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Neuroanatomical Correlates of Cognitive Aging: Evidence From Structural Magnetic Resonance Imaging

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To examine putative brain substrates of cognitive functions differentially affected by age the authors measured the volume of cortical regions and performance on tests of executive functions, working memory, explicit memory, and priming in healthy adults (18–77 years old). The results indicate that shrinkage of the prefrontal cortex mediates age-related increases in perseveration. The volume of visual processing areas predicted performance on nonverbal working memory tasks. Contrary to the hypotheses, in the examined age range, the volume of limbic structures was unrelated to any of the cognitive functions; verbal working memory, verbal explicit memory, and verbal priming were independent of cortical volumes. Nevertheless, among the participants aged above 60, reduction in the volume of limbic structures predicted declines in explicit memory. Chronological age adversely influenced all cognitive indices, although its effects on priming were only indirect, mediated by declines in verbal working memory.

Cognitive aging is a selective process. It affects mental functions associated with greater mental effort, speed demands, novelty, and informational complexity ("fluid" abilities) significantly more than those that rely on overlearned behavioral patterns and previously acquired expertise ("crystallized" abilities) (Horn, 1986; Salthouse, 1992a). The selective declines in cognition coincide with differential changes in the brain that are more marked in the association cortices than in primary sensory areas (for reviews see Kemper, 1994; Raz, 1996; Waldemar, 1995). In this report we examine the relations between age-sensitive and age-invariant cognitive functions and their putative cortical substrates.

Selectivity of cognitive aging is especially apparent in memory and executive functions. Whereas younger adults consistently show a substantial advantage in free and cued recall, recognition memory is affected to a much lesser extent (Verhaeghen, Marcoen, & Goosens, 1993), and repetition priming shows very little or no age-related declines (LaVoie & Light, 1994; Mitchell, 1993). Moreover, some types of priming are resistant even to the effects of Alzheimer's disease, which has a devastating impact on the explicit memory (e.g., Postle, Corkin, & Growdon, 1996). Convergent evidence from animal studies, observations on humans with brain lesions, and in vivo neuroimaging investigations indicates that explicit memory depends on two subdivisions of the central nervous system: the limbic–diencephalic system (Andreasen et al., 1995; Eichenbaum, 1994; Kapur, Friston, Young, Frith, & Frackowiak, 1995; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1993; Stern et al., 1996) and the prefrontal cortex (Andreasen et al., 1995; Kapur et al., 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Petrides, Alivisatos, & Evans, 1995). Some functional neuroimaging studies indicate that the posterior association cortex (e.g., inferior parietal lobule) may also play a role in episodic memory, although other investigations failed to replicate this finding (for review see Cabeza & Nyberg, 1997). In contrast to explicit memory, repetition priming requires no limbic–diencephalic support (Squire et al., 1993), and there is little evidence that it is subserved by any coherent brain system. For example, the primary visual cortex may play an important role in priming of printed words (Gabrieli, Fleischman, Kean, Reminger, & Morell, 1995; Kean, Gabrieli, Fennema, Growdon, & Corkin, 1991; Squire et al., 1992), but it is apparently irrelevant to priming of line patterns (Postle et al., 1996), and, as some recent neuroimag-

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ing data suggest, priming tasks that call for an organized semantic search may also depend on the prefrontal cortex (Demb et al., 1995; Kapur et al., 1994).

Although study of memory has been traditionally a central topic in cognitive gerontology, there is another area of cognitive activity that shows evidence of substantial negative effects of age—the executive functions (West, 1996). The term *executive* is somewhat amorphous and ill-defined. It encompasses a broad range of cognitive skills, such as monitoring one's recent and past performance, generating future goals, inhibiting prepotent overlearned responses, and alternating behavioral patterns in response to feedback. A classic example of an executive task is the Wisconsin Card Sorting Test (WCST), in which participants are asked to classify and sort stimuli on one of the three characteristics, to discover changes in sorting rules using feedback, and to alter their response accordingly. Age differences in WCST scores are comparable in magnitude to those observed in free recall, although the range of the estimates of age effects on this task is quite large, extending from 0.3 (Haaland, Vranes, Goodwin, & Garry, 1987) to 1.5 (Parkin & Walter, 1992, Experiment 1) standard deviations.

The bulk of empirical evidence suggests that executive functions depend on the integrity of the prefrontal cortex (Kimberg & Farah, 1993; Roberts & Pennington, 1996; Stuss & Benson, 1984). However, specific tasks (e.g., WCST) sensitive to prefrontal lesions rely on distributed neural circuitry and may lack specificity (Anderson, Damasio, Jones, & Tranel, 1991; Berman et al., 1995; Eslinger & Grattan, 1993). Distribution of specialized functions within the prefrontal cortex is even less clear. Although dorsolateral regions have been implicated in performance on WCST (e.g., Ragland et al., 1997), the intact orbito-frontal cortex may also be necessary for altering response in the process of task performance, as destruction of that region results in a dramatic increase in perseveration (Freedman & Oscar-Berman, 1986; Oscar-Berman, McNamara, & Freedman, 1991). Because executive tasks, such as WCST, are quite complex and combine inhibitory, strategic, and monitoring functions, performance on those tasks depends on the integrity of multiple prefrontal regions.

The role of the prefrontal cortex in cognitive aging has been underscored by several theorists who have focused on age-related changes in management of cognitive resources and, specifically, working memory (WM)—an ability to process information while maintaining intermediate products, goals, and associated strategies of processing on-line (Moscovitch & Winocur, 1992; Salthouse, 1994a). Working memory has been conceptualized as a complex system comprised of a modality-free central executive and modality-specific subordinate modules (Baddeley, 1986). Among the specific WM modules, the best explored is the articulatory loop, for which phonological mechanisms are fairly well established (Baddeley, 1996). The nature of another important WM module, the visual–spatial sketch pad, is less clear, although its close links to mental imagery are apparent (Logie, 1995). Because the elderly perform worse than their younger counterparts on a variety of tasks involving mental imagery (Dror & Kosslyn, 1994; Thompson & Kliegl, 1991), it is possible that declines in WM underpin age-related differences in the ability to generate, store, and manipulate mental images. The importance of WM in cognitive aging has been amply demonstrated because older people show moderate deficits on a variety of WM tasks (Salthouse, 1992a, 1994a; Verhaeghen et al., 1993). Yet, the cognitive mechanisms underlying age differences in WM are still unclear.

Examination of the evidence of cerebral localization of WM and its relation to brain regions preferentially affected by aging may help to answer these questions. The preponderance of evidence indicates that WM relies on several cortical structures. Although earlier models of WM emphasized its almost exclusive dependence on polymodal prefrontal association areas (Goldman-Rakic, 1987; Petrides, Alivisatos, Meyer, & Evans, 1993; Smith et al., 1995), more recent data suggest that modality-specific secondary association cortices play an important role in supporting this resource (Cohen et al., 1994; Courtney, Ungerleider, Keil, & Haxby, 1996; D'Esposito et al., 1995; Gabrieli, Singh, Stebbins, & Goetz, 1996; Smith, Jonides, & Koeppe, 1996; Stern et al., 1995). Inasmuch as performance on WM tasks engages specific processing modules, the integrity of the brain areas subserving them is also expected to affect the outcome of WM tests. For example, performance on WM tasks that call for extensive use of visual imagery depends on the visual association cortices (fusiform and inferior temporal) and, possibly, primary visual areas as well (Farah, Hammond, Levine, & Calvanio, 1988; Kosslyn, 1994; Mellet, Tzourio, Denis, & Mazoyer, 1995; Roland & Gulyás, 1995). Tests of visual–spatial abilities require generation of images and their manipulation in visual–spatial WM (Kosslyn, 1994); individual differences in performance on tests of visuospatial ability can be explained by variability in WM components (Shah & Miyake, 1996); and visual association cortices become metabolically active during performance on such tasks (Deutsch, Bourbon, Papanicolaou, & Eisenberg, 1988). Activation patterns on functional magnetic resonance imaging (fMRI) suggested that the fusiform cortex may play an important role in explicit memory by providing support for encoding of novel pictorial stimuli (Stern et al., 1996). Thus, the evidence supports the association between nonverbal WM and visual cortices.

As the selective age-related changes in the brain and in cognitive performance occur in the same time frame, it is highly plausible that aging of specific cognitive functions stems directly from differential aging of specific cortical structures. To date, however, this proposition has acquired only limited empirical support. Experiments with aging rodents suggest that senescent declines in some memory functions are associated with damage to the hippocampal formation and prefrontal cortex (Zyzak, Otto, Eichenbaum, & Gallagher, 1995), and in humans, functional neuroimaging began to reveal the links between age-related deficits in encoding and regional reduction of brain activity (Bäckman et al., 1997; Grady et al., 1995; Madden et al., 1996). Unfortunately, the number of activation neuroimaging studies of aging and the number of participants within those studies are too small to allow any definitive conclusions (for review see Madden & Hoffman, 1997).

Structural neuroimaging affords an opportunity to study the relationships between age differences in the brain and age-dependent changes in cognition in relatively large samples. However, the early attempts to elucidate the neuroanatomical basis of cognitive aging relied on relatively crude measures of the brain (computed tomography), and revealed only general associations between nonspecific age-related atrophy markers and performance on a battery of broad-range neuropsychological tests in healthy elderly (e.g., Albert, Duffy, & Naeser, 1987). Later, some MRI studies demonstrated that the burden of brain hypointensities of vascular origin predicts deficits on neuropsychological tests (Breteler et al., 1994; Junqué et al., 1990), although others failed to find any connections between neuropsychological performance and MRI signs of mild cerebrovascular disease (for review see Raz, 1996). Attempts to relate adult age differences in regional cerebral metabolism of glucose or oxygen to cognitive performance yielded contradictory and inconclusive results (Duara et al., 1984; Eustache et al., 1995; Haxby et al., 1986). In a more recent study of the healthy elderly, a significant positive association was found between the hippocampal volume and performance on delayed memory tests (Golomb et al., 1994). However, it is unclear whether age-related decline in delayed recall is uniquely associated with hippocampal atrophy. The impact of these interesting findings is limited by the lack of a double-dissociation comparison between the cognitive functions and brain regions.

The double-dissociation approach is the cornerstone of experimental neuropsychology (Kolb & Wishaw, 1995). In this method, the goal is to establish not only an association between region A and behavior X, and region B and behavior Y, but also the lack of a relationship between A and Y, and B and X. To formulate and test double-dissociation hypotheses in human in vivo imaging, one needs a set of reliable regional measures of cortical volume and a reasonable range of variability in both structural and cognitive measures. When double-dissociation logic is extended to several pairings of regional brain characteristics and cognitive tasks it produces a multiple-dissociation framework. Uncomplicated aging, with its regional pattern of brain changes and selective vulnerability of cognitive functions, may provide a suitable model for quasi-experimental studies of double and multiple dissociations of cognitive functions and cerebral structures.

The objective of the research presented in this article was to conduct a multiple-dissociation study of relationships between brain regions and specific cognitive functions using a normal life-span sample in which structural brain measures and indices of cognitive performance were obtained within a relatively narrow time frame. To attain this objective, we obtained structural brain measures and indices of cognitive performance from a carefully selected sample of healthy adults spanning a wide age range. We attempted to dissociate four cerebral regions—prefrontal (dorsolateral and orbital) and parietal (inferior parietal) polymodal association cortices, visual processing areas (primary and secondary), and the limbic regions (hippocampus and parahippocampal gyrus)—and seven cognitive functions—executive (exemplified by strategic flexibility or resistance to perseveration), WM, explicit memory, and repetition priming, with verbal and nonverbal varieties included in each of the examined memory domains.

We expected that all cognitive functions except priming would be affected by age. However, we hypothesized that whereas both verbal and nonverbal memory would be affected by the differences in the prefrontal cortex (PFC) and the volumes of limbic structures (no dissociation), only verbal memory would depend on the volume of inferior parietal lobule, and only nonverbal memory would be affected by shrinkage of the visual cortices but not vice versa (a double dissociation). Another hypothesized dissociation was between the volume of the PFC and executive functions versus limbic structures and explicit memory: We expected to find significant associations between the brain and cognitive variables within these pairs of variables but not across the pairs. Working memory, verbal and nonverbal, was expected to be affected by changes in the PFC volume (no dissociation), but only its nonverbal variety was expected to depend on the visual cortices, whereas the verbal (but not nonverbal) WM was hypothesized to be associated with the inferior parietal lobule volume—a double dissociation. Better priming was expected to be associated with larger visual and prefrontal cortices but unrelated to the volume of the hippocampus, thus dissociating from explicit memory.

In addition to the set of hypotheses regarding brain–cognition relationships, we formulated several hypotheses concerning the role of WM in higher-level cognitive abilities. We expected that verbal and nonverbal WM would dissociate between the verbal and nonverbal explicit memory functions, that both types of verbal memory would predict strategic flexibility, and that none of the variables would be associated with priming.

Method

Participants

The data for this study were collected in an ongoing investigation of neuroanatomical correlates of age-related differences in cognition (see Raz et al., 1997 for a description of the full sample). The participants were screened for history of known cardiovascular, neurological, and psychiatric pathology, head trauma, alcohol and drug abuse, thyroid problems, and diabetes mellitus using a telephone interview and a mail-in questionnaire. In addition, all participants were screened for dementia and depression using a modified Blessed Information–Memory–Concentration Test (Blessed, Tomlinson, & Roth, 1968) and Geriatric Depression Questionnaire (Radloff, 1977), with cutoff scores of 30 and 15, respectively. All participants were strongly right-handed (75% and above on the Edinburgh Handedness Questionnaire: Oldfield, 1971).

Of the total sample ($N = 166$), 113 participants had a full set of neuroimaging and cognitive data. Their MRI scans were examined by an experienced neuroradiologist (J. D. Acker) for signs of space-occupying lesions and cerebrovascular abnormalities, and only the participants without evidence of possible cerebrovascular disease were retained in the sample. Clinical criteria—numerous punctate lesions, lacunar infarcts, significant unilateral concentration of white-matter hyperintensities—were used in the screening

procedure. Finally, we excluded participants who were taking blood pressure medication. Although people who control their hypertension with medication are probably no more prone to cerebrovascular disease than normotensive elderly (Fukuda & Kitani, 1995), some researchers have suggested that even mild age-related hypertension may exert differential negative effects on cognitive performance of the elderly participants (Boone, Miller, & Lesser, 1993; Elias, D'Agostino, Elias, & Wolf, 1995) and that anti-hypertensive medication may produce deficits in some neuropsychological functions (Waldstein, Manuck, Ryan, & Muldoon, 1991, but see Elias et al., 1995). Altogether, 18 participants were excluded: 9 on high blood pressure medications but with clinically normal scans, 5 normotensives with MRI evidence of cerebrovascular disease, and 4 with problems in both areas. Thus, the final sample consisted of 95 participants with mean age of 44.02 ± 16.35 years and mean formal education of 16.14 ± 2.73 years. The age range was 18–77 years and the distribution was approximately rectangular: Twenty-three participants were less than 30 years old, 27 fell between 31 and 45 years of age, 23 were in the 46–60 age bracket, and 22 were older than 60. The sample included 41 men (mean age: 42.98 ± 17.24; mean education: 16.38 ± 3.05 years) and 54 women (mean age: 44.82 ± 15.76; mean education: 15.96 ± 2.49 years). Sex differences in age and education were not significant, $t(93) = .54$ and .47, respectively, and educational attainment was unrelated to age ($r = .09$, *ns*).

MRI Protocol

Imaging was performed at the Diagnostic Imaging Center, Baptist Memorial Hospital, Memphis, Tennessee, on a 1.5T Signa scanner (General Electric Co., Milwaukee, WI). The protocol is described in greater detail in our previous publications (Raz, Torres, et al., 1995; Raz et al., 1997). All volumetric measures were performed on the reformatted images acquired using T_1-weighted 3-D spoiled gradient recalled acquisition sequence (SPGR, 124 contiguous axial slices, TE = 5 ms, and TR = 24 ms, FOV = 22 cm, acquisition matrix 256 × 192, slice thickness = 1.3 mm, and flip angle = 30°). For cerebrovascular diagnostic screening, we used a Fast Spin Echo sequence of interleaved T_2 and proton-density weighted axial images.

Reformatting and Alignment of MR Images

After acquisition, the SPGR images were transferred to the General Electric Independent Console and reformatted off-line to allow for correction of images for effects of head tilt, pitch, and rotation. Standard neuroanatomical landmarks were used to bring each brain into a unified system of coordinates and to correct the deviations in all three orthogonal planes. In this standard position, the sagittal plane cut through the middle of the interhemispheric fissure. The axial plane passed through the anterior–posterior commissure (incorporating the AC-PC line) and through the orbits, perpendicular to the sagittal plane. The coronal plane was leveled by the orbits and the auditory canals and passed perpendicular to the axial plane. Reformatted images were cut into sections 1.5 mm apart and saved on a VHS tape. The thickness of the reformatted slices was 0.86 mm (one linear pixel), and the voxel size was 1.11 mm^3.

Computerized Analysis of the MRI Scans

The MRI images were transferred to the VHS tape and digitized via a TARGA M-8 frame-grabber board (AT&T Corp., Murray Hill, NJ). A trained operator displayed each image on the video monitor screen with standard brightness and contrast and outlined the areas of interest (AOIs) using a digitizing tablet. The areas were computed using JAVA software (Jandel Scientific Co., San Rafael, CA), and the volumes of regions of interest (ROIs) were calculated by multiplying the AOI areas by the interslice distance and summing the products using the "basic volume estimate" (Uylings, van Eden, & Hoffman, 1986).

Delineation of the ROIs

Trained operators (blind to the participants' calendar age and sex) manually traced all ROIs. The set of slices containing each ROI was split, at random, into two equal groups, each to be traced by a different operator. In occasional regions of partial voluming, the operator interpolated the line between two clearly definable segments of the cortical border. We resolved all questionable cases by consulting the correlative and general brain atlases (DeArmond, Fusco, & Dewey, 1976; Duvernoy, 1988; Montemurro & Bruni, 1988; Nieuwenhuys, Voogd, & van Huijzen, 1988; Ono, Kubik, & Abernathey, 1990; Talairach & Tournoux, 1988). In identification and tracing of the ROIs, our objective was reliable, conservative sampling that included less than the totality of a given structure, while avoiding encroachment into other ROIs. All structures were measured separately for each hemisphere. Interrater reliability was assessed using the formula for two fixed raters (ICC(3): Shrout & Fleiss, 1979). For all ROIs the ICC (3) values exceeded .90. Because we have described the tracing rules in our previous publications (Raz, Torres et al., 1995; Raz et al., 1997), an abridged description is provided below.

Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) included superior, middle, and inferior frontal gyri and covered Brodmann areas 8, 9, 10, 45, and 46. The DLPFC was defined as the gray matter located between the most dorsomedial point of the cortex and the orbital sulcus, located rostrally to the genu of corpus callosum and posterior to about 40% of the distance between the frontal pole and the genu.

Orbito-Frontal Cortex

The volume of the orbito-frontal cortex (OFC) was estimated from the same slices as DLPFC, using the most lateral branch of the orbital sulcus as the lateral boundary and the olfactory sulcus as the medial boundary. The OFC included parts of Brodmann areas 11 and 47. Thus, OFC and DLPFC were complementary parts of an ROI labeled the prefrontal cortex (PFC).

Visual (Pericalcarine) Cortex

The volume of the visual (pericalcarine) cortex (VC) was estimated as the volume of the cortical ribbon lining the calcarine sulcus. This sulcus appeared as the most ventromedial sulcus in the temporal–occipital cortex at the coronal slice that is mid-vermis or immediately caudal to mid-vermis and was measured on the anterior 50% of the coronal slices between the mid-vermis slice and the occipital pole. The inferior and superior boundaries of this ROI were defined as the point at which the opening of the sulcus occurred. At this point a line was drawn horizontally so that no cortex (dorsal or ventral) outside of the calcarine sulcus was included. This ROI contained mainly the primary visual cortex (Brodmann area 17) and some of the secondary visual area (Brodmann area 18) as well.

Fusiform Gyrus

The fusiform gyrus (FG), which spans temporal and occipital lobes, was measured on successive coronal slices beginning with the level of the anterior commissure to the last slice on which the splenium of the corpus callosum was present. After that, the posterior fusiform gyrus range was determined as 33% of the distance between the occipital poles and the most anterior slice on which the splenium is no longer present. The FG as demarcated here covered Brodmann areas 37 and 19 (inferior part).

Inferior Parietal Lobule

The rostral–caudal range for estimate of the inferior parietal lobule (IPL) volume was defined as 65% of the distance between the posterior commissure to the slice caudal to the end of the splenium of the corpus callosum. The most superior branch of the lateral sulcus served as the inferior boundary. This ROI included mainly Brodmann area 40.

Parahippocampal Gyrus

Parahippocampal gyrus (PHG) volume was estimated from coronal sections beginning with the first slice on which the temporal stem became discernible up to the most caudal slice that showed the pulvinar. To discriminate the hippocampal formation and PHG, the subiculum was excluded from the PHG. This ROI included almost the entire entorhinal cortex (Brodmann area 28) as well as additional PHG area.

Hippocampal Formation

Hippocampal formation (HC) was measured on a series of coronal slices between the first slice showing the mammillary bodies and the one on which the fornices are seen rising from the fimbria. Care was taken not to include the amygdala in this ROI. We were unable to separate the hippocampus proper from the rest of the formation—we use the term hippocampus only as a matter of convenience.

Tasks and Procedures

The following cognitive tasks were administered to each participant individually in well-lit, quiet rooms. The order of task administration was allowed to vary across participants to accommodate their personal schedules.

Working Memory: Verbal

The participants performed two verbal WM tasks: Computation Span (CSPAN) and Listening Span (LSPAN) (Salthouse, Mitchell, Skovronek, & Babcock, 1990). Both measure the ability for simultaneous storage and processing of verbal information and are very similar in structure, administration procedure, and scoring. In CSPAN, the participant is asked to solve simple arithmetic problems while simultaneously remembering the last digit in each problem. In LSPAN, the participants listen to simple sentences. After each sentence, they are asked to answer a question about its content and to report its final word.

The first three trials of each WM task contain one item each. That is, the participant is presented with one arithmetic problem (CSPAN) or with one sentence (LSPAN). The additional groups of three trials contain one more item than the last: the second set contains two items, the third set contains three items, and so forth. Participants are administered blocks of three trials beginning with one item and progressing as high as seven items each. Regardless of the participant's performance, testing is stopped at seven items in each trial.

Three indexes of participants' performance on the WM tasks are computed: Simple Span (SS), Absolute Span (AS), and Total Span (TS). To get an item correct, the participant must solve the arithmetic problem (CSPAN) or answer the question correctly (LSPAN) and correctly identify the final number (CSPAN) or the final word (LSPAN). To get a trial correct, the participant must get all items correct within that trial. The SS is computed on each block of three trials (with the same number of items). If a participant's response is correct on two or three of the trials, one point is assigned. If the participant is correct on only one out of three trials, the score is 0.5 points. Once the participant misses two out of the three trials in the same block, the scoring of SS is discontinued. The AS is calculated by summing the number of correct items across all trials. To have the number of items added to their total, the participant must get all items in that trial correct. The TS is scored as the total number of items that a participant gets correct. These items are scored even if the participant misses other items within that trial. In this study, we opted for the AS as an index of WM performance because of its superior psychometric properties (Engle, Cantor, & Carullo, 1992). The SS produces too narrow a range to make it useful for correlational analyses, and the TS score (especially for CSPAN) may be prone to capitalization on chance because it counts single successful items scored on the trials even when the participant fails the remainder.

Working Memory: Nonverbal

This construct was measured by two tests. The first, size judgment span, was modified after Cherry and Park's (1993) version. Participants were read aloud lists of objects and animals and asked to repeat each list with the objects arranged in order of their size from the smallest item to the largest. The first list was two items long (e.g., violin, ship). After successful completion of at least two of three trials, the list was incremented by one item. The cumulative number of correct trials constituted the score on this test.

The second task used to measure nonverbal WM was the spatial relations test (#19) from the Woodcock–Johnson Psychoeducational Battery—Revised (Woodcock & Johnson, 1989). In this task, participants are shown a whole shape and are required to choose a correct combination of components from a series of six disjointed shapes presented on the same board. The item difficulty increases across trials as the shapes become complex and abstract. The total number of correct responses is the score on this task. Although designated as a test of "spatial abilities," the task exerts considerable demands on WM as the participant is required to mentally assemble the correct shape from its parts and to manipulate (rotate and translate) some of the components to the positions that would allow the assembly operation. Correlations between similar spatial tasks and measures of visual–spatial WM are quite high (Shah & Miyake, 1996), and analogous tasks have been used for assessment of visual–spatial WM in young and older adults (Kirasic, Allen, Dobson, & Binder, 1996). The reliability of this test is $r = .82$ (Woodcock & Mather, 1989).

Explicit Memory: Verbal

Memory for names. This auditory–visual paired-associates task is a subtest (#1) from the Woodcock–Johnson Psychoeduca-

tional Battery—Revised (Woodcock & Johnson, 1989). At the acquisition phase, the participants learn to associate a picture of an imaginary "space creature" with the creature's name. At the test phase, the participants are shown a picture of a target creature and an array of nine additional creatures. They are asked to point to the picture of a creature that has just been presented as well as to all previously presented creatures. The participants also are asked to name the creatures to which they have pointed. If a participant makes an error, the examiner provides the correct response. The level of difficulty increases progressively as the participant is required to remember the names of more space creatures. The score is the total number of correct responses, and the reliability of this test is $r = .91$ (Woodcock & Mather, 1989).

Paired-associates learning (PAL). This is a subtest from the Wechsler Memory Scale—Revised (Wechsler, 1987). In each trial of the exposure phase, participants hear the same eight pairs of words (four pairs with high association value and four pairs with low association value). During the test phase they are read the first word of each pair and asked to provide the second word. The index of performance is the total number correct in the first three trials. The participants who fail on the third trial are administered additional trials until all eight items are completed correctly or until a total of six trials has been given. The test–retest reliability of immediate PAL is .60.

Logical memory (LM). This is a subtest from the Wechsler Memory Scale—Revised (Wechsler, 1987). At the acquisition phase, the participants hear a short story. Immediately afterward, they are asked to repeat as much of the story as they remember. This procedure is repeated with a second short story. The score is the number of correct pieces of information recalled from both stories. The test–retest reliability of this test is .74.

Memory for Names (MFN), LM, and PAL–delayed. These are the same tasks readministered after a half-hour delay. At the initial study stage of the LM and PAL the participants are warned that the delayed test would be administered, whereas no such warning is given at the initial MFN administration. The reliabilities of the delayed memory indexes were .91 for MFN, .75 for LM, and .41 for PAL.

California Verbal Learning Test. In the California Verbal Learning Test (CVLT, The Psychological Corporation, San Antonio, Texas), the participant hears a list of grocery items five times. After each presentation the participant is asked to recall as many words as possible, regardless of order. Although the list contains 16 words that are evenly distributed across four categories, participants are not told that the words can be categorized. A second list of grocery items is presented after the fifth presentation of the initial list, and the participant is immediately asked to recall these items. Next, the participant is asked to recall the items from the first list. After that, a cued recall test is administered: The participant is asked to recall all the items that fall into a particular category. These two tests provide the indices of short-delay free and cued recall. After a 20-min delay the participants are administered free recall, cued recall, and a yes–no recognition test of the first list.

The computer-assisted scoring of CVLT produces a number of indices. In addition to the short-delay free and cued recall of List A Trials 1–5, List A Trial 1 and 5, and immediate recall of List B, and recognition of List A, the measures of ability to organize the material by chunking and categorization, and resistance to intrusions are provided. Most of these indices are highly correlated, some (especially difference scores) have limited reliability, and some are geared to clinical assessment of individuals more than toward correlational analyses. In this study, we used List A delayed free recall as one of the explicit memory measures. Split-half reliability of this index is .92 (Delis, Kramer, Kaplan, & Ober, 1987).

Explicit Memory: Nonverbal

Buildings Memory Test (MV-2). This paper-and-pencil test from ETS Factor-Referenced Test Kit (Ekstrom, French, Harman, & Dermen, 1976) is administered in two stages. First, the participants are shown a map of a fictitious urban location with landmark buildings on it. After studying the map for 4 min, they are shown a blank map and asked to pick the landmarks from a menu and to locate them on the map. Test–retest reliability of this test is .80 (Ekstrom et al., 1976).

Line Patterns Recognition Test. This test was a part of a priming task (see Priming section below). Stimuli were selected from 350 line patterns generated using a procedure modified from Musen and Treisman (1990). Each pattern consisted of five lines and was generated by connecting points on a 3 × 3 dot matrix according to five pseudorandom numbers. Pattern repetitions and simple rotations were eliminated. Participants' task was to view the patterns briefly exposed on a computer screen and to reproduce them on a 9-point grid printed on a paper sheet. Exposure duration for each participant was determined before the study phase using an adaptive staircase procedure. In a sample of 100 patterns that were not used in the main experiment, we determined for each participant the stimulus onset asynchrony (SOA) at which about 50% of the patterns could be reproduced. The initial pattern was exposed for 700 ms, and exposure duration was increased by 50 ms after inaccurate responses and decreased by 50 ms after each accurate drawing. A reversal was an inaccurate drawing followed by an accurate drawing. Participants performed this task until 10 reversals occurred. The SOA for each participant was the median stimulus duration time at which these reversals occurred. Participants completed a multiple-choice vocabulary test as a 5-min distractor task immediately after threshold determination.

During the study phase trials, a fixation point appeared in the middle of the screen, followed by a pattern for 3 s and then a 7-s interval during which the screen was blank. Participants were asked to decide whether or not each pattern was symmetrical. Participants then completed another 5-min distractor task (Digit Span from the Wechsler Adult Intelligence Scale—Revised; Wechsler, 1981).

Next, the implicit memory task was performed. Each studied pattern was presented one at a time on the screen for the SOA determined in the threshold task. Fifty distractor patterns were also presented, randomly intermixed with the studied patterns. Participants were asked to draw each pattern that appeared on the screen and then were asked to press any key to go on to the next item. A priming score was computed by subtracting the proportion of accurately drawn patterns that were not studied from the proportion of accurately reproduced studied patterns. Immediately after the priming task, participants completed another 5-min distractor task (a multiple-choice vocabulary test).

Explicit memory was then measured in a four-alternative forced-choice recognition task. On each trial of that task one studied pattern was presented on the screen with three distractors. Participants were asked to choose which one of the four patterns they had seen during the study phase. The explicit memory score was the proportion of studied line patterns accurately identified (hit rate).

Repetition Priming: Verbal

Word-stem completion. In the study phase, the participant is presented with words on a computer screen and asked to count aloud the number of vowels in each word. One target word was chosen for each of the 40 three-letter word stems in the Graf and Williams (1987) norms. The selected target words had been used to complete stems an average of 12.2% ($SD = 4.3\%$) of the time for

each stem. A list of 20 low-frequency words (median frequency = 12 per million; Kučera & Francis, 1967) was selected. The study stimuli were five to eight letters long ($M = 5.9$, $SD = .86$), and were never the most frequent completion for their respective stem. The test stimuli were three-letter stems from the original master list of 40 words. After an approximately 5-min delay filled by a distractor task (CFIT 2A-Test 1; Cattell & Cattell, 1973), the participant is presented with a list of stems and asked to say aloud the first word that comes to mind and begins with the presented three letters. The differences between the proportion of stems completed to words presented at the study stage and the proportion of baseline words was the priming score. After a 3- to 4-min break, the participants were administered an explicit, cued-recall test. They were again presented with the first three letters of a word. However, this time they were asked to complete the stems with the words previously seen during the vowel-counting phase. The last phase of the word-stem completion task consists of free recall of the words. For both cued- and free-recall tests, the proportion of correct responses served as the performance indexes.

Category exemplars priming. During the study phase of this task, the participants are presented with a descriptive phrase containing only the first letter of the last word (e.g., "violets are b..."). The participants are asked to complete the last word of the phrase. The materials consisted of 20 target exemplars of semantic categories selected from Howard (1980) and McEvoy and Nelson (1982) and normed on 100 undergraduates. Exemplar targets were selected by the norming sample an average of 8.2% of the time ($SD = 6.1\%$) for each category and represented 1 of an average of 8.1 ($SD = 3.5$) alternative responses per category. If the participant made an error or did not respond, the correct answer was provided. After a 5-min delay filled by a distractor task (CFIT 3A-Test 2; Cattell & Cattell, 1973), the participant is presented with a name of a category (e.g., colors) and asked to provide the first exemplar of that category that comes to mind. The priming score is the proportion of old exemplars minus the proportion of the new exemplars provided for each category. After the priming test, the participants perform a cued-recall (explicit) test. They are again presented with category labels, but this time they are asked specifically to give the exemplar of the category that was presented during the study phase. Finally, participants are asked to recall all the exemplars presented at the study phase. For both cued- and free-recall tests, the index of performance is the proportion of correct responses (hit rate).

Repetition Priming: Nonverbal

The Line Patterns Priming task is described above in the *Explicit Memory: Nonverbal* section.

Executive Functions Task

The computerized version of the Wisconsin Card Sorting Test (WCST, Neuroscan Corp., Herndon, VA) was administered. On the WCST, the participant's task is to sort cards with geometric designs into categories by the shape, color, or number of the designs that appear on the cards. The participants are asked to match a card that appeared in the lower right corner of the computer screen with one of the four cards displayed at the top of the screen. The participants are told that the feedback about the correctness of their decision would be provided by the computer, but that the examiner could not provide them with additional information about performance on the task.

The WCST provides a number of indices intended to measure executive functions: the total number of errors, the number of perseverative errors, the number of perseverative responses, the number of categories attained, and the learning-to-learn index (Heaton, Chelune, Talley, Kay, & Curtis, 1993). For the purposes of assessing the construct of strategic flexibility, we used only the number of perseverative responses and perseverative errors. Although believed to be useful in individual clinical assessment, the other listed indices are highly intercorrelated, and only the first four of them have acceptable reliability. The long-term test–retest reliability estimates for perseverative responses range between .24 and .90, with a median of .75 (Paolo, Axelrod, & Tröster, 1996; Pennington, Bennetto, McAleer, & Roberts, 1996).

A perseverative response was counted as a response that was incorrect according to the current rule but would have been correct using the rule valid for the previous set. However, a response could also be classified as an ambiguous response if it matched the stimulus card on more than one dimension. If an ambiguous response was correct but occurred within a series of unambiguous perseverative responses and matched the principle on which these unambiguous perseverations were made, it was counted as a perseverative response. Thus, strictly speaking, not all perseverative responses are incorrect. A perseverative error was counted as a perseverative response that was also incorrect.

Results

The pattern of correlations among the regional cortical volumes and age (Table 1) was similar to that observed in the larger sample (Raz et al., 1997): the volume of the PFC was significantly more affected by aging than the volumes of the other ROIs (Steiger's $Z^* = 1.68$, $p < .05$, one-tailed, for the closest correlation).

No sex differences in cognitive performance were observed, with the exception of the spatial relations test on which men performed somewhat better than women, $t(93) = 2.24$, $p < .05$. When the number of comparisons is taken into account, even this difference was not significant. Thus, sex was not entered as an independent variable into the analyses. The correlations between cognitive variables and age (Table 2) followed the expected pattern, with the executive functions and explicit memory showing stronger negative relations to age than the priming tests. However, the magnitude of age effect on memory was somewhat lower than that reported in the literature.

Data Conditioning and Analyses

The multiple dissociation hypotheses formulated in this study were tested in the framework of path analysis, which is a system of hierarchically nested systems of linear regression models with an increasing number of restrictions on association between the variables.

As in any study addressing multiple relationships between brain and behavioral constructs, the large number of interrelated cognitive variables in this study presents a number of problems: inflation of Type I error, multicollinearity, and imperfect reliability. Bearing in mind these potential pitfalls, we reduced the data by creating composite scores to represent theoretically defined cognitive domains. All variables appearing in Table 2 were included in this analysis except for the explicit memory indices derived from the

Table 1
Descriptive Statistics for Cortical Region-of-Interest Volumes and Age, and Correlations Among Them

Regions of interest	Age	PFC	FG	HC	PHG	IPL	VC
Prefrontal cortex (PFC)	−.46***	—					
Fusiform gyrus (FG)	−.30**	.40***	—				
Hippocampus (HC)	−.24*	.44***	.32***	—			
Parahippocampal gyrus (PHG)	−.01	.17	.33***	.18	—		
Inferior parietal lobule (IPL)	−.15	.11	.37***	.20*	.11	—	
Visual (pericalcarine) cortex (VC)	−.26**	.28**	.25*	.32***	.01	.17	—
M	43.99	24.65	14.66	5.28	4.51	8.12	4.31
SD	16.63	3.64	1.73	0.63	0.52	1.59	1.03

Note. $N = 95$. All volume measures are in cm^3. Correlations ≥.20, .26, and .32 are significant at $ps < .05$, .01, and .001, respectively.
*$p < .05$. **$p < .01$. ***$p < .001$.

verbal priming tasks and the nonverbal priming index derived from the line-pattern priming task. Explicit memory indices derived from the verbal priming tasks were not delayed-recall measures. In addition, they correlated with the priming scores obtained from the same tasks. These correlations ranged from $r = .37$ between free recall of stems and stem completion category free recall and category priming score to $r = .61$ between cued recall of stems and stem completion, with the median $r = .46$, $p < .001$. The nonverbal priming index could not be included in the analysis because no consistent priming was observed on the line-pattern priming task. The mean score of 0.001 ($SD = .08$) and a zero correlation with age leave room for little systematic variation in the line-pattern priming scores and render this index uninformative. Because of a considerable skew in the distribution of the perseverative errors and responses on WCST (skewness >1.6 and kurtosis >2.5 for both scores), log-transformed values were used in all subsequent analyses.

Although the main impetus for assigning specific variables to specific composites was theoretical, we attempted to substantiate our composite indices formally through a principal-factors analysis. In this analysis, the goal of data reduction is accomplished by creating a set of linear combinations

Table 2
Descriptive Statistics for Cognitive Measures and Their Correlations With Age

Variable	*M*	*SD*	*r* (age)
WCST total errors	37.33	23.66	.47
WCST perseverative errors	19.52	16.28	.40
WCST perseverative responses	22.45	20.36	.40
WCST nonperseverative responses	17.81	12.05	.38
WCST categories attained	4.36	2.03	−.49
CVLT cued recall—short delay	13.43	2.35	−.26
CVLT free recall—short delay	12.77	2.50	−.21
CVLT cued recall—long delay	13.58	2.18	−.24
CVLT free recall—long delay	13.14	2.47	−.27
WMS–R, paired-associates learning, immediate	20.13	3.02	−.40
WMS–R, paired-associates learning, delayed	7.48	0.87	−.25
WJ memory for names, immediate	56.43	12.13	−.27
WJ memory for names, delayed	25.59	9.07	−.39
WMS–R, logical memory, immediate	30.53	5.69	−.29
WMS–R, logical memory, delayed	26.97	6.31	−.28
Buildings memory (MV-2)	8.53	3.05	−.39
Computation span, absolute	18.04	11.75	−.31
Listening span, absolute	28.03	13.35	−.37
Size judgment span	9.79	1.77	−.25
WJ spatial relations	26.51	4.18	−.31
Line-pattern recognition (hit rate)	0.37	0.09	−.27
Line-pattern priming	0.00	0.81	−.00
Word-stem completion	0.29	0.15	−.12
Cued recall, word-stem study list (hit rate)	0.45	0.14	−.21
Free recall, word-stem study list (hit rate)	0.17	0.15	−.41
Category exemplars priming	0.16	0.13	−.03
Cued recall, category study list (hit rate)	0.49	0.24	−.39
Free recall, category study list (hit rate)	0.28	0.16	−.37

Note. WCST = Wisconsin Card Sorting Test; CVLT = California Verbal Learning Test; WMS–R = Wechsler Memory Scale—Revised; WJ = Woodcock–Johnson Psychoeducational Battery. $N = 95$. Correlations ≥.20, .26, and .32 are significant at $ps < .05$, .01, and .001, respectively.

of original variables that capture the variance of the original set. These linear combinations (principal components) contain variables that correlate highly among themselves but not with the members of other components. The components can be rotated, that is, fitted with new weights or coefficients that alter the relationship among the factors according to a prescribed rule. For example, rotating the components under the varimax criterion amounts to maximizing the variance between them and minimizing the variance within each combination of variables. The intent of this procedure is to create the uncorrelated linear combinations of variables called factors. Because the number of factors is smaller than the number of variables, the data reduction goal is accomplished. The closer the variance explained by the factors is to the total variance of the original set, the more faithfully the reduced data set reflects the original one.

We used standard factor-analytic procedures, retaining the components with eigenvalues greater than 1 and rotating them using the varimax criterion. The resulting system of principal factors accounted for 69% of the variance in the original data set, which is a reasonable approximation. The factors were readily interpretable, and descriptive labels were assigned to each of them. This analysis replicated a common pattern observed in normal as well as pathological samples, that is, dissociation between executive functions as measured by the WCST and memory (e.g., Paolo, Tröster, Axelrod, & Koller, 1995; Sullivan et al., 1993). Some overlap between the factors was apparent, with explicit memory factors (verbal and nonverbal) sharing a significant amount of variance with WM factor. The factor loadings (correlations between the original variables and the composite scores) are presented in Table 3.

Based on the results of the factor analysis and the theoretical considerations, five composite cognitive indices were created by summation of the standardized scores of the variables that loaded on each component as shown in Table 3. Because the correlations between two verbal and two nonverbal WM tests were only moderate (*r*s ranging between .31 and .44) and because of the theoretical distinction between the two groups of tests, they were separated into two composites, in spite of loading on the same factors. The same reasoning was applied to the spatial relations test, which loaded on both WM and explicit memory factors.

As a result of the data reduction process, six cognitive indices were created: failure of flexibility or perseveration (Persev), which was a sum of standard scores of log-transformed counts of perseverative errors and perseverative responses; verbal explicit memory (Exp_v), which included delayed-recall indices of paired-associates learning, logical memory, and face–name association learning, and CVLT long-delay cued and free recall; nonverbal explicit memory (Exp_{nv}), which was a sum of line-pattern recognition and buildings memory test scores; priming, which was a sum of stem completion and category completion priming scores; verbal WM (WM_v), which was a combination of CSPAN and LSPAN absolute scores; and nonverbal WM (WM_{nv}), which was computed from standardized scores on the spatial relations test and the size judgment test.

In testing multivariate models, it is advisable to reduce the number of the variables to about 1:10 variable per observation for better stability of the estimates and lesser capitalization on chance (Pedhazur, 1982). To adhere to this criterion, we decided to forgo testing hypotheses about hemispheric differences and combined both hemispheres and some ROI volumes into composite regions. Thus, HC and PHG volumes were combined to form a limbic ROI, and VC was combined with FG to form a visual ROI, and DLPFC was summed with OFC to form the prefrontal cortex (PFC) region. In addition, on the basis of theoretical considerations, we decided to create the brain region composites according to which members of the composites play similar roles in the targeted cognitive processes, as explained in the

Table 3
Principal-Factors Analysis of Cognitive Measures

Variable	F1: Explicit, verbal	F2: Explicit, nonverbal	F2: Working memory	F3: Executive	F4: Priming
CVLT—Free recall, long delay	.92				
CVLT—Cued recall, long delay	.91				
WMS–R, logical memory, delayed	.48				
WJ memory for names, delayed	.47		.46		
WMS–R, paired associates, delayed	.45	.47			
Building memory (MV-2)		.66			
Line-pattern recognition		.79			
Computation span			.85		
Listening span			.76		
WJ spatial relations		.64	.46		
Size judgment span			.56		
WCST, perseverative responses				.96	
WCST, perseverative errors				.95	
Category priming					.79
Word-stem completion					.75
Percentage of variance accounted	17.60	13.41	14.98	13.55	9.84

Note. CVLT = California Verbal Learning Test; WMS–R = Wechsler Memory Scale—Revised; WJ = Woodcock-Johnson Psychoeducational Battery; WCST = Wisconsin Card Sorting Test. $N = 95$, varimax rotation. Only loadings greater than .40 are shown. Total variance explained by components with eigenvalues greater than 1 is 69%.

introduction of this article. All brain volumes were adjusted for height in order to compensate for body-size differences between the sexes. The adjustment was performed using the weights from linear regressions of each ROI volume on height. Zero-order correlations among the composite variables and age are presented in Table 4.

Path Analysis

A complex pattern of correlations among brain and cognitive variables presented in Table 4 cannot be interpreted without taking into account their mutual influence. To that objective, we used a classical path analysis approach (Pedhazur, 1982). In path analysis, a series of hierarchical linear models is constructed by imposing a progressively larger number of restrictions on allowed effects. Such an approach postulates unidirectional flow of the variance within the hierarchy of the variables: Downstream variables can cause or affect the upstream variables, but not vice versa. Restrictions on the model are imposed by setting specific intervariable paths to zero, thus assuming that there is no relationship between the given pairs of variables. In constructing the models, we were guided by considerations of parsimony and theoretical interpretability.

The theoretical considerations guided the construction of the hierarchy within the models. Age was presumed to be measured without error and not influenced by any of the downstream variables. Brain volumes that formed the second tier in the path model could be affected by age, but not by the cognitive indices. Working memory (verbal and nonverbal) was relegated to the next tier, under the assumption that age and brain changes could affect these variables, but in relation to the other cognitive indexes their role was that of relatively primitive precursors. Finally, the indices of explicit memory, priming, and failure of flexibility (perseveration) formed the fourth tier of the model. The assumption was that these variables represented the most complex cognitive functions potentially influenced by all of the other variables but not exerting any reciprocal effects on them. Under the parsimony criterion we searched for the smallest number of variables and effects to account for the observed data.

The full model, against which the first reduced model was tested, postulated (rather unrealistically) that all brain variables affected all cognitive variables, with age affecting all variables in the model. The first reduced model was created by imposing 12 restrictions on the full model by turning respective paths to zero. This model reflected the hypotheses formulated in the introduction to this study. Within the path-analytical framework, we were able to test the multiple-dissociation hypotheses proposed in the introduction of this article. The hypothesized significant relations would be indicated by significant path coefficients, which are equivalent to standardized regression coefficients for regression equations containing upstream variables as predictors of the downstream variables. Thus, the dissociation between pairs of variables is expressed in the pattern of significance of the respective path coefficients. In addition to the hypotheses stated a priori, after inspection of the zero-order correlations,

Table 4
Zero-Order Correlations Among Composite Cognitive Indexes, Combined Regions of Interest (Adjusted for Height), and Age

Variable	Age	WCST	ExpV	ExpNV	PrimV	WMv	WMnv	PFC	Limbic	Visual
WCST composite (perseveration)	.44***	—								
Explicit memory, verbal (ExpV)	−.39***	−.49***	—							
Explicit memory, nonverbal (ExpNV)	−.38***	−.26**	−.47***	—						
Priming, verbal (PrimV)	−.10	−.13	.15	.07	—					
Working memory, verbal (WMv)	−.39***	−.36***	.44***	.27**	.26**	—				
Working memory, nonverbal (WMnv)	−.35***	−.33***	.52***	.48***	.13	.48***	—			
Prefrontal cortex (PFC)	−.51***	−.42***	.17	.20*	−.04	.27**	.29**	—		
Limbic cortex	−.18	−.23*	.13	.14	.01	.21*	.21*	.47***	—	
Visual cortices	−.35***	−.29**	.08	.21*	−.09	.11	.33***	.45***	.43***	—
Inferior parietal lobule	−.15	.01	−.01	.04	−.02	.20*	.11	.08	.17	.34***

Note. WCST = Wisconsin Card Sorting Test. $N = 95$.
*$p < .05$. **$p < .01$. ***$p < .001$.

we decided to test an ad hoc hypothesis that verbal WM affects priming performance.

In the reduced Model I (Figure 1A), 12 paths were set to zero; this model explained the data just as well as the full model, as indicated by the goodness-of-fit index, $\chi^2(12) = 6.08$, *ns*. This model was reduced by imposing 13 additional restrictions as illustrated in Figure 1B. The reduced Model I (Figure 1B) fit the data as well as the reduced Model I $\chi^2(13) = 13.64$, *ns*. Thus, the effects of all brain variables o verbal WM, explicit memory, and priming were nil. Change in the volume of the limbic and inferior parietal cortice were not associated with age differences in any of th

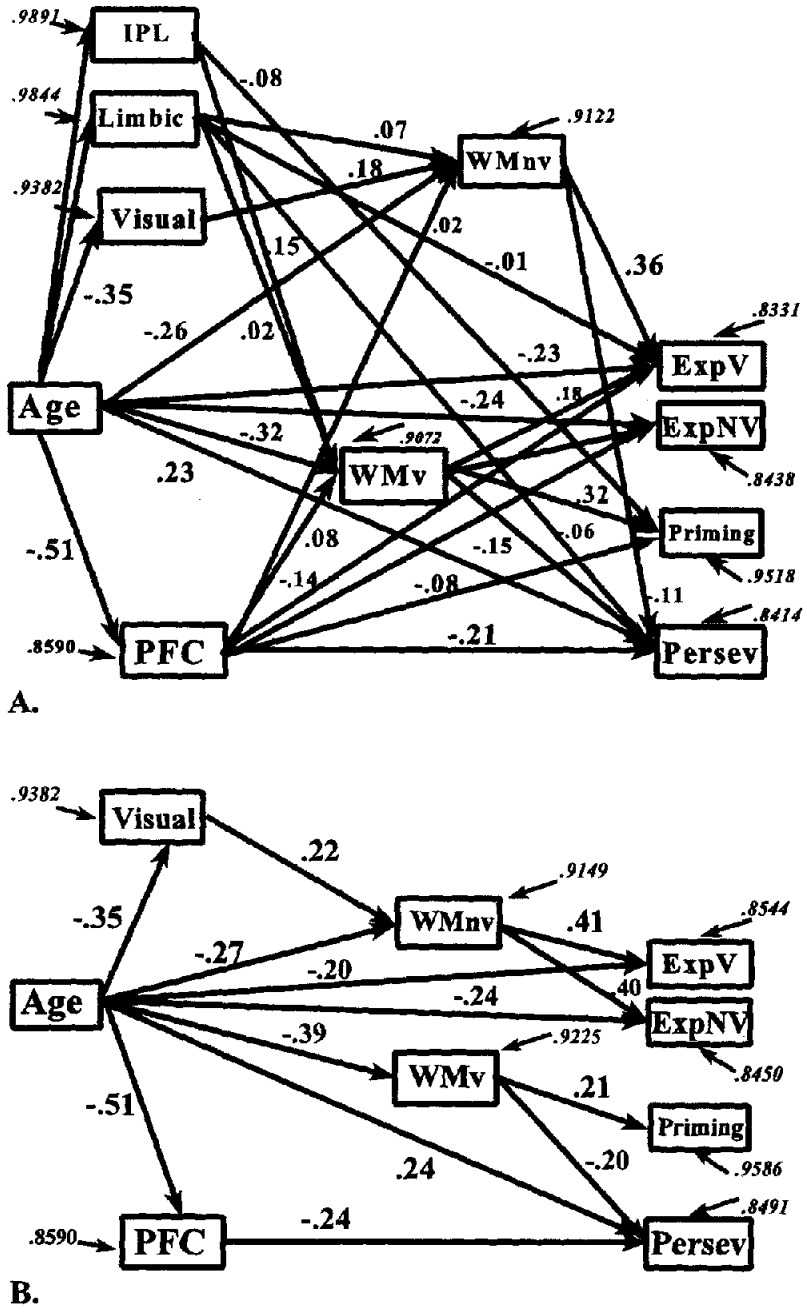


Figure 1. Path analysis of associations between region-of-interest volume and cognitive measures. The numbers on the paths are standardized path coefficients; the numbers at the boxes are residuals. A: Reduced Model I. Only the paths consistent with the hypothesized relations are indicated. B: Reduced Model III. Only statistically significant paths were retained. This model is accepted as the best fit to the data. IPL = inferior partial lobule; WMnv = working memory, nonverbal; WMv = working memory, verbal; ExpV = explicit memory, verbal; ExpNV = explicit memory, nonverbal; PFC = prefrontal cortex; Persev = perseveration.

cognitive variables and were completely removed from the model.

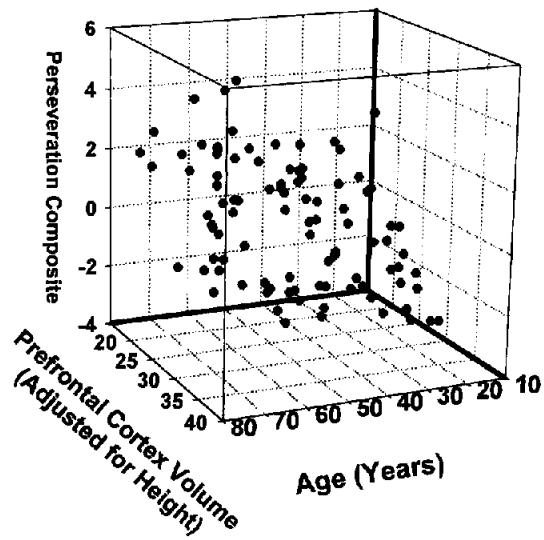
The next step was to test Model II against two models with one additional restriction each. In the reduced Model IIIa, the significance of the effect of the PFC volume on perseveration was tested. Removal of this path resulted in a significant worsening of the fit, $\chi^2(1) = 10.25$, $p < .001$. The path was retained in the model and the next (parallel, not hierarchically nested) Model IIIb tested the effect of visual cortices on nonverbal WM. Removal of that path also resulted in reduction of goodness of fit, $\chi^2(1) = 4.58$, $p < .05$. Thus the model depicted in Figure 1B was accepted as the best-fit solution for the present data set.

This final model reveals a double dissociation between two pairs of variables: PFC–perseveration and visual cortex–WM_{nv}. The trivariate scatter plots presented in Figure 2 show that the observed associations between perseveration and PFC and WM_{nv} and visual cortex were not due to the influence of a small number of outliers. The plots show moderately strong linear relationships among age, respective brain regions, and cognitive indices.

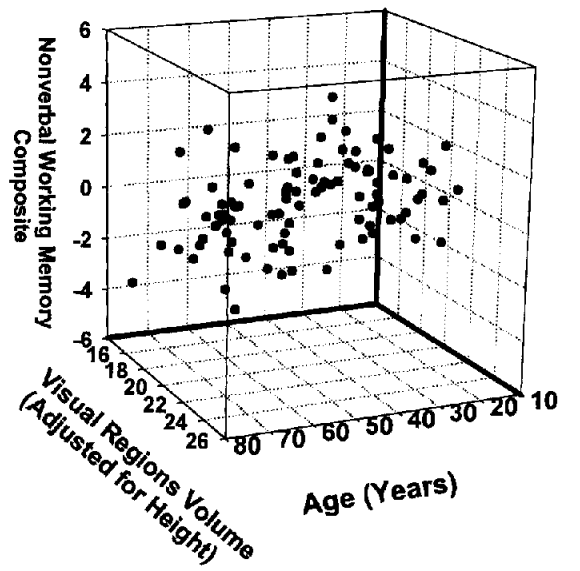
Follow-Up Analyses

In the final model (Figure 1), a failure of flexibility (perseveration), was predicted by age and age-related changes in the PFC volume. A question may arise as to whether this link is specific to perseveration or if perhaps any index of deficit on WCST would show the same pattern. To test this hypothesis, we substituted in the final model the perseveration composite with the number of nonperseverative responses, and two simultaneous regressions of these measures on age and PFC volume adjusted for height were compared. The results of this analysis reveal that although both measures were significantly predicted by the selected linear combination ($R^2 = .15$ for nonperseverative and $R^2 = .25$ for perseverative errors, the difference test $Z^* = 1.32$, *ns*), the adjusted effects of age and PFC volume were considerably different. In the regression equation for nonperseverative errors, only the standardized weight associated with age was significant, $\beta = .34$, $t(92) = 3.00$, $p < .005$, with PFC volume showing no reliable effect, $\beta = -0.08$, $t(92) = -0.64$, *ns*. In the equation for perseverative errors, the effects of both age and PFC volume were significant: $\beta = .31$, $t(92) = 2.94$, $p < .005$ for age and $\beta = -.26$, $t(92) = 2.46$, $p < .02$ for the PFC.

To examine the possibility that among the oldest participants who scored low on the memory composite, hippocampal volume was a meaningful predictor of mnemonic performance, we computed correlations between height-adjusted hippocampal volume and explicit memory composites in a subsample of older participants (age = 60–77, $n = 22$). In this subsample, the correlations between the limbic cortex volume and explicit memory indices were .44 ($p < .05$) for the verbal and .66 ($p < .001$) for the nonverbal composite, respectively. Notably, the association between age and limbic volume in this small sample with a restricted age range was stronger than in the full sample, $r = .42$, $p < .05$. This relationship between the limbic volume



A.



B.

Figure 2. Trivariate scatter plots of age, brain regional volumes (adjusted for height), and cognitive indexes. A: Age, prefrontal gray matter, and Wisconsin Card Sorting Test perseveration composite. B: Age, visual cortices, and nonverbal working memory composite.

(adjusted for height), age, and explicit memory is illustrated in a trivariate scatter plot of the total sample in Figure 3.

We also examined the significant structural–cognitive paths of the final model for hemispheric differences and found none. For both parts of the double dissociation between visual cortex–nonverbal WM and prefrontal cortex–

perseveration, there was not even a trend toward a difference between the hemispheres.

In the final model, nonverbal WM exercised direct effects on both indices of explicit memory. We examined whether verbal WM, correlated with its nonverbal counterpart, could be a significant influence as well. To this end we regressed each explicit memory index on age and on each of the WM measures. This subsidiary analysis shows that, with age controlled, the effect of verbal WM on verbal explicit memory ($\beta = .31$, $p < .005$) was comparable to, albeit somewhat smaller than, that of the nonverbal WM ($\beta = .41$, $p < .001$). In contrast, nonverbal WM was associated with nonverbal explicit memory ($\beta = .40$, $p < .001$) but not with its verbal counterpart ($\beta = .14$, *ns*).

Discussion

In this study, we examined the neuroanatomical substrates of cognitive aging. We demonstrated a hypothesized double dissociation between two cognitive functions (nonverbal WM and strategic flexibility) and their brain substrates—visual and prefrontal cortices. Although we observed several significant associations among the cognitive measures, no other hypothesized dissociations between brain–cognition relationships were confirmed.

Executive Function—Strategic Flexibility

Our findings replicate a well-known observation that the likelihood of perseveration increases with age. The new result is that this deficit is mediated by age-related shrinkage of the PFC. This is the first direct evidence of such a relationship in healthy participants, and it bolsters the belief that executive function deficits are not disease-related artifacts but are part and parcel of the normal aging process.

The generalizability of this finding is limited by its dependence on a single executive function sometimes labeled "reactive flexibility" (Eslinger & Grattan, 1993). Although there is little doubt that age is associated with declines in this function, it is also possible that other aspects of a complex cognitive task (WCST) are adversely affected by aging (Hartman, Bolton, & Sweeny, 1996) and that other aspects of flexibility may be differentially affected by regional brain changes (Eslinger & Grattan, 1993). In accord with Hartman et al. (1996), but in contrast to other reports (e.g., Lehto, 1996), we observed significant direct effects of WM on perseverative behavior. It is notable that in spite of the fact that WCST stimuli are visual–spatial, the observed association was with the verbal WM, not its nonverbal counterpart. It is unclear whether this represents a meaningful distinction. It is possible, however, that individuals with weaker WM skills could have been at a disadvantage on a task that calls for maintaining verbal instructions and strategies on-line while performing an ostensibly visual–spatial task. As the follow-up analysis shows, the link between perseveration and PFC volume is not just another expression of general age-related cognitive decline, but a specific association between shrinkage of a specific brain region and a specific cognitive function. Even though

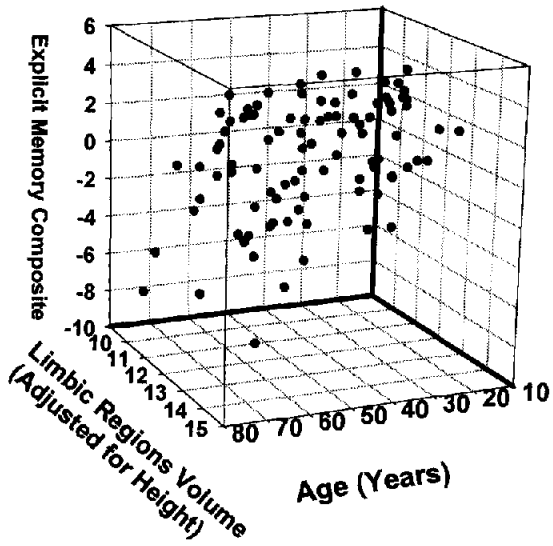


Figure 3. A trivariate scatter plot of age, limbic regions volume (adjusted for height), and explicit memory composite.

performance on WCST is influenced by a number of cognitive processes, and WCST may be problematic as a measure of executive functions (Pennington et al., 1996), we observed an independent specific association between PFC volume and perseveration despite the seemingly "noisy" measures. Future research may shed more light on the nature of age-related increases in perseveration by refining the measures and taking into account the aspects of the task that were not addressed in this article. For example, temporal memory deficit may prevent older participants from keeping track of their responses to previous stimuli, thus inducing perseverative responses (Hartman et al., 1996). This hypothesis is especially plausible because the elderly show declines in memory for temporal order of activities (Spencer & Raz, 1994), and temporal memory is impaired in patients with frontal lesions and Parkinson's disease (Sagar, Sullivan, Gabrieli, Corkin, & Crowdon, 1988; Shimamura, Janowsky, & Squire, 1990).

Working Memory

A complex picture of structure–function relationship emerges from our analysis of effects of age and regional differences in brain volume on WM. Although direct effects of age on verbal and nonverbal WM were comparable (in accord with the literature, e.g., Salthouse, 1995), we observed a specific link between localized age-related differences in brain volume and nonverbal WM. Age-related shrinkage of the cortical regions associated with visual processing predicted decline in performance on the nonverbal WM tasks. Mild shrinkage of the primary VCs and somewhat greater reduction in the volume of the FG adversely affect performance on the tasks that depend on an individual's ability to generate and manipulate mental images. These findings are in agreement with recent reports of age-related reduction in regional blood flow within visual association cortices during processing of verbal and figural

stimuli (Grady et al., 1995; Madden et al., 1996), covert naming of visually presented stimuli (Smith, Andersen, et al., 1996), and encoding of highly imageable words (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1996). However, contrary to the prediction based on current theories, we found no direct effects of the PFC volume on either of the WM composites.

Specificity of the role played by the PFC in WM has been questioned in the past (Cohen et al., 1994), and it is possible that prefrontal activation observed on many WM tasks stems from an increase in general mental effort and allocation of attention. Indeed, a recent study indicates that only when two tasks are combined in a dual-task paradigm does the PFC exhibit a significant activation, whereas single WM tasks—semantic or spatial—activate modality-specific secondary cortices (D'Esposito et al., 1995). When the blood oxygenation patterns during the delayed-response WM task are examined in the whole brain, both dorsolateral PFC and posterior parietal cortex (areas 5, 7, 39, and 40) are activated (Mattay et al., 1996). Moreover, on the same set of stimuli, demands for analytic solution preferentially activate dorsolateral prefrontal areas, whereas a figural approach to solution produced greater activation of the FGs and the parietal areas (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). Activation of visual association cortices by visual WM tasks has been demonstrated as well (Salmon et al., 1996). Patients with significant prefrontal lesions showed performance deficits only on spatial WM tasks demanding application of an efficient search strategy, whereas verbal and visual tasks similar to the tests used in our study produced no measurable impairment (Owen, Morris, Sahakian, Polkey, & Robbins, 1996). Other task differences may be important, because recent reports show no significant association between performance on N-back tasks frequently used in functional neuroimaging studies of WM and so-called "loaded" or "complex" span tasks used in cognitive aging research (Roberts & Corkin, 1997).

Experimental (fMRI and positron emission tomography [PET]) studies that emphasized the role of the PFC in WM and our quasi-experimental (structural MRI) investigation that failed to reveal significant links between the two are fundamentally different. Unlike our study, functional neuroimaging experiments focus on the processes that accompany performance on WM tasks and not on the result of these processes (i.e., WM proficiency). Although effortful operations related to managing WM are likely to rely on the PFC circuitry, the resulting performance on the WM task (and age-related differences in performance) may be more closely associated with other variables, such as speed of processing (see discussion of this and other methodological limitations below).

Explicit Memory

Not surprisingly, we observed a significant age-related decline in free-recall, paired-associates learning, as well as in memory for object location and line-pattern recognition. These deficits were in part mediated by the reduction in WM. Thus, although no direct effects of brain regional volumes on explicit memory variables were observed, age-related reduction in the volume of the VCs was indirectly associated with poor explicit memory. These results are in accord with the cumulative evidence that supports the notion of WM as one of the major constraints on mnemonic processes affected by aging (Salthouse, 1992a, 1992b). As indicated by the follow-up analysis, verbal WM may contribute to explicit memory in the verbal domain, but it is irrelevant to nonverbal memory. The nonverbal WM, on the other hand, is a significant predictor of both types of explicit memory. The relationship between nonverbal WM and a composite measure of verbal recall is especially interesting, because the composite included a wide range of tests from prose recall to paired-associates learning of face–name combinations. This finding is consistent with the hypothesis that age-related difficulty in generation and manipulation of mental images (Dror & Kosslyn, 1994) may underlie age-related deficit in recall (Thompson & Kliegl, 1991). This finding is also consistent with reports that long-term retrieval of location and identity information about objects results in activation of the FG (Moscovitch, Kapur, Köhler, & Houle, 1995).

Contrary to expectations, we found no direct effects of any of the examined brain variables on explicit memory. Given the high reliability of the measures, the minuscule magnitude of the effects, and a reasonable sample size, these negative findings cannot be attributed to a lack of statistical power or unreliability. The reason for this absence of associations is unclear. It is possible that explicit memory is affected only by extensive damage to the limbic circuitry, such as that observed in amnesia or Alzheimer's disease. We observed no significant age differences in parahippocampal volume and only mild age-related shrinkage of the hippocampus. Another recent study of healthy men also found no consistent association between the volume of the HC and performance on assorted tests of delayed recall (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995).

It is possible that reports of positive association between the hippocampal volume and memory (i.e., Golomb et al., 1994) included more memory-impaired elderly than in our sample. Indeed, samples with a high percentage of participants who meet criteria for age-associated memory impairment (AAMI) reveal links between hippocampal volume and performance on some memory tests (Soininen et al., 1994). The diagnostic category of AAMI includes participants at the lower end of the distribution of memory scores and is created by imposing an arbitrary cutoff. The follow-up analysis of the older participants in our sample shows that shrinkage of the limbic cortex is associated with poor memory performance among the participants who could have fallen into this category. This evidence also supports the contention that only when the hippocampus and associated limbic structures lose a substantial proportion of their volume (which approximates the loss observed in lesions causing amnesia) does the link between these structures and age-related memory declines become apparent. Notably, a recent PET study of memory-dependent activation in young and older adults showed no evidence of significant hippocampal involvement in either age group (Bäckman et al., 1997).

The whole hippocampal and parahippocampal volumes could have been measures too crude for exploration of relationships between brain and cognition. Different compartments of the limbic–diencephalic system may be associated with different facets of explicit memory. For example, encoding may rely mainly on the subicular region of the HC, whereas retrieval may depend on the activation of the posterior PHG (Gabrieli, Brewer, Desmond, & Glover, 1997). We could not measure these subdivisions of HC and PHG reliably, and in memory tests administered to the participants of our study the scores were determined by both encoding and retrieval. Thus, an important distinction between two fundamental mnemonic processes was obscured.

Examination of other limbic and diencephalic regions may prove fruitful in the search for structural substrates of age-related differences in recall. For example, lesions in the medio-dorsal thalamus have been consistently linked to amnesia (Squire et al., 1993), and functional neuroimaging studies show that memory tasks invoke significant activation in this structure (Andreasen et al., 1995). In one life-span sample, oxygen consumption in the left thalamus predicted immediate paired-associates recall regardless of age (Eustache et al., 1995). Unfortunately, the thalamic nuclei (medio-dorsal and anterio-ventral) that are involved in memory functions can be only roughly identified and are extremely difficult to demarcate and measure on MRI scans. As a result, very little is known about age-related changes in the thalamus, not to mention its role in cognitive aging.

The role of the PFC in age-related memory declines may be difficult to establish because of the relative weakness of the association between the function and its proposed substrate. The finding that even patients with sizable frontal lobe lesions are not always impaired on explicit memory tasks (Swick & Knight, 1996) puts our results in a proper context. In fMRI and PET activation studies, the PFC was associated with effortful search and organization of material but not with the proficiency of recall (Wagner, Gabrieli, Desmond, Joaquim, & Glover, 1996), although some recent evidence suggests that activation is greater when retrieval is successful (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). Prefrontal activation contingent on cued recall of verbal stimuli is unrelated to age even when a sizable age-related deficit in performance is observed (Bäckman et al., 1997), and there is no association between the prefrontal volume and the degree of memory impairment in nondemented elderly (Hänninen et al., 1997). Thus, a combination of a weak effect and proficiency-oriented measures employed in our study might have left little room for a significant association between normally declining prefrontal volumes and explicit memory.

Priming

We observed none of the hypothesized associations between verbal repetition priming scores and brain variables. Verbal priming may be such a robust phenomenon that only complete obliteration of its neuroanatomical substrate can bring a noticeable decrement (Gabrieli et al., 1995). A recent study of patients with prefrontal lesions suggests that even under those drastic circumstances, there may be no significant decline in performance on conceptual priming tests (Gershberg, 1997). In normal elderly as in young adults, repetition priming of visually presented verbal stimuli results in equal deactivation of the extrastriatal cortices (Bäckman et al., 1997).

Although we observed no direct effects of age on verbal priming, the indirect adverse influence of age mediated by verbal WM was noticed. This unexpected finding may be interpreted in several ways. It may mean that age-related declines in WM limit one's ability to conduct the lexical and semantic search needed for stem completion and category priming tasks. In our study, the index of WM could have captured the same common variance that was reported to be shared by word-stem completion and perseveration on the WCST (Davis et al., 1990; Winocur, Moscovitch, & Stuss, 1996). When we examined the correlations between the two measures in a subsample of the oldest participants (age 61–77), we found that, indeed, the priming scores correlated with the number of perseverative errors, $r = -.45$, $p < .05$. However, this correlation was only slightly reduced, $r = .37$ (*ns*) after the verbal WM index was partialed out.

It is also possible that the association between verbal priming and a WM reflects restricted capacity to deploy attention and to become aware of covert mnemonic implications of priming tasks. Age differences in test awareness mediated by WM have been advanced as an explanation of small though not negligible age-related declines in priming performance (Rybash, 1996). After all, WM is an ability to coordinate information from multiple sources in present, past, and projected future (Baddeley, 1993), and this ability may be necessary for gaining insight into covert mnemonic demands of the task. Our experience with other samples drawn from the same population indicate that differential test awareness may indeed account for age differences in stem-completion priming (Raz, Dorfman, & Gunning, 1995). Performance on at least one of the priming tasks used in this study (word-stem completion) is influenced by allocation of attentional resources (Gabrieli, Stone, et al., 1996). In addition, sizable correlations between the indirect (priming) and direct (recall) measures obtained from the priming tasks suggest possible contamination of priming indices by explicit memory, which can also account for the common correlations with WM.

Methodological Limitations

The findings reported in this study are bound by a number of limitations. First, the regional cortical volume estimates were obtained from MRI scans. Although we used state-of-the-art MRI equipment, its resolution is not yet sufficient to define the borders of neuroanatomical areas with histological precision. As such, our measures provide only a crude approximation of reality, although they constitute an improvement over the previous reports on neuroanatomical correlates of cognition. Current developments in MRI technology (Miller, Mark, Ho, & Haughton, 1996) promise a more precise parcellation of cortical mantle that will eventually permit a more specific examination of the relationship

between structure and cognition. The meaning of reliable age-related differences in the regional cortical volume that we observed on the MRI is unclear. Reduction in cortical volume may represent loss of neurons, shrinkage of their bodies, pruning of the dendritic arbor, or even nonneural changes such as reduction in vascular density. All these events are expected to have a negative impact on behavior, yet structural MRI studies cannot elucidate specific neurobiological mechanisms that underlie cognitive aging. In addition, comparison of regional brain volumes across individuals is inherently difficult. Although we believe that ROI definition by anatomical markers used in this study is a step ahead in the direction of greater specificity, even the boundaries of well-defined structures differ among the brains (Rajkowska & Goldman-Rakic, 1995). In the context of correlational analysis, the result of random individual variation (noise) is that the magnitude of the associations between brain structures and cognitive functions is underestimated.

In designing this study, we set the hypotheses in a multiple-dissociation framework. The results reported here present a mixed verdict on such an approach. Although we were able to demonstrate a double dissociation between cortical substrates of perseveration and nonverbal WM, other proposed dissociations were not upheld. There are several reasons for this approach being only partially successful, some having to do with the brain measures, and others, with the cognitive tasks. Most of these reasons are probably related to the fact that because of a relatively small size of our sample, the number of variables in the linear models was restricted a priori.

Several variables known to bear on age-related changes in performance were excluded, the most important being speed of processing, frequently listed among the critical factors in cognitive aging. Thus, in the presented path models, the variance that could have been attributed to speed of processing is subsumed under the calendar age and WM. Studies in cognitive aging reveal a complex relationship among speed, WM, and age. Some analyses suggest that age-related declines in WM stem from reduction in speed of processing (Salthouse, 1994b, 1996; Salthouse, Fristoe, & Rhee, 1996) and that age-related cerebrovascular lesions (Junqué et al., 1990) and history of cardiovascular disease (Earles & Salthouse, 1995) may mediate this slowing. Because the participants of this study were screened for health problems and, specifically, for cerebrovascular disease and hypertension, the mediating effects of speed or latent cerebral disease are unlikely to account for a large proportion of the variance in the observed structure–function relationships.

Finally, age-related differences in cognitive performance do not necessarily stem from deterioration of specific brain regions or the brain as a whole; they may result from sensory changes not measured in this study but frequently found in aging samples (Baltes & Lindenberger, 1997). Although the participants in our study were screened for gross vision and hearing defects, more subtle age-related deficits in both sensory modalities could have affected cognitive processes (Baltes & Lindenberger, 1997; Raz, Millman, & Moberg, 1990).

In summary, in spite of the enumerated limitations, the results reported here strongly suggest that differential cognitive aging reflects selective aging of the brain. The pattern of cognitive sparing and decline may be an expression of relative vulnerability of, mostly, the secondary and tertiary association areas of the brain to the effects of age. There are very few studies of neuroanatomical correlates of cognitive aging. We hope that future accumulation and integration of information across multiple studies will help determine the robustness of the associations reported here as well as to test new hypotheses about the structure–function relationships in normal aging.

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