC, this idea predicts an age-related increase in PFC activity (Cabeza et al., 2004; Grady et al., 1994).

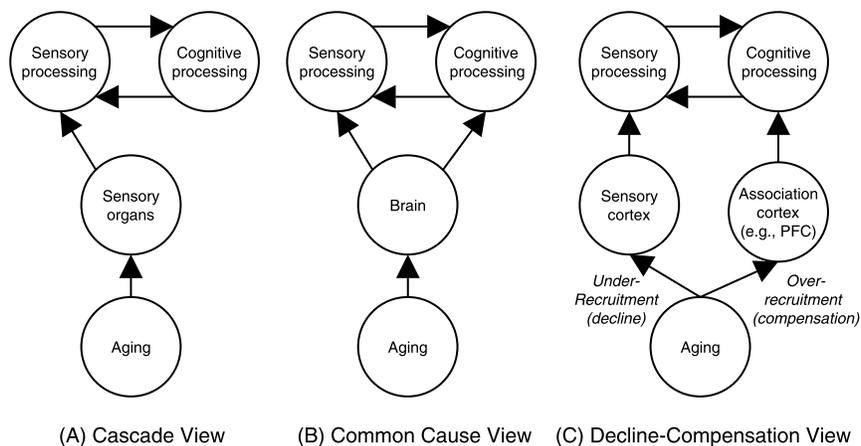


FIG. 1.3. Three views of perceptual and cognitive decline in aging.

Thus, if one enlarges the sensory deficit theory with assumptions regarding brain mechanisms and functional compensation, this theory predicts that under-recruitment of sensory processing in sensory cortex may be compensated by over-recruitment of top-down processes mediated by PFC (see Figure 1.3-C). Thus, the expanded theory predicts that, *compared to younger adults, older adults will tend to show reduced visual cortex activity but increased PFC activity*. As described in the next section, this prediction has been confirmed by many functional neuroimaging studies.

#### *Neuroimaging Evidence for the Expanded Sensory Deficit Theory*

Consistent with the expanded sensory deficit theory, several functional neuroimaging studies have found the pattern previously described as PASA: an age-related decrease in posterior activity coupled with an age-related increase in PFC activity (see Table 1.1). This finding was first reported by Grady et al. (1994) during face matching and location matching tasks. According to the authors, older adults compensated for visual processing deficits (occipital decrease) by recruiting higherorder cognitive processes (frontal increase). Given that in this study older adults were as accurate as younger adults but significantly slower than younger adults, Grady et al. further suggested that additional PFC recruitment allowed older adults to maintain a good level of performance *at the expense* of slower RTs. As indicated by Table 1.1, the PASA pattern has been found during perception, attention, working memory, problem solving, and episodic memory tasks.

The fact that PASA has been found across a variety of cognitive func-

tions is consistent with the assumption of the sensory deficit theory that age-related sensory deficits have a global impact on cognitive functions. However, there is considerable variability in the localization of occipital decreases and frontal increases. In order to demonstrate that the PASA pattern is truly general, it is necessary to compare the effects of aging on brain activity during different cognitive tasks, directly and within participants. This was the main goal of an fMRI study in which we directly compared age-related differences in activity during working memory, visual attention, and episodic retrieval (Cabeza et al., 2004). To identify task-independent age effects, we used a conjunction procedure that isolated age-related differences in activity that occurred in each and every cognitive task.

As illustrated by Figure 1.4, conjunction analyses yielded the PASA pattern: whereas the visual cortex showed an age-related reduction in activity in all three tasks, the prefrontal cortex showed an age-related increase in activity in all three tasks. These findings demonstrate that exactly the same occipital and PFC regions can display identical age-related differences in activity across different cognitive tasks. Task-independent, age-related decreases in visual cortex activity provide strong support for the sensory deficit theory, while task-independent, age-related increases in PFC activity are consistent with Grady et al.'s (1994) hypothesis that age-related increases in PFC activity could compensate for age-related decreases in visual cortex activity.

To investigate the idea of compensation more directly, we calculated the correlations between age-related differences in occipital and PFC activity. In the working memory task, we found a significant negative correlation between these two effects ( $r = -0.5, P < 0.02$ ). In other words, those older adults who showed the weakest occipital activations tended to also show the strongest PFC activations. This finding is relevant to the distinction between common cause (Figure 1.3-B) and cognitive neuroscience (Figure 1.3-C) views of the sensory deficit theory. Whereas the common cause view predicts that the neural correlates of age-related sensory and cognitive deficits should be *positively* correlated, the cognitive neuroscience view, which assumes that top-down cognitive processes may compensate for sensory deficits, predicts negative correlations between sensory and PFC activity in older adults. Thus, our findings were more consistent cognitive neuroscience view.

The expanded sensory deficit theory predicts that, compared to younger adults, older adults will tend to show reduced occipital activity (sensory deficit) but increased prefrontal activity (compensatory top-down cognitive processes). This idea is supported by many functional neuroimaging studies showing age-related decreases in occipital activity coupled with age-related increases in frontal activity (PASA pattern). In

one study, the PASA pattern was found in the same participants across three different tasks, and a negative correlation consistent with the compensation idea was found between age-related differences occipital and frontal regions (Cabeza et al., 2004). Finally, if one assumes that sensory deficits may appear not only as a general reduction in sensory processing but also as difficulty in recruiting specialized sensory operations, the sensory deficit theory would be consistent with recent evidence of age-related dedifferentiation in stimulus-specific processing in ventral temporal regions (Park et al., 2004).

### **Resources Deficit Theory**

Craik and collaborators (Craik, 1983, 1986; Craik & Byrd, 1982) suggested that aging is associated with a reduction in the amount of attentional resources, which results in deficits in demanding cognitive tasks. A corollary of the resource deficit theory, the *environmental support hypothesis* (Craik, 1983, 1986), predicts that age-related differences should be smaller when the task provides a supportive environment which reduces attentional demands. Among other findings, the resources deficit theory is supported by evidence that when attentional resources are reduced in younger adults, they tend to show cognitive deficits that resemble those of older adults (Anderson et al., 1998; Jennings & Jacoby, 1993).

#### ***Adding Assumptions regarding Brain Mechanisms and Compensation***

Regarding neural correlates, Craik (1983) originally suggested that older adults' deficits in processing were related to a reduction in the efficiency of frontal lobe functioning. On the basis of this assumption, the resources deficit theory can predict weaker PFC activity in older adults than in younger adults. However, if one further assumes the effects of aging can be detected only in the PFC regions recruited by a particular task, then the foregoing prediction could be specified as follows: older adults will tend to show reduced activity in PFC regions recruited by younger adults. Moreover, given that the most dramatic differences in PFC activity across tasks are differences in lateralization, the prediction could be stated as follows: *older adults will tend to show reduced activity in the PFC hemisphere differentially engaged by younger adults.*

Regarding compensatory mechanisms, one way in which older adults could counteract deficits in the particular pool of cognitive resources required by a cognitive task is to tap into other pools of cognitive resources. Returning to the notion of lateralized cognitive functions, if one task is particularly dependent on cognitive processes mediated by one hemisphere, the other hemisphere represents an alternative pool of

cognitive resources. Thus, in the case of PFC-mediated cognitive resources, if older adults have deficits in PFC activity in one hemisphere, they may compensate for these deficits by recruiting contralateral PFC regions. Combining the first prediction of age-related decreases in the PFC hemisphere differentially engaged by younger adults with the assumption of a compensatory mechanisms involving contralateral PFC recruitment, the expanded resources deficit theory makes the following second prediction: *older adults will tend to show a more bilateral (less asymmetric) pattern of PFC activity (i.e., HAROLD)*. Both the first prediction and the second prediction have received considerable support from functional neuroimaging studies.

#### *Neuroimaging Evidence for the Expanded Resources Deficit Theory*

The first prediction that older adults will show reduced activity in the PFC hemisphere differentially engaged by younger adults is supported by many functional neuroimaging studies. For example, during tasks in which younger adults recruit mainly right PFC, such as visuospatial working memory (e.g., Grady et al., 1998; Lamar, Yousem, & Resnick, 2004; Mitchell et al., 2000), older adults often show weaker activations in right PFC. Conversely, during tasks in which younger adults recruit primarily left PFC, such as episodic encoding tasks (e.g., Cabeza et al., 1997; Grady et al., 1995, 2002; Logan et al., 2002; Schiavetto et al., 2002), older adults frequently display weaker activity in left PFC. Consistent with the resources deficit hypothesis there is evidence that under conditions of divided attention younger adults show reductions in PFC activity that resemble those associated with aging. In the aforementioned PET study by Anderson and collaborators (2000), younger and older adults were scanned during encoding and retrieval of word pairs both under full attention and under divided attention. As shown by Figure 1.5, during encoding, activity in a region known to be critical for successful encoding operations, the left ventrolateral PFC, was similarly reduced by aging and by divided attention. This finding suggests that older adults' difficulty with encoding is partly due to a reduction in resources, such as that displayed by younger adults under divided attention.

There is also functional neuroimaging evidence supporting the corollary of the resources deficit theory: the environmental support hypothesis. With additional brain assumptions, this corollary predicts that age-related differences in activity will tend to be larger in conditions that require more self-initiated processing resources and smaller in conditions that provide more environmental support. Consistent with this prediction, age-related reductions in left PFC activity during episodic retrieval tend to occur more frequently for recall than for recognition tasks. Moreover, a study

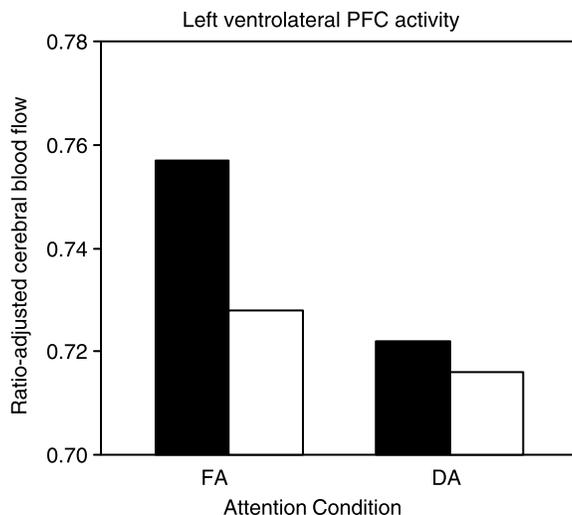


FIG. 1.5. Ratio-adjusted blood flow values during encoding in left ventrolateral prefrontal cortex (PFC) as a function of age group and attentional condition (FA = full attention, DA = divided attention). Adapted from Anderson et al. (2000).

that directly compared the effects of aging on recall activity vs. recognition activity found larger deficits in the more demanding recall task (Cabeza et al., 1997). Differences related to environmental support can also be found during encoding. As is clear in Table 1.3 and previously discussed in the encoding section, age-related reductions in left PFC activity tend to be more frequent for intentional learning (Anderson et al., 2000; Cabeza et al., 1997; Grady et al., 1995, 2002; Logan et al., 2002; Schiavetto et al., 2002) than for incidental learning conditions (see however, Stebbins et al., 2002). Consistent with this idea, an fMRI study that directly compared intentional vs. incidental encoding conditions found age-related decreases in left PFC activity in the former but not the latter (Logan et al., 2002). This finding provides strong support for the environmental support hypothesis.

Finally, there is also functional neuroimaging evidence supporting the second prediction made by the expanded resources deficit theory, that is, that older adults may compensate for resource deficits in one hemisphere by recruiting the contralateral hemisphere. As reviewed before, this finding (HAROLD) has been consistently observed in many cognitive domains, including perception, attention, language, semantic memory, episodic encoding and retrieval, working memory, and inhibitory control processes. (Cabeza, 2002). Consistent with the expanded resources theory, the HAROLD pattern has been linked to compensatory mechanisms.

First, it has been found to be positively correlated with cognitive performance (Reuter-Lorenz et al., 2000). Second, it has been found to be more pronounced in high-performing than in low-performing older adults (Cabeza et al., 2002; Daselaar et al., 2003b; Rosen et al., 2002). Finally, a recent study using transcranial magnetic stimulation (TMS) found that in younger adults episodic retrieval performance was impaired by TMS of right PFC but not of left PFC, whereas in older adults it was impaired by either right or left PFC stimulation (Rossi, Miniussi, Pasqualetti, Babiloni, Rossini, & Cappa, 2004). This result indicates that the left PFC was less critical for younger adults, and was used more by older adults, consistent with the compensation hypothesis.

The expanded resources deficit theory predicts that, compared to younger adults, older adults will show reduced activity in the PFC hemisphere differentially engaged by younger adults, particularly under conditions providing less environmental support, but that older adults will compensate for this deficit by recruiting contralateral PFC regions. Consistent with the first prediction, older adults often show reduced activity in right PFC during visuospatial working memory and episodic retrieval, and reduced left PFC activity during episodic encoding. Also, the latter reduction was observed in younger adults under divided attention conditions (Anderson et al., 2000). Moreover, consistent with the notion of environmental support, age-related PFC reductions tend to be smaller for recognition than for recall (Cabeza et al., 1997) and for semantic encoding than for intentional encoding conditions (Logan et al., 2002). Finally, consistent with the second prediction, there is converging evidence from many different cognitive domains that older adults compensate for reductions in PFC activity in one hemisphere by recruiting the contralateral PFC hemisphere (HAROLD).

### Speed Deficit Theory

One of the most popular cognitive aging theories is that older adults' cognitive deficits reflect a general reduction in the speed of cognitive processes (for a review, see Salthouse, 1996). According to Salthouse (1996), low processing speed is assumed to impair cognitive performance because of two mechanisms: the time required by early operations reduces the time available for later operations (*limited time mechanism*), and the products of early operations are lost or irrelevant by the time later operations are completed (*simultaneity mechanism*). This view is supported by evidence that processing speed declines steadily with age, that this slowing shares considerable variance with age-related deficits in cognitive measures, and that processing speed is a strong mediator of cognitive decline in structural equation models (for a review, see Salthouse, 1996).

### *Adding Assumptions regarding Brain Mechanisms and Compensation*

One possible neural mechanism for age-related slowing is white matter deterioration. The whitish appearance of white matter tracts is due to the fat-containing glial cells forming the myelin sheath around axons connecting gray matter regions. The myelin sheath dramatically increases the speed of neural transmission along axons, and hence, its deterioration can lead to a slowing in neural communication. Thus, the speed deficit theory predicts that older adults' increased RTs in cognitive tasks should be correlated with measures of white matter deterioration. In addition to white matter decline, there is another way in which brain changes may lead to age-related slowing: an increase in the size of the neural network supporting cognitive performance. In general, it is reasonable to assume that a larger network involving more brain regions or more distant brain regions will tend to be slower than a smaller, circumscribed network. Thus, the aforementioned evidence that older adults tend to recruit frontal regions even for relatively simple sensory/perceptual tasks (PASA) can also be interpreted as consistent with the speed deficit theory. As Cheryl Grady speculated, older adults' recruitment of frontal regions may allow them to maintain accuracy at the expense of slower RTs (Grady et al., 1994). Given that this evidence was reviewed within the context of the sensory theory, we will focus here on the prediction regarding white matter changes. As for compensatory mechanisms, if one assumes that older adults may recruit additional brain regions to support performance, then one could predict that activation in these brain regions may lead to faster RTs in older adults but not in younger adults. In sum, with the addition of assumptions regarding neural mechanisms and compensation, the expanded speed deficit theory predicts that *in older adults reduced speed is correlated with white matter deficits and that they may show activations predicting faster RTs that are not displayed by younger adults.*

### *Neuroimaging Evidence for the Expanded Speed Deficit Theory*

Consistent with the expanded speed deficit theory, several studies have found significant correlations between age-related slowing and measures of white matter integrity, such as WMHs and DTI. As reviewed earlier in this chapter, Soderlund and colleagues (Soderlund et al., 2003) found that periventricular WMHs were associated with reduction in motor speed. Also, the DTI measures of fractional anisotropy (FA) and diffusivity (ADC) were found to predict slower RTs in older adults. For example, Madden and colleagues (2004) found a significant relationship between age-related FA decline and RT during visual detection—with older adults showing a greater dependence on fronto-striatal circuitry than younger

adults. Additionally, performance on tasks assessing executive functioning and processing speed show significant correlations with DTI measures in older adults (O'Sullivan, Jones, Summers, Morris, Williams, & Markus, 2001; Persson et al., 2006; Stebbins et al., 2001). Again, declines in speeded performance show a strong correlation with declining white matter integrity in frontal regions (see Figure 1.6). Results suggest that degradation in white matter underlies age-related decline in processing speed and cognitive tasks dependent upon frontal functioning.

Whereas the results of structural MRI studies suggest that white matter deficits may lead to age-related slowing, the results of functional MRI studies suggest that older adults may boost speed by recruiting PFC regions. For example, Reuter-Lorenz et al. (2000) found that in conditions in which PFC activity was unilateral in younger adults, those older adults who showed bilateral PFC activations were faster during a working

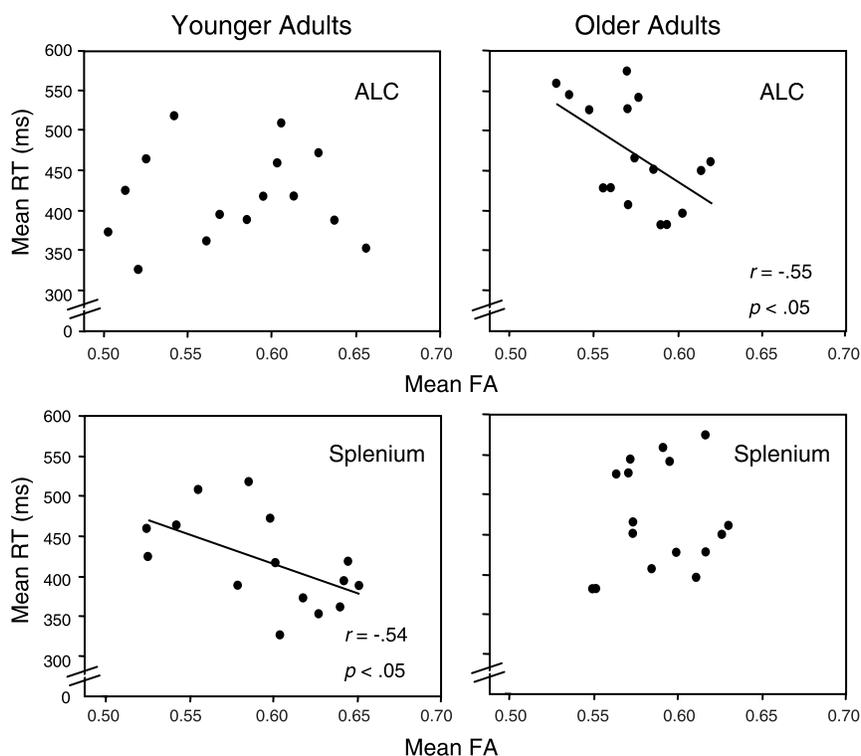


FIG. 1.6. Correlations between mean response time (RT) and mean fractional anisotropy (FA) for the anterior limb of the internal capsule. Reprinted from Madden et al. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage*, 21(3), 1174–1181, © 2004, with permission from Elsevier.

memory task. Thus, under certain conditions, increased PFC activity in older adults may help them increase the speed of their cognitive processes. This finding may seem inconsistent with the aforementioned suggestion that a larger network that includes anterior brain regions may be slower than a more circumscribed posterior set of regions (Grady et al., 1994). One way in which these two ideas can be harmonized is to assume that involving anterior brain regions may slow down responses in younger adults but speed them up in older adults. This pattern was reported by Rypma and D'Esposito (2000) during a working memory task.

The expanded speed deficit theory predicts that in older adults reduced speed is correlated with white matter deficits and that they may show activations predicting faster RTs that are not displayed by younger adults. Consistent with the first prediction, several structural MRI studies have found significant correlations between RT slowing in older adults and measures of white matter integrity, such as WMHs and DTI measures. Consistent with the second prediction, a few PET and function MRI have associated increased PFC activity in older adults with faster RTs. It has been suggested that the relationship between PFC activity and speed may change with aging so that greater PFC activity may be associated with slower RTs in younger adults but with faster RTs in older adults. Thus, PFC recruitment may compensate for age-related slowing due to white matter decline.

### **Inhibition Deficit Theory**

A fourth popular theory of cognitive aging is the inhibition deficit theory, which attributes age-related cognitive deficits to a decline in the inhibitory control of working-memory contents (Hasher & Zacks, 1988; Zacks, Hasher, & Li, 2000). When inhibitory control fails, goal-irrelevant information gains access to working memory, and the resulting "mental clutter" impairs working-memory operations, including the encoding and retrieval of episodic information (Zacks et al., 2000). Evidence supporting the inhibition view includes results showing that, compared to young adults, older adults make more indirect semantic associations and better remember disconfirmed solutions and to-be-forgotten information (for a review, see Zacks et al., 2000).

#### *Adding Assumptions regarding Brain Mechanisms and Compensation*

The brain basis of inhibition may be described at very different levels of analysis, from inhibitory synapses, to inhibitory neurohormonal systems, to inhibitory functional connections among regions in a distributed

network. Given that neuroimaging can only investigate the latter, here we focus only on inhibitory effects within large-scale networks. At this level, it is generally assumed that an important function of PFC is to inhibit activity in posterior associative cortices and in sensory and motor cortices. Therefore, when expanding the inhibitory deficit theory with assumptions regarding brain activity, it is critical to distinguish between the *regions that exert the inhibition* (inhibitory control regions), whose activity should increase when inhibition occurs, and the *regions affected by the inhibition* (inhibited regions), whose activity should decrease when inhibition occurs. Accordingly, the expanded inhibitory deficit theory predicts that *older adults should show weaker activity than younger adults in inhibitory control regions but greater activity than younger adults in inhibited regions* (i.e., a disinhibition phenomenon). Conversely, if one assumes that older adults may compensate for these deficits, one may also expect an *age-related increase in alternative inhibitory control regions*.

#### ***Neuroimaging Evidence for the Expanded Inhibition Deficit Theory***

Consistent with the expanded inhibition deficit theory, there is evidence that older adults show reduced activity in inhibitory control regions and greater activity in inhibited regions than younger adults. As an example of the former, Jonides and colleagues have shown an age-related decrease in the activity of a region associated with controlling interference during verbal working memory, left ventrolateral PFC (Jonides, Marshuetz, Smith, Reuter-Lorenz, Koeppel, & Hartley, 2000b). In each trial of the task, subjects maintained four target letters for 3 sec and then decided whether a probe matched any of the four target letters. In a high-recency condition, half of the probes did not match any target letter in the current trial but matched a target letter in the immediately preceding trial. In the low-recency condition, in contrast, the probe did not match any target letter in the two preceding trials. Thus, inhibitory control was critical in the high-recency but not in the low-recency condition. The high-recency minus the low-recency condition yielded an activation in the left PFC. An ROI analysis indicated that in older adults this activation was significantly weaker than in young adults and was not reliable. A combined measure of accuracy and reaction times yielded an interference effect for negative trials in which the probe matched a target letter in the preceding trial. Since this interference effect was larger for older than for young adults, the authors concluded that aging diminishes the efficacy of the left PFC in inhibiting the interfering effects of prepotent processes.

There is also evidence supporting the prediction that older adults will show greater activity than younger adults in regions that must be inhibited. For example, in an early PET study we found that an insular

region that is often deactivated during memory tasks showed greater activity in older adults than in younger adults during an episodic encoding task (Cabeza et al., 1997). Unlike the case in which increased activity in older adults is associated with better performance, this activation showed a *negative* correlation with subsequent recall performance, suggesting that engaging insular regions during encoding is detrimental for encoding and could reflect a lack of inhibition in older adults. More recently, Gazzaley, Cooney, Rissman, and D'Esposito (2005) investigated the effects of aging on the inhibition of stimuli-specific regions during a working memory task. Participants were presented with alternating faces and scenes under three instruction conditions: remember the faces and ignore the scenes, remember the scenes and ignore the faces, and passively view faces and scenes. As illustrated by Figure 1.7, in younger adults, activity in brain region sensitive to scene processing was enhanced by the instruction to remember scenes and suppressed by the instruction to ignore the scenes, compared to the passive view condition, whereas in older adults only the former instruction produced an effect. In other words, older adults' selective attention was able to up-regulate task-relevant activity but failed to down-regulate task-irrelevant activity.

Finally, there is evidence that older adults may compensate for reduced activity in inhibitory control regions recruited by younger adults by recruiting other additional brain regions, such as areas in the contralateral PFC hemisphere. For example, such evidence was found for the *Go/No-go* task. In this task, participants must respond to targets (*Go* trials) while inhibiting prepotent responses to distractors (*No-go* trials). In younger adults, inhibitory control in the *Go/No-go* task is usually associated with activity in right PFC (e.g., Garavan, Ross, & Stein, 1999). In an fMRI study, Nielson et al. (2002) found that in older adults, inhibitory control elicited significant activity not only in right PFC but also in left PFC. This finding is consistent with the HAROLD model, and provides support for the idea that older adults may compensate for inhibitory control deficits by recruiting additional brain regions.

The expanded inhibition deficit theory predicts that, compared to younger adults, older adults will show weaker activity in inhibitory control regions but greater activity in inhibited regions (i.e., a disinhibition). Regarding compensation, this view predicts that older adults will compensate for deficits in recruiting the inhibitory deficits activated by younger adults by activating alternative inhibitory control regions. Consistent with the first prediction, activity in regions associated with inhibitory control in younger adults, such as left ventrolateral PFC during verbal working memory (Jonides et al., 2000b), was found to be reduced in older adults. In contrast, older adults showed increased activity in regions that show the effect of inhibition, such as the insula during

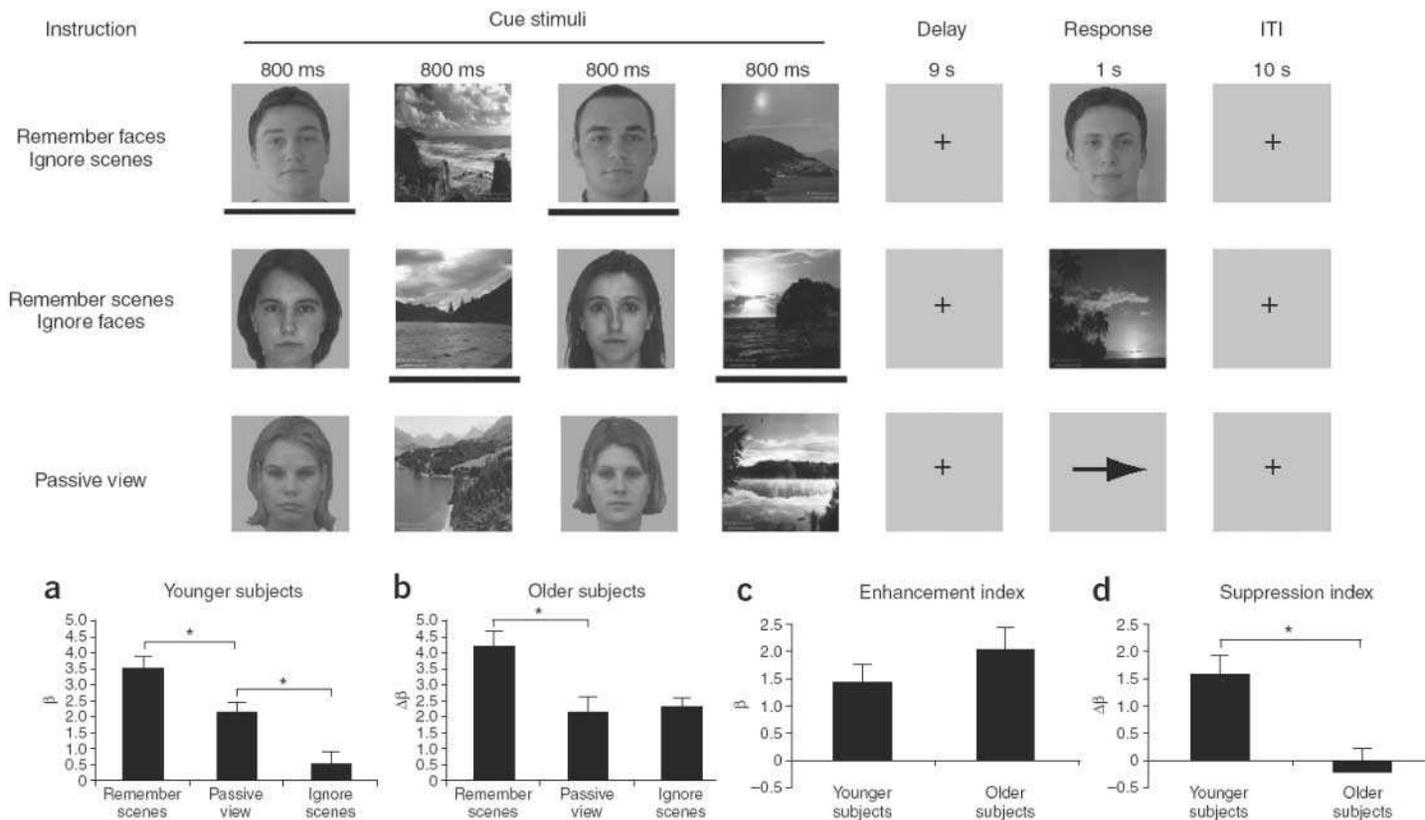


FIG. 1.7. Experimental framework indicating the three task conditions/instructions and response requirements. In the response period of the two memory tasks participants were required to report with a button press whether the stimulus matched one of the previously presented stimuli. Below are fMRI data showing a selective deficit of top-down suppression in older adults. Reprinted by permission from Macmillan Publishers Ltd: *Nature Neuroscience* (Gazzaley et al. (2005)), © 2005.

encoding (Cabeza et al., 1997) and stimuli-specific ventral temporal regions during working memory (Gazzaley et al., 2005). Possibly compensating for these inhibitory deficits, older adults have been found to show bilateral PFC activations during inhibition tasks that show lateralized activations in younger adults (Nielson et al., 2002).

### **Recollection Deficit Theory**

Whereas the sensory, resources, speed, and inhibition deficit theories are general cognitive aging theories that apply to all cognitive domains, the recollection deficit theory is specific to the episodic memory domain. *Recollection* refers to the retrieval of a past event that is accompanied by the recovery of specific associations or contextual details, whereas *familiarity* refers to the feeling that an event occurred in the past even in the absence of specific associations or contextual details. Among other methods, recollection and familiarity can be distinguished using the *remember-know procedure* (for a review, see Gardiner, 2001; Tulving, 1985), in which subjects use introspection to distinguish between test cues that elicited recollection (*Remember response*) and those that elicited familiarity (*Know response*). According to the recollection deficit theory, episodic memory deficits in older adults are larger for recollection than for familiarity, and in some cases, they are significant only for recollection and not for familiarity. This view is also supported by evidence that older adults are more impaired in recollection than in familiarity (Yonelinas, 2002), which has been demonstrated using the Remember/Know paradigm (Bastin & Van der Linden, 2003; Davidson & Glisky, 2002; Java, 1996; Mantyla, 1993; Parkin & Walter, 1992), ROC curves (Howard, Bessette-Symons, Zhang, & Hoyer, 2006), and the process-dissociation procedure (Jennings & Jacoby, 1993). Given that recollection involves the retrieval of associations between core and contextual elements of an episode, this evidence is also consistent with theories that postulate associative (Naveh-Benjamin, 2000) and source memory (Johnson et al., 1993) deficits in older adults.

#### ***Adding Assumptions regarding Brain Mechanisms and Compensation***

Adding brain assumptions to the recollection deficit theory is straightforward because several researchers have proposed differences between the neural correlates of recollection and familiarity. Within MTL, one popular idea supported by lesion, electrophysiology, and functional neuroimaging studies with laboratory animals and human participants is that recollection (or relational memory) is more dependent on the hippocampus, whereas familiarity (or item memory) is more dependent on cortical MTL regions (Eichenbaum, Otto, & Cohen, 1994), such as the

perirhinal cortex (Aggleton & Brown, 1999; Brown & Aggleton, 2001). Thus, on the basis of this idea, one could link older adults' deficits in recollection to hippocampal dysfunction. As for compensation assumptions, if one assumes that familiarity and rhinal regions are less affected by aging, then recollection deficits in older adults could be attenuated by greater reliance on familiarity and rhinal functions. As illustrated by Figure 1.1, a recent longitudinal volumetric MRI study found that age-related atrophy was significant in the hippocampus but not in rhinal cortex. In sum, if one expands the recollection deficit theory of aging with assumptions regarding the neural mechanisms and functional compensation, this view predicts that, *compared to younger adults, older adults will tend to show reduced recollection-related activity in the hippocampus but increased familiarity-related activity in rhinal cortex.*

#### *Neuroimaging Evidence for the Expanded Recollection Deficit Theory*

We recently found fMRI evidence supporting the recollection-deficit theory in a study in which participants were scanned while recognizing words studied before scanning. Brain activity associated with recollection and familiarity were distinguished using confidence ratings under the assumption that most recollection-based responses are mainly "definitely old" responses whereas the frequency of familiarity-based responses increases gradually from "definitely new" to "definitely old." Therefore, recollection-related activity was identified with a quasi-exponential function and familiarity-related activity with a linear function. The main finding of the study was a double dissociation between recollection-related activity in hippocampus, which was reduced by aging, and familiarity-related activity in rhinal cortex, which was increased by aging (see Figure 1.8). In addition, regression analyses based on individual trial data showed that changes in hippocampal activity predicted recognition performance in both younger and older adults, whereas changes in rhinal activity predicted recognition only in older adults. Finally, network analyses that linked hippocampal and rhinal activity to activity in the rest of the brain yielded a dissociation in functional connectivity: whereas connectivity within a hippocampal-retrosplenial/parietotemporal network was reduced by aging, connectivity within a rhinal-frontal network was increased by aging. These findings indicate that older adults compensate for hippocampal deficits by relying more on rhinal cortex, possibly through a top-down frontal modulation. This finding has important clinical implications, since early AD impairs both hippocampus and rhinal cortex and in its earliest stages it often affects rhinal cortex to a greater extent than the hippocampus.

The expanded recollection deficit theory predicts that, compared to

younger adults, older adults will show reduced recollection-related activity in the hippocampus but increased familiarity-related activity in rhinal cortex. Consistent with this prediction, during a recognition memory test, we found that hippocampal activity that showed an exponential pattern associated with recollection was attenuated in older adults, whereas a rhinal region that showed a linear pattern associated with familiarity was enhanced in older adults. Consistent with the idea of compensation, the rhinal activation predicted recognition performance only in older adults, and it was more directly linked to frontal activity in older adults than in younger adults.

### Summary

In sum, with the addition of assumptions regarding neural mechanisms and functional compensation, existing cognitive aging theories can be easily linked to available functional neuroimaging data. The expanded versions of these theories yield specific predictions that can be investigated in structural and functional neuroimaging studies, and in general, these predictions are consistent with the extant evidence.

## CONCLUSIONS

In the first section of the chapter we reviewed resting neuroimaging studies of aging. Results indicate that while the brain undergoes significant structural change with age, age-related atrophy differs across and within regions. Regarding volumetric measures of gray matter, studies have shown that the frontal lobes exhibit the steepest rate of decline, followed by the parietal, then temporal lobes, with the occipital lobes showing little if any volume loss. Measures of white matter volume and integrity (i.e., FA) also showed differential aging effects throughout the brain. Similar to gray matter decline, age-related white matter degradation and DA dysfunction are greater in anterior compared to posterior regions. Correlations between these measures and cognitive function emphasize the importance these changes have on cognitive functions.

In the second section of the chapter we reviewed PET and fMRI studies of aging in the domains of visual perception, attention, language, working memory, implicit memory, and episodic memory encoding and retrieval. In addition to many task-specific differences, these studies revealed two consistent patterns of age-related differences in brain activity: a posterior-anterior shift in activity in older adults (PASA), and a general reduction in the asymmetry of brain activity (HAROLD). Furthermore, studies exhibiting both activation patterns make the same general

conclusion—increased activation in prefrontal regions acts as a compensatory mechanism for age-related deficits in other brain regions (in PASA studies, occipital regions, and in HAROLD studies, contralateral PFC regions). This increased recruitment of higher-order cognitive processes may be indicative of: (a) alternate strategies employed by older adults when presented with cognitively demanding tasks; and (b) the subtle rearrangement of neural networks. As discussed, direct support for the compensation accounts of PASA and HAROLD has come from functional neuroimaging studies that correlated individual activation patterns with performance, or that directly compared high- and low-performing older adults.

In the final section of the chapter we integrated both the structural and functional neuroimaging measures with traditional theories of cognitive aging. As noted, the majority of cognitive aging theories were constructed to account for behavioral differences among age groups and did not consider neural activations. However, in order for a theory to continue to be informative in regards to neuroimaging methodologies, it must be expanded to both explain and be predictive of neuroimaging studies. The theories mentioned above have just that capability. As is the case with the behavioral literature, different aspects of the neuroimaging literature support each of the “extended” major theories of cognitive aging. This provides a rich foundation on which we can continue to build our understanding of cognitive aging. Advancements in neuroimaging and development of other methodologies must continually be integrated with theory development in order to not only understand *what* changes occur in aging, but *why* these changes take place.

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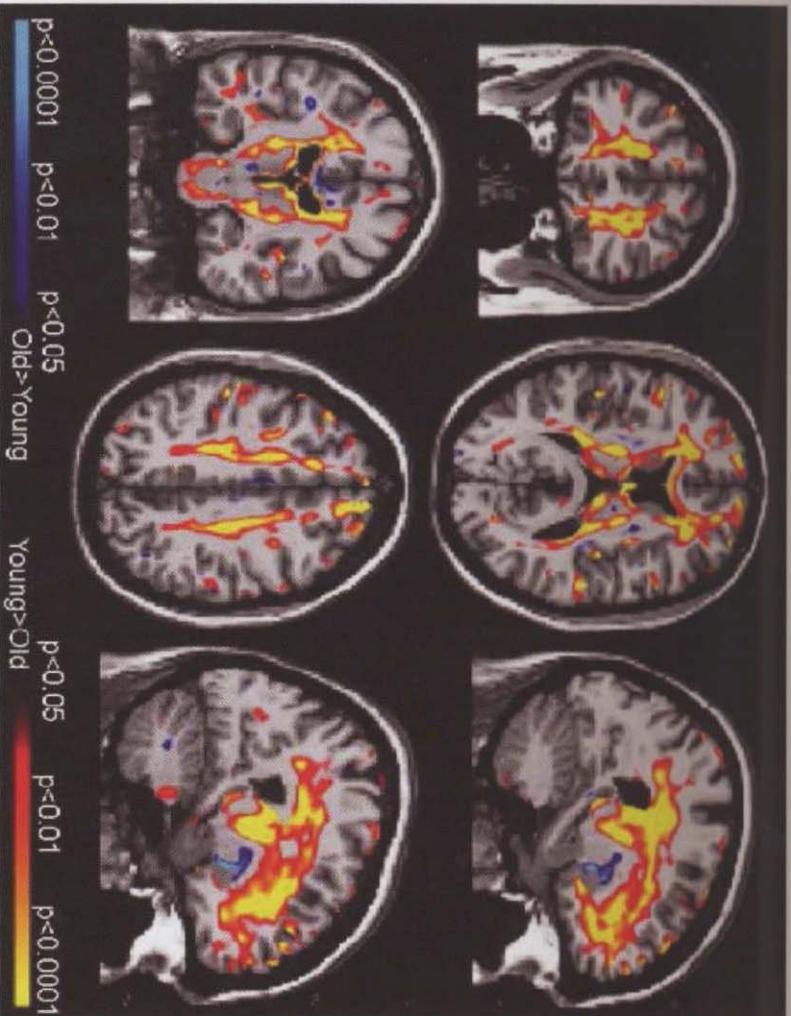


FIG. 1.2. Age-related decline in fractional anisotropy (FA) in older adults compared to younger adults. Yellow regions represent areas of greatest age-related decline. Reprinted from Salat et al. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of Aging*, 26(8), 1215-1227. © 2005, with permission from Elsevier Inc.

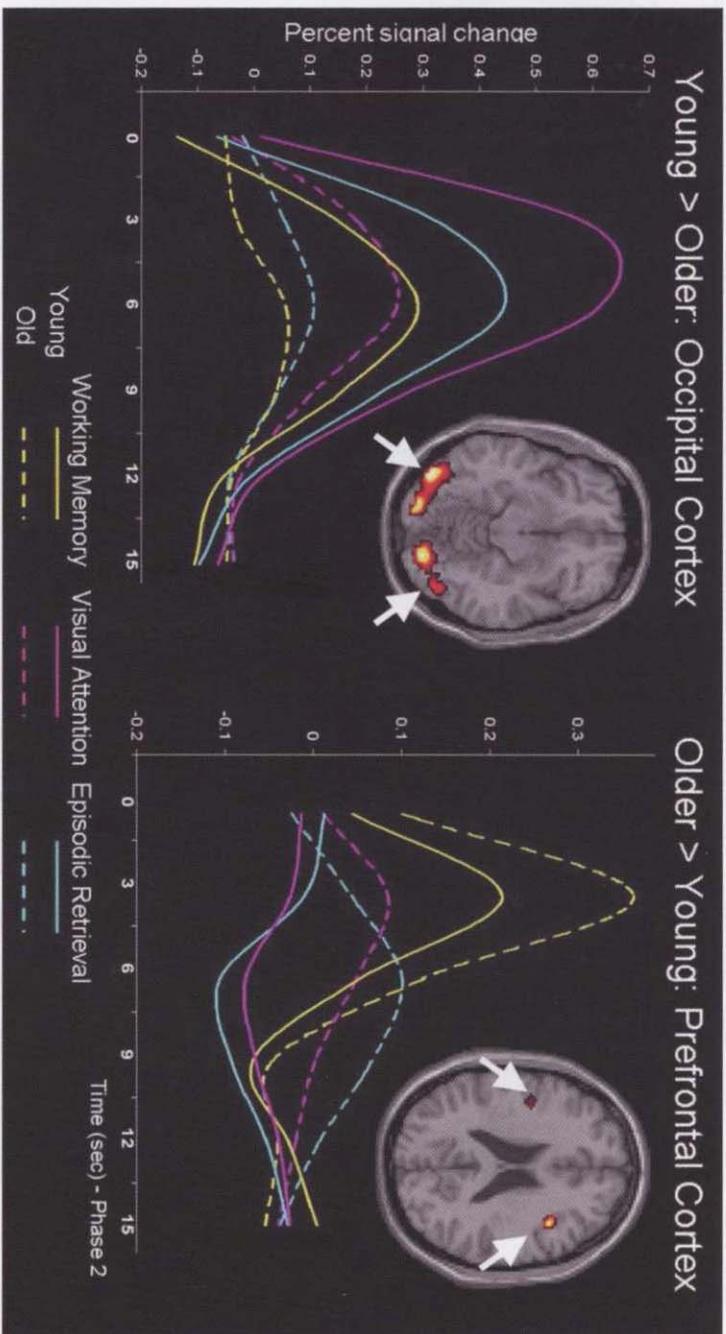


FIG. 14. Task-independent age effects. Compared to younger adults, older adults showed weaker activity in occipital cortex, but greater activity in frontal regions. The time-course plots are from left BA19 ( $x, y, z = -23, -84, -8$ ) and right BA45 ( $x, y, z = 41, 12, 21$ ). Reproduced by permission of Oxford University Press from Cabeza et al. (2004b). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex*, 14(4), 364–375.

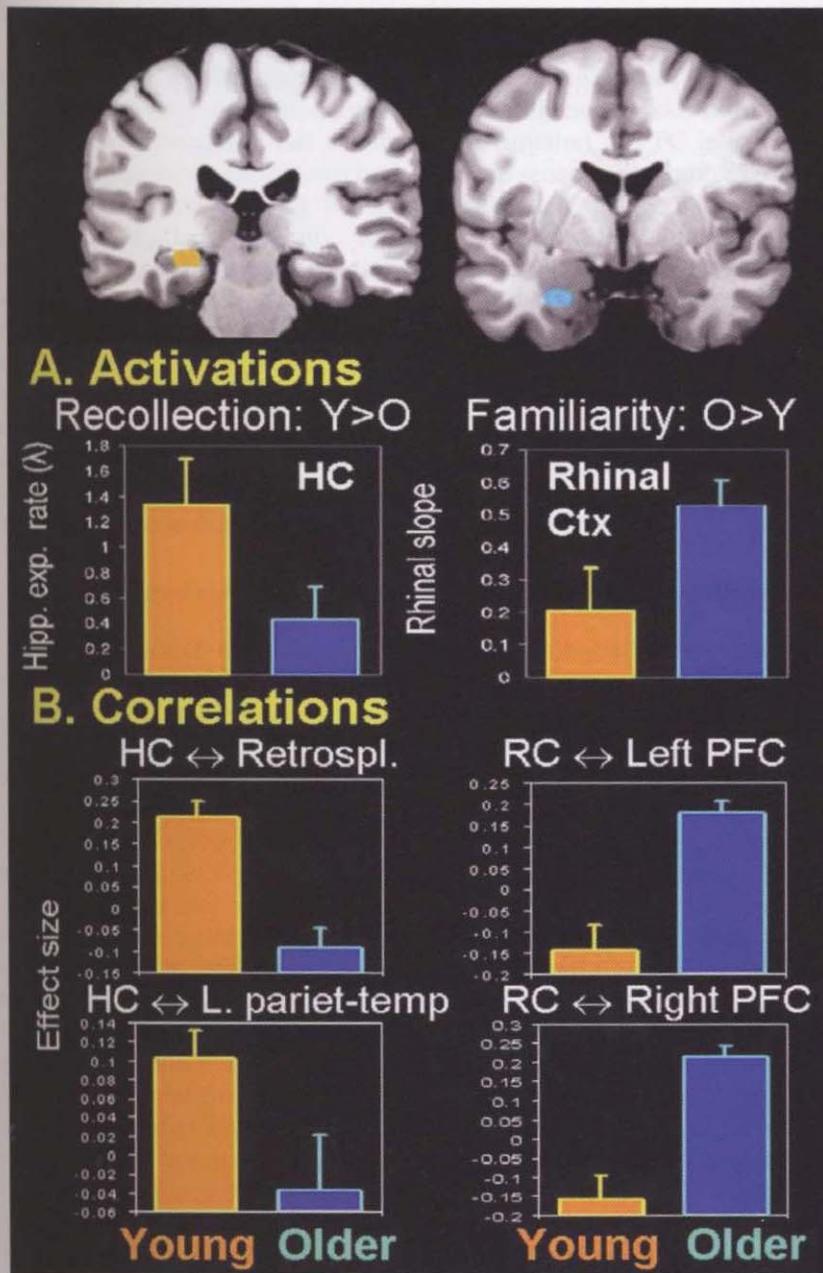


FIG. 1.8. Double dissociation between recollection-related activity in the hippocampus, attenuated by aging, and familiarity-related activity in the rhinal cortex, enhanced by aging. Reproduced by permission of Oxford University Press from Daselaar et al. (2006). Effects of healthy aging on hippocampal and rhinal memory functions: An event-related fMRI study. *Cerebral Cortex*, 16, 1771–1782.