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Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities

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Abstract

Forty-eight healthy adults aged 65–85 were recruited for structural magnetic resonance scans after an extensive neuropsychological battery that ensured a high degree of variability across the sample in performance on long-term memory tests, and on tests traditionally thought to rely on prefrontal cortex. Gray matter volumes were measured for three gyri in the frontal lobe (superior, middle, inferior), six gyri in the temporal lobe (superior, middle, inferior, fusiform, parahippocampal, and hippocampus), and the occipital lobe. Gray matter volumes declined across the age range evaluated, but with substantial regional variation—greatest in the inferior frontal, superior temporal, and middle temporal gyri but negligible in the occipital lobe. Both memory performance and executive function declined as the number of hyperintense regions in the subcortical white matter increased. Memory performance was also significantly correlated with gray matter volumes of the middle frontal gyrus (MFG), and several regions of temporal neocortex. However, the correlations were all in the negative direction; better memory performance was associated with smaller volumes. Several previous reports of significant negative correlations between gray matter volumes and memory performance are described, so that the possible reasons for this surprising finding are discussed.

Keywords: Gray matter; Magnetic resonance (MR); Elderly

1. Introduction

Numerous aspects of brain anatomy change with advancing age. Postmortem studies show that decreased brain weight and volume (largely attributed to shrinkage of neurons, especially the dendritic arbor), decreased density of noradrenergic, dopaminergic, serotonergic and muscarinic receptors in the cortex, and increased accumulation of lipofuscin are all associated with age at time of death (Esiri, 1994; Kemper, 1994; Peters, Morrison, Rosene, & Hyman, 1998; Powers, 2000). In vivo measurements of whole brain volumes by computerized tomography and magnetic resonance (MR) likewise show declines in cross-sectional studies comparing subjects of different ages. Age-related volume decrements are observed in both cerebral gray matter and white matter, although white-matter decline may begin later in life (Coffey, 2000; Courchesne et al., 2000; Jernigan et al., 2001; Raz, 2000). In late life, white matter shows additional changes such as prolongation of T1 and T2 relaxation time constants (indicative of increases in free water), and increases in the prevalence of hyperintense spots on T2-weighted images. The regional distribution of age-related changes has not been fully characterized, but there is fairly widespread agreement that prefrontal cortex shows the largest volume loss with age, temporal cortex generally shows losses, and the occipital lobe is relatively spared (Coffey, 2000; Raz, 2000; Raz et al., 1997).

Cognitive abilities in elderly as compared to young adults have also received a great deal of research attention, with evidence of relative sparing and loss across different aspects of perception and cognition. Episodic memory is one domain in which healthy older adults clearly perform worse than younger adults, in contrast to smaller age effects for retrieval from semantic memory (general knowledge) and for perceptual priming of recently experienced stimuli (Albert, 1994; Ardila & Rosselli, 1989; Bäckman, Small, Wahlin, &

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Table 1
Frontal lobe volumes and cognitive tests in healthy participants

Study (notes)	Sample	Sample	Normalize	Cognitive tests	Correlations
Raz et al., 1993 (a)	Twenty-nine adults (age 18–78)	Dorsolateral prefrontal gray, prefrontal white	Residual after cranial vault and vault and	Fluid intelligence (CFIT), vocabulary	ns
Hanninen et al., 1997	Forty-seven older adults (mean age 71.1)	Frontal lobe	None	WCST, categories WCST, preservation Verbal fluency, letter Verbal fluency, category Benton visual recognition WMS paired associates	ns ns left, −0.28 right ns 0.25 left, ns right ns ns
Gur et al., 1998	Seventeen mid-age adults (mean age)	Frontal lobe	Change in volume over 2 years	Attention/vigilance composite WCST Verbal intelligence composite (including verbal fluency) Spatial organization composite Verbal memory composite Visual memory composite Speed-processing (including WAIS digit-symbol, trails A and B, Stroop) Fine manual/motor functions	ns ns 0.53* ns ns ns ns ns
Raz et al., 1998	Ninety-five adults (age 18–77)	Dorsolateral prefrontal gray	Residual after subject height	WCST, perseveration Verbal memory Nonverbal memory Verbal priming Verbal working memory Nonverbal working memory	−0.42 ns 0.20 ns 0.27 0.21
Baare et al., 1999	Fourteen young adults (mean age 26.9)	Prefrontal gray	Divide by brain volume	CVLT, long-delay cued-recall Verbal fluency, letter Verbal fluency, semantic WMS-R visual reproduction 2	ns ns 0.68 (Spearman *r*)
Schretlen et al., 2000	One hundred and ninety-seven adults (age 20–92)	Frontal lobe	None	+WCST, categories	0.21
Sowell et al., 2001 (b)	Thirty-five children (age 7–16)	Frontal gray	Residual after brain volume	CVLT, delayed free recall Rey-Osterrieth, delayed recall	**−0.56** **−0.50**
MacLullich et al., 2002 (c)	Ninety-five older men (age 65–70)	Frontal lobe	None	Verbal fluency Raven's matrices NART WAIS, digit-symbol Benton vis. Retention WMS-R, visual reproduction Rey AVLT WMS-R, logical memory	ns 0.22 left, 0.25 right 0.23 left, ns right 0.26 left, ns right 0.23 left, 0.22 right ns ns ns
Salat et al., 2002	Thirty-one older adults (mean age 84.0)	IFG grey MFG grey SFG grey, orbital grey	Residual after cranial vault	Conditional association errors (SFG only) Working memory (orbital only) Object alternation	**−0.47** **−0.46** ns
Sanfilipo et al., 2002	Twenty-seven mid-age adults (mean age 35.7)	Prefrontal gray Prefrontal white	Residual after cranial vault and age	WCST composite WAIS, digit-symbol Buschke selective reminding Verbal fluency composite WMS-R, visual reproduction Verbal intelligence composite	ns 0.44 (gray) ns ns ns ns

Table 1 (*Continued*)

Study (notes)	Sample	Sample	Normalize	Cognitive tests	Correlations
Gunning-Dixon & Raz, 2003 (d)	One-hundred and thirty-nine older adults (mean age 63.7)	Prefrontal gray	Residual after height	WCST perseveration	−0.30
				Working memory composite	0.30

Correlations indicating associations between larger volumes and better performance in standard font; correlations indicating associations between smaller volumes and better performance in bold; * correlation value estimated from published sample size and probability level. Correlations are Pearson except where Spearman rank-order correlation is indicated. (a) In Raz et al. (1993), correlations between fluid intelligence and volumes of prefrontal gray and white matter were significant before removing variance associated with head size and age. (b) The delayed memory measures in Sowell et al. (2001) were residuals after adjusting for immediate recall. (c) The significant correlations between raw volumes and performance in MacLullich et al. (2002) became non-significant when normalized for cranial vault size. (d) The relationship between prefrontal gray volume and working memory became non-significant after accounting for the effect of age on working memory. CFIT: Cattell culture-fair intelligence test; WCST: Wisconsin card sorting test, perseveration is an error score, categories is number of categories achieved; NART: national adult reading test; Rey AVLT: Rey auditory verbal learning test; CVLT: California verbal learning test; WMS-R: Wechsler memory scale-revised; WAIS: Wechsler adult intelligence scale. See original articles for details about cognitive testing procedures.

Larsson, 2000; Light, 1991; Nyberg, Bäckman, Erngrund, Olofsson, & Nilsson, 1996; Schmand et al., 1997). More recently it has been suggested that an assortment of abilities thought to be dependent on prefrontal cortex—working memory, task-switching, speeded verbal fluency, directing attention away from irrelevant stimuli, setting response criteria, and monitoring performance—are particularly susceptible to advancing age (Chao & Knight, 1997; Craik & Grady, 2002; MacPherson, Phillips, & Della Sala, 2002; West, 1996, 2000; Zacks & Hasher, 1991; but see also Band, Ridderinkof, & Segalowitz, 2002; Greenwood, 2000 for skepticism about a unidimensional "frontal theory of aging"). Many recent studies have evaluated relationships between cognitive abilities and brain volumes assessed in MR scans. In samples of patients with neurological diagnoses, smaller volumes are generally associated with worse performance. In samples with Alzheimer's disease, dementia with Lewy bodies, Down syndrome, traumatic brain injury, subcortical cerebrovascular injury, and organic amnesia of mixed etiology, volumes of the hippocampi (and sometimes other regions of the temporal lobe) are positively correlated with memory performance in a variety of tests (Barber, McKeith, Ballard, Gholkar, & O'Brien, 2001; Bigler et al., 1997, 2004; Deweer et al., 1995; Jernigan, Ostergaard, & Fennema-Notestine, 2001; Köhler et al., 1998; Kopelman et al., 2001; Krasuski, Alexander, Horwitz, Rapoport, & Schapiro, 2002; Mungas et al., 2002; Petersen et al., 2000; Wilson et al., 1996).

However, results of volume/cognition correlations for groups of healthy individuals have been much less consistent. The hippocampus has received a great deal of attention in structural MR studies, but as the accompanying review paper (Van Petten, in press) notes, correlations between hippocampal volume and memory performance have been positive, negative, and null in different reports. Fewer studies have evaluated the relationship between memory and other regions of the medial temporal lobe; we are aware of three reports of a null relationship between volume of the parahippocamapal gyrus in healthy subjects (Köhler et al., 1998; Lupien et al., 1998; Petersen et al., 2000), and one significant positive correlation (Tisserand, Visser, Van Boxtel, & Jolles, 2000). Relationships between prefrontal cortical volumes and cognition have also received less attention than the hippocampus; Table 1 summarizes all eleven studies of which we are aware. The cognitive tests administered in the prefrontal studies are too various to allow a formal meta-analysis, but the table does not show a high degree of consistency across studies and includes significant correlations that are both positive (larger volumes associated with better performance), and negative (smaller volumes associated with better performance).

The extant literature provides rather weak support for the simplest account of regional structure/function relationships in healthy subjects, namely that "bigger is better". Perhaps a more reasonable account of volume/cognition relationships is that one should expect no relationship in a neurologically intact adult, because even gray matter volume is a crude measure that reveals little about relative proportions of neurons and astrocytes, synaptic densities, ratios of excitatory to inhibitory synapses, patterns of synaptic connectivity, numbers of receptors for various transmitter substances, and other factors that contribute to neural efficiency. However, the fact remains that below-normal volumes have been clearly associated with cognitive deficits in samples with neuropathology. Because apparently normal aging is also associated with reductions in brain volume, it is of some interest to know whether this source of tissue loss also results in cognitive decline. Below, we describe some motivations for undertaking another volumetry study, then the methods and the results of the present examination of cognitive performance, temporal and prefrontal volumes in a group of cognitively intact older adults.

2. The present study

2.1. Region selection

One rationale for a new volumetry study is that finer subdivision of the cortex might reveal volume/cognition relations not evident in previous studies. Although age-related volume loss has uniformly been reported in measurements of the whole frontal lobe, only one recent study has ex-

amined individual frontal gyri and cognitive measures in older adults, and reported regionally specific relationships between superior and orbital gray matter and working memory (Salat, Kaye, & Janowsky, 2001). In the present study, gray matter volumes of the inferior, middle, and superior frontal gyri are measured separately.

As regards long-term memory across the lifespan, the hippocampus has received a great deal of attention (Van Petten, in press), but the rest of the temporal lobe has been considered less often, and rarely subdivided. The hippocampus is a small structure, and many older studies measured less than its full volume because it is difficult to visualize the entire anterior–posterior extent in standard coronal slices (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995). When very small volumes are evaluated, small measurement uncertainties in both the MR and the memory variables may be sufficient to preclude finding subtle but real volume/cognition associations. In the present study, coronal slices were aligned perpendicular to the long axis of the hippocampus, and covered its full length, permitting more complete volume estimation of this structure. Moreover, regions of the temporal lobe outside the hippocampus are important for normal memory function as well. Although differential roles of the hippocampus and other medial temporal regions are a topic of some debate, the parahippocampal gyrus is frequently damaged in cases of human amnesia. Animal studies, intracranial ERP recordings, and hemodynamic imaging all suggest an important role for the parahippocampal gyrus in memory (Brown & Aggleton, 2001). The same sorts of evidence indicate modulations of activity in the inferior temporal gyri (ITG) and fusiform gyri related to both encoding and retrieval of visual stimuli (both objects and, in humans, words (Baker, Sanders, Maccotta, & Buckner, 2001; Fahy, Riches, & Brown, 1993; Fernandez et al., 2001; Moscovitch, Kapur, Kohler, & Houle, 1995; Otten & Rugg, 2001; Sobotka & Ringo, 1993)). We thus measured six regions of the temporal lobe: superior, middle, inferior, fusiform, and parahippocampal gyri as well as the hippocampus.

2.2. Subject selection and cognitive assessment

In volumetry/cognition studies, there is a tradeoff between the power to detect small effects offered by very large numbers of subjects, and a thorough characterization of each subject's cognitive status which may not be feasible for very large samples. For the evaluation of normal aging, intensive neuropsychological examination is desirable because it offers some assurance that subjects with incipient dementia are excluded. However, the likelihood of detecting relationships between volumes and cognitive status will also increase as the range of cognitive performance increases, so that an extremely homogeneous sample may also be undesirable. The compromise reached in the present study was to scan a moderate size sample of 48 older adults who were selected from a larger pool of approximately 100 individuals who had undergone about 4 h (two sessions) of neuropsychological evaluation. Subjects were invited for MR scans when they scored within the normal range of all the standardized tests used, but showed above- or below-average performance on tests of memory, or tests thought to depend on prefrontal cortex. This approach combines the benefits of assuring the cognitive intactness of the sample, but maximizing range of performance.

Because understanding the relationships among a variety of cognitive abilities and a variety of brain regions is one goal of volumetry/cognition studies, measuring a large number of regions and a large number of cognitive abilities is desirable. However, such a "wide net" approach may also increase the likelihood of obtaining spuriously significant correlations. At the same time, applying a statistical correction for multiple tests may be too stringent, given that small magnitude effects might reflect genuine relationships. Our compromise approach was to combine a large number of neuropsychological tests into two composite measures based on a factor analysis showing shared variance between a set of five memory tests (memory factor or M-factor), and shared variance between five other tests traditionally associated with frontal lobe function (frontal factor or F-factor, see Section 3 for detail). The factor score approach allows incorporation of a large number of neuropsychological measures of cognitive ability, while reducing the number of statistical tests employed to detect volume/cognition relationships.

We have previously utilized the two composite neuropsychological factors to study individual differences in the memory performance of older adults. After removing variance due to age alone, high scores on the M-factor have been associated with better performance in discriminating studied from unstudied words in experimental recognition tests (both two-alternative forced-choice and old/new formats (Davidson & Glisky, 2002; Glisky, Polster, & Routhieaux, 1995)). Although the individual measures which contribute the F-factor score do not include any tests of long-term memory, the F-factor has also proved influential for performance in memory tests, but in a different manner than the M-factor. High scores on the F-factor have been associated with better performance on source memory tests that require decisions about studied conjunctions of stimulus attributes (e.g. whether a word is spoken in the same or a different voice as when initially studied (Davidson & Glisky, 2002; Glisky, Rubin, & Davidson, 2001)), better performance on exclusion memory tests that require decisions about which study list a word belonged to (Davidson & Glisky, 2002), and lower false alarm rates in old/new recognition tests (without an impact on hit rates (Rubin, Van Petten, Glisky, & Newberg, 1999)). Event-related potential (ERP) studies in similar paradigms in young adults have identified focal prefrontal potentials during source memory tests as compared to item memory tests, and have additionally linked the amplitude of prefrontal potentials to the ability to resist making false alarms in an associative memory test (Senkfor, 2002; Senkfor & Van Petten, 1998; Van Petten, Luka, Rubin, & Ryan, 2002; Van Petten, Senkfor, & Newberg,

2000). Our previous work is thus consistent with the view that the M-factor indexes basic memory ability, while the F-factor indexes other abilities dependent on prefrontal cortex that contribute to performance in some memory tests, such as selecting an encoding strategy, guiding memory search during the retrieval phase of memory tests, and evaluating the correspondence between stimuli and response criteria.

Our a priori predictions were thus that the M-factor score would be associated with gray matter volumes of medial and perhaps inferior regions of the temporal lobe, while the F-factor score would be associated with prefrontal volumes. Gray matter volume of the occipital lobes was measured as a control structure expected to have no relationship to either composite neuropsychological measure.

2.3. Normalization for head size and age

Most structural MR studies devoted to aging and/or cognition perform some sort of normalization for head or body size prior to analysis of volume measures. The (usually unstated) motivation for normalization is that brain size will be driven, in part, by the size of the sensory receptive surfaces (skin, retina, etc.) and the number of muscle fibers in the body, and that these are noise factors for understanding aging or cognition. However, the appropriate method of normalization is not completely obvious, and may differ depending on whether aging per se or cognition/volume relationships are of greater interest. If the primary interest is in age-related tissue loss, brain volumes corrected for internal volume of the skull (cranial vault) have face-value validity—a widening gap between intracranial volume and brain volume with increasing age can only indicate tissue loss. In a cross-sectional study, normalizing volumes by cranial vault also helps to distinguish aging from cohort effects created by the general increase in body and brain size over the last century (Miller & Corsellis, 1977).

In contrast, normalizing by skull size may not be appropriate when the focus is on cognitive abilities. Because brain growth during development drives skull growth, removing variance associated with cranial vault size may be akin to throwing out the baby with the bath water—attenuating genuine relationships between the size of brain structures and cognitive abilities. Some researchers thus normalize brain volumes for body height rather than intracranial vault size (see (Raz et al., 1997) for discussion of normalization strategies). However, this would also seem to have a potential drawback in an elderly sample, because the presence of osteoporosis in some individuals can lead to an old-age height that is some inches shorter than in young adulthood. Given the lack of a perfect solution to this issue, we report correlations for both vault-corrected and raw volumes when examining the impact of age on brain volumes.

A similar question arises about the treatment of age when analyzing relationships between cortical volumes and cognitive measures. Given the typical observation of age-related brain shrinkage, some published studies examine partial correlations between regional volumes and cognitive measures after variance due to age has been removed. If one assumes the causal chain that aging causes brain shrinkage, and this shrinkage in turn causes cognitive decline, then partialling out the effect of age will tend to eliminate volume/cognition relationships. In fact, significant volume/cognition correlations before age-correction which approach zero after age-correction might be taken as a strong sign that age-related shrinkage influences cognitive performance (see Tisserand et al., 2000; for an example of this pattern of results). However, correcting for age before examining volume/cognition relationships is appropriate under other views of the causal relationships. An analysis that removes the average effect of age on a given region will serve to mark individuals as having large/small gyral volumes for their age, and to detect whether deviations from the average are associated with stronger/weaker cognitive performance. Such an analysis thus focuses on individual differences rather than age per se. A volume/cognition relationship that survives age-correction (as in Gur et al., 2000) indicates that cognitive heterogeneity in the sample is not primarily due to chronological age, but remains compatible with two rather different interpretations. On the one hand, a sample in which some subjects have pathological atrophy and low cognitive performance will yield such a result. On the other hand, such a result could also arise from an intrinsic (non-pathological) relationship between the volumetric and cognitive measures if there is sufficient variability in both, and relatively little of that variability is correlated with the age of the subjects in the sample. We do not know which of these causal perspectives is likely to be correct, and so examine correlations between volumes and cognitive performance using both raw volumes and residual volumes after removing variance due to cranial vault size and age.

2.4. White matter hyperintensities (WMHs)

The temporal and frontal lobe gyral measurements reported here are for gray matter, which could be more securely assigned to individual gyri than the underlying white matter. However, increased prevalence of bright spots in the white matter of healthy individuals has been a robust finding in MR aging studies. Severity of WMH has sometimes been linked with risk factors for vascular disease such as hypertension, ischemic heart disease, and diabetes (but without agreement as to individual factors or how severe they must be). The physiological genesis and functional impact of such MR signal changes may vary according to their location and visual appearance (Coffey, 2000; Gunning-Dixon & Raz, 2000; Pantoni & Garcia, 1997). Some authors suggest that those located along the borders of the ventricles reflect breakdown of the ependymal lining, and are both more common and less reflective of pathology than hyperintensities in the white matter underlying the cortex (Coffey, 2000). We thus quantified WMHs underlying the cortical mantle but

not periventricular hyperintensities. Small round (punctate) hyperintensities are likely to reflect shrinkage of tissue surrounding a blood vessel, leaving a fluid-filled space. Larger irregularly shaped patchy hyperintensities may reflect more severe (although still subclinical) ischemic damage to myelin and/or axons (Fazekas, Schmidt, Kleinert, Kapeller, & Roob, 1998). We thus quantified punctate and patchy WMHs separately.

Some studies of WMHs in healthy older adults have reported no correlation with cognitive status, but a recent meta-analysis of 23 such studies concluded that there is indeed a modest correlation between WMH burden and poor performance in tests of executive function (related to the F-factor used here) and memory (Gunning-Dixon & Raz, 2000). We thus examine the joint impact of WMH number and gray matter volumes on cognitive performance.

3. Methods

3.1. Subjects

Forty-eight individuals aged 65.5–85.8 years of age (mean 73.2) participated in an MR scan and a battery of cognitive tests. All were community-dwelling and in generally good health as assessed by screening interviews and questionnaires prior to participation. Thirty-three were women (mean age 74.0) and 15 were men (mean age 71.5; not statistically different from female age). Mean years of formal education was 15 (range of 10–20). Exclusionary criteria were current or past diagnosis of neurological or psychiatric disorder (excepting peripheral neuropathy such as carpal tunnel syndrome or nerve injury due to trauma), a past head injury that resulted in skull fracture or loss of consciousness for more than 5 min, heart attack, major coronary artery disease leading to bypass or angioplasty, depression as indicated by the mood assessment scale (Spreen & Strauss, 1998), prior or current treatment for alcohol abuse, and current consumption of more than 10 alcoholic drinks per week. Other exclusionary criteria were those that might make an MR scan risky: metal in the body, or claustrophobia. Three men and 13 women who reported hypertension controlled by medication were included. Six men and seven women with mild ischemic heart disease participated (four of these also had hypertension). One man and one woman with non-insulin-dependent diabetes were also included.

Participants were recruited from a larger pool of older adults who volunteer to participate in memory studies at the University of Arizona. The roughly two-to-one ratio of women to men in the current MR sample reflects the over-representation of women among the more than 400 individuals participating in our aging and memory studies over the last 9 years; US census data from 1990 indicate a female/male ratio of 1.48/1 in the over-65 population nationally. In the larger pool, all individuals take standardized neuropsychological tests including the Wechsler memory scale III (WMS-3; Wechsler, 1997), and the Wechsler adult intelligence scale revised (WAIS-R; Wechsler, 1987) or Wechsler abbreviated scale of intelligence (WASI, 1999). Those scoring within the normal range according to published norms for the standardized tests (within two standard deviations of the mean for their age group) may then choose to participate in various memory experiments; those scoring outside the normal range are referred to neurological clinics and excluded from the research pool. Individuals were recruited to undergo MR scans from a group of approximately 100 currently active research participants. Average time between the neuropsychological battery and MR scan was 6 months.

3.2. Cognitive measures

For the current sample who underwent MR scans, mean performance IQ was 116 (S.D. 13), and mean verbal IQ was 120 (S.D. 9). On the WMS-3, mean index score for Immediate Memory was 117 (S.D. 14, 87th percentile for adults in the same age range); mean index score for general memory (i.e. delayed memory) was 118 (S.D. 15, 88th percentile). Despite this generally high level of cognitive ability, we sought to maximize variability in specific cognitive domains by recruiting only participants who scored above or below the mean of the larger sample (by at least 0.2 standard deviations) on tests of memory, and/or tests thought to rely on prefrontal cortex.

The two orthogonal measures used for subject selection are based on factor analyses of a larger set of neuropsychological tests (Glisky et al., 1995). The M-factor score reflects performance on tests of recognition and recall from episodic memory, including three tests from the WMS-3 (logical memory I, verbal paired associates I, face recognition I), one from the Wechsler memory scale revised (visual paired associates II), and the long-delay cued-recall measure of the California verbal learning test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The F-factor score reflects performance on five tests traditionally considered sensitive to frontal lobe damage: number of categories achieved in the modified Wisconsin card sorting test, number of words generated in response to initial letters F, A, and S in the controlled oral word association test, mental arithmetic test from the WAIS-R, and the backward digit span and mental control tests of the WMS-3 (Benton & Hamsher, 1976; Hart, Kwentus, Wade, & Taylor, 1988; Wechsler, 1987; Wechsler, 1997). Table 2 shows performance levels on the 10 individual cognitive tests for the 48 current subjects. “M” and “F” scores were assigned to each participant by comparing their performance to a normative group of 100 older adults tested at the University of Arizona, and averaging their z-scores (standard deviations from the mean) for the two sets of tests. In the current MR sample, F-factor scores range from negative 1.50 to positive 1.27 (mean −0.20), and M-factor scores range from negative 1.73 to positive 0.73 (mean −0.05), ensuring substantial cognitive variability within the sample.

Table 2
Neuropsychological tests

	Mean	S.E.	Range
Tests contributing to M-factor			
Verbal paired associates I (WMS-3)	21.6	0.9	3–31
Visual paired associates II (WMS-R)	5.6	0.1	2–6
Logical memory I (WMS-3)	23.5	0.9	5–33
Face recognition I (WMS-3)	36.0	0.6	25–46
CVLT, long-delay cued-recall	11.3	0.4	6–16
Tests contributing to F-factor			
Wisconsin card sort cued recall	4.9	0.2	0–6
Controlled oral word association	45.1	1.7	25–86
Mental arithmetic (WAIS-R)	12.7	0.5	5–19
Mental control (WMS-3)	29.4	1.0	15–40
Backward digit span (WMS-3)	7.0	0.3	2–12

Ten subjects had positive scores (above the mean of the larger sample) for both the M and the F-factors, 12 had negative scores on both factors, 12 had negative F-factors but positive M-factors, and 14 had positive F-factors but negative M-factors.

In addition to the "M" and "F" factor score measures, relationships between the MR measures, verbal IQ (VIQ), and performance IQ (PIQ) are also analyzed. In follow-up analyses examining the individual tests contributing to the factor scores, three memory tests from the WMS-3 or WMS-R not included in the M-factor are also included: logical memory 2, verbal paired associates 2, and visual paired associates 1. The eight memory tests include four that test immediate memory (those with a "1" in their names) and four that test memory after a delay of about 20 min (those with a "2" in their names, plus the long-delay cued-recall test of the CVLT). A different way to categorize the memory tests is that two are free recall (logical memory 1 and 2), five are cued-recall (verbal paired associates 1 and 2, visual paired associates 1 and 2, the CVLT measure), and one is recognition (face recognition 1). Individual tests contributing to the F-factor were also analyzed, together with the number of perseverative errors on the WCST (mean 4.75, S.D. 6.44).

3.3. MR scan protocol

Three sets of MR scans were acquired on a GE Signa 1.5 T magnet. The first consisted of a sagittal T1-weighted localizer scan, used to identify the hippocampal formation. This image was used to position 3 mm thick coronal slices acquired perpendicular to the long axis of the left hippocampal body. Thirty-two T2-weighted coronal images were acquired from just anterior to the amygdala to the trigones of the lateral ventricles, using a fast spin echo sequence (TR = 400, TE = 96, FOV = 22 × 16, matrix = 256 × 192, NEX = 2, scan time = 4.48 min). These images served the dual purpose of providing high resolution images of temporal lobe structures, and highlighting possible white matter pathology. Finally, a set of 1 mm T1-weighted axial images were obtained using a 3D SPGR sequence (TR = 26, TE = 5, FOV = 22×16, matrix = 265×192, NEX = 2, scan time = 16.02 min). The volume was positioned so that the entire cerebrum fell within the 124 slices of the acquisition volume. Because these images were obtained with isovolume voxels of 1 mm, they could be flipped from the axial to sagittal plane without significant error (Plante, Boliek, Binkiewicz, & Erly, 1996).[1] This last set of images was used to obtain volumes of the entire cerebrum and frontal gyri in the axial plane, and cranial vault measures at the sagittal midline.

3.4. MR measurements

A team of operators were trained in the computerized segmentation of the regions of interest (ROIs) employed in this study; all were blind to the age and cognitive status of the subjects, and each specialized in one brain region (e.g. all occipital lobes were measured by a single operator). General segmentation procedures involved identifying relevant neuroanatomic features that defined each ROI. The ROIs were hand-traced by computer mouse on a slice-by-slice basis for each subject, so that individual variations in neuroanatomy were captured by the segmentation. Once the ROI was removed from the surrounding tissue, operators segmented gray matter from white matter, cerebral spinal fluid (CSF), and other tissue (e.g. meninges, large vessels). Segmentation of tissue types was done on a slice-by-slice basis so that operators could assess local areas of signal change in white matter to accurately separate these from gray matter. The volume of the relevant tissue types was then calculated for the summed slices of the ROI.

The cranial vault measurement at the sagittal midline included all supratentorial gray and white matter plus CSF. Total cerebral volume consisted of gray and white matter. Volumes within smaller cortical ROIs consisted of gray matter only. In the frontal lobe, these were the superior, middle, and inferior gyri. In the temporal lobe, these were the hippocampal formation and the superior, middle, inferior, fusiform, and parahippocampal gyri. Finally, gray matter within the occipital lobe was measured as a control structure expected to show little relationship to either age or the cognitive abilities assessed. Figs. 1 and 2 illustrate the frontal, temporal, and occipital ROIs. Detailed methods for segmentation and identification of each ROI are provided in the Appendix A.

Signal intensity changes within the white matter were also evaluated and ranked. To ensure that these were sampled over a standard region across brains of different sizes, a subset of coronal slices was evaluated, starting anteriorally in

[1] The choice of scan protocols represented a solution to a problem with multiple constraints: (1) T2-weighted images are best for viewing white-matter hyperintensities; (2) images oriented perpendicular to the long axis of the hippocampus are superior for measuring the volume of that structure, but do not include the prefrontal ROIs; (3) T2-weighted scans are considerably longer in duration than other scan protocols; and (4) even optimally healthy elderly subjects are unlikely to generate movement-free MRI data with sessions exceeding an hour. We thus used faster SPGRs in a standard plane of section to capture the frontal lobes, but T2s aligned to the hippocampus for both the temporal lobe measures and the WMH counts.

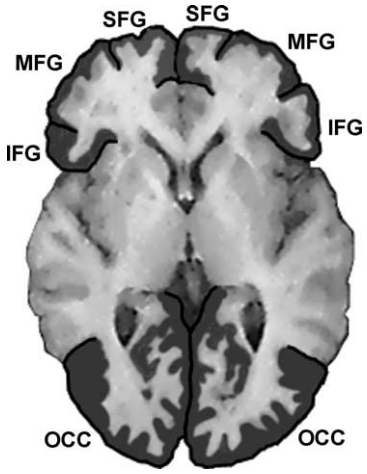

Fig. 1. Regions of interest in the frontal and occipital lobes, illustrating segmentation of gray matter from a T1-weighted MRI scan. SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; OCC: occipital lobe.

the first slice in which the putamen could be seen, and ending posteriorly at the first slice in which the temporal-occipital sulcus was visible. Within this range, adjacent pairs of consecutive 3 mm slices were averaged to produce a series of 6 mm slices, effectively filtering the data in the *z*-direction. This served to decrease random signal variation that could be mistakenly identified as patchy or punctate signal changes.

Two types of white matter features were assessed. The first consisted of diffuse intensity changes, apparent on the T2-weighted images as patches of white matter with intensities that appeared to fall between those typical of white matter and those typical of gray matter. The severity of these patchy abnormalities was assessed by the number of gyri showing such changes in each coronal slice, summing across slices, and then dividing by total number of slices. The second type of white matter anomaly was visually distinct from the first, and consisted of hyperintense spots on the T2-weighted scans that were symmetrical in shape and had a relatively distinct border. This class certainly included

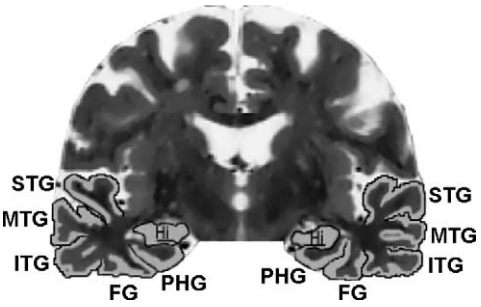

Fig. 2. Regions of interest in the temporal lobe, illustrating segmentation of gray matter and hippocampus (Hi) from a T2-weighted MRI scan. STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; FG: fusiform gyrus; PHG: parahippocampal gyrus.

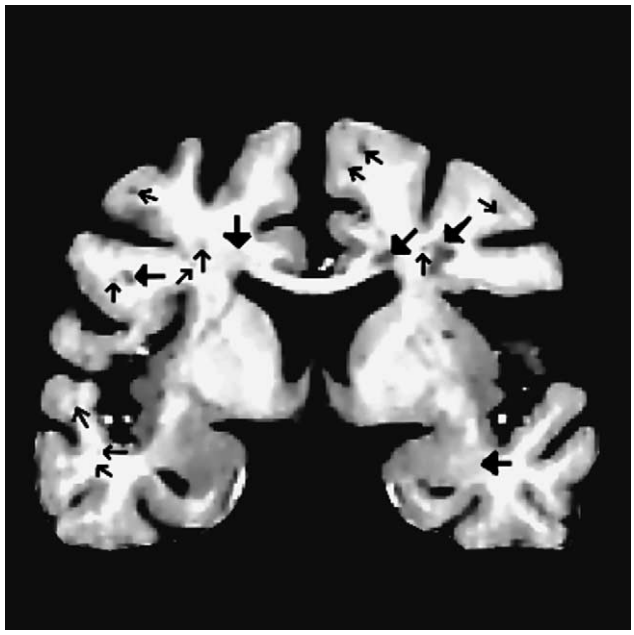

Fig. 3. Reverse T2 image showing patchy (solid arrow heads) and punctate (open arrow heads) abnormalities in the white matter of the frontal and temporal lobe. Contrast and brightness of the image have been enhanced. Note that similar abnormalities within the cortical gray and sulci were not counted in the white matter abnormality count. Furthermore, abnormalities within or around the basal ganglia and external capsule were not counted due to the difficulty of distinguishing between the narrow border of white matter and other gray matter structures in this region.

blood vessels (typically punctate, but sometimes dilated in appearance), but probably also included other types of phenomena that met the visual criteria. These punctate features were counted, regardless of size, so that higher counts corresponded to greater numbers of these hyperintensities. Both sorts of changes within the white matter were evaluated on the T2 images, which highlighted the patchy intensity changes, and on intensity-inverted versions of these images, which tended to highlight the punctate hyperintensities. Fig. 3 shows examples of both patchy and punctate hyperintensities.

3.5. Reliability

After segmentation of all scans was completed, operators each randomly selected three brains (six hemispheres) for reanalysis of each ROI (different random samples across ROIs). The ROIs corresponding to each slice were re-extracted and the areas for each ROI at that slice recalculated. This resulted in six re-measurements of each structure (60 total). The left column of Table 3 shows the correlations between original and retest volumes for each structure, which averaged 0.93. The second column shows the average percent discrepancy between original and re-measured volumes. There is little uniformity in the correspondence between these two metrics of measurement error. Note, for instance, that the occipital lobe yielded a substantially

Table 3
Test/retest and cross-subject variability of volumetric measures

Region of interest	Test/retest correlation	Percent difference between test and retest	Standard deviation as percent of mean	Range of variation across brains
Inferior frontal gyrus	0.94	2.6	45.7	156
Middle frontal gyrus	0.92	2.4	24.6	257
Superior frontal gyrus	0.97	3.3	17.3	330
Hippocampus	0.78	3.5	16.4	118
Parahippocampal gyrus	0.97	4.8	15.5	92
Fusiform gyrus	0.99	4.5	18.7	122
Inferior temporal gyrus	0.95	8.0	13.9	97
Middle temporal gyrus	0.87	8.0	18.2	390
Superior temporal gyrus	0.99	6.2	14.2	88
Occipital lobe	0.95	3.9	23.3	295
Mean	0.93	4.7	20.8	195

Note: the first column shows Pearson r for the correlation between initial and re-measured volumes of each ROI. The second column shows the percent discrepancy between original and repeated measures. The third column shows the average absolute difference between volumes from an individual brain ($n = 48$) and the mean volume of that gyrus (or lobe), as a percent of the mean volume. The right column shows the range of cross-subject variability in volume: largest individual volume minus the smallest, divided by the smallest.

higher correlation between test and retest than did the hippocampus, although the percent discrepancy between the two measurements is slightly worse for the occipital lobe. This is because correlational measures are strongly influenced by the numerical range of values analyzed. Because the hippocampus is a small structure, the numerical range of volumes across brains was restricted to 2.92 cm^3, while the range across occipital lobes was 52.0 cm^3. Percent discrepancy scores, in contrast, are standardized to the size of the ROI evaluated. We believe that the percent discrepancy metric allows a more transparent evaluation of the impact of measurement error for a dataset. Discrepancy between test and retest is clearly noise. For correlational analyses of MR and cognitive measures, variation among subjects is desirable, and can be regarded as signal. The third and fourth columns of Table 3 show summary measures of cross-subject variability: the standard deviation as a percent of the mean of each ROI, and the range of variation across brains. Comparison across the columns of Table 3 suggests a generally adequate signal-to-noise ratio (SNR), but also regional variability in SNR. The potential impact of measurement error on statistical outcomes is addressed in Section 4.

4. Results

Results are organized according to: (1) the impact of age and educational level on the various MR measures, and then relationships between the MR measures and (2) IQ; (3) the F-factor; and (4) the M-factor. For the latter three sections, we begin with a regression analysis attempting to predict cognitive performance from the MR and demographic variables. When a significant regression is obtained, simple correlations between each MR variable and the cognitive measures are examined, as well as partial correlations for the volumetric measures after normalizing for cranial vault size and age.

4.1. Age

4.1.1. Cerebral volumes

Table 4 shows mean values for hemispheric volumes, frontal and temporal lobe gyri. Visual inspection of the

Table 4
Volumetric measures and age

	Mean (se)	Age correlation
Cerebral hemispheres (gray and white)	1092 (22)	−0.47*** (−0.52***)
Occipital lobes	40.3 (1.4)	−0.02 (−0.08)
Superior temporal gyrus	11.2 (0.2)	−0.30* (−0.38**)
Middle temporal gyrus	8.1 (0.7)	−0.37** (−0.44**)
Inferior temporal gyrus	6.6 (0.4)	0.09 (0.01)
Fusiform gyrus	6.5 (0.8)	−0.19 (−0.25)
Hippocampus	3.6 (0.9)	−0.24 (−0.30*)
Parahippocampal gyrus	3.6 (0.8)	−0.10 (−0.05)
Left neocortical temporal	32.4 (0.6)	−0.30* (−0.38**)
Left medial temporal	7.2 (0.1)	−0.25 (−0.28)
Right neocortical temporal	32.8 (0.6)	−0.18 (−0.28)
Right medial temporal	7.3 (0.2)	−0.14 (−0.15)
Temporal	39.9 (0.7)	−0.27 (−0.35*)
Superior frontal gyrus	30.4 (0.8)	−0.19 (−0.26)
Middle frontal gyrus	21.6 (0.8)	−0.28 (−0.33*)
Inferior frontal gyrus	4.5 (0.3)	−0.35* (−0.33*)
Left prefrontal	57.4 (1.5)	−0.36* (−0.42**)
Right prefrontal	57.9 (1.4)	−0.30* (−0.37**)
Prefrontal	57.6 (2.7)	−0.35* (−0.42**)

All volumes in cm^3. Except where noted, volumes reflect gray matter only and are the average of left and right hemispheres. "Prefrontal" is the sum of the superior, middle and inferior frontal gyri; "temporal" is the sum of the six temporal lobe gyri listed; "neocortical temporal" is the sum of the superior, middle, and inferior temporal gyri plus the fusiform gyrus; "medial temporal" is the sum of hippocampus and the parahippocampal gyrus. Correlations between age and volumes are partial correlations after variance due to cranial vault size is removed; simple correlations with raw volumes in parentheses.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

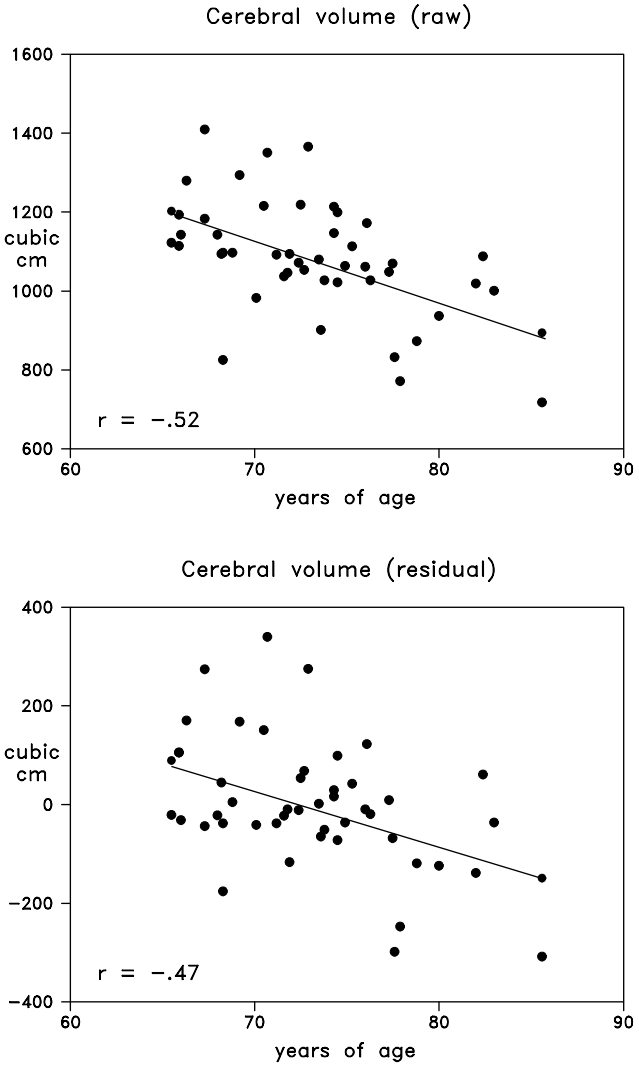

Fig. 4. Top panel: relationship between volume of the cerebral hemispheres (gray plus white matter) and age. Bottom panel: residual cerebral volume (after removing variance due to cranial vault size) is plotted against participant age in years.

scans indicated larger ventricles and widened cortical sulci in all or nearly all of the subjects as compared to our experience with young brains (Clark & Plante, 1998; Jackson & Plante, 1996). Fig. 4 (top) shows a decline in raw volume of the cerebrum across the sampled age range of 65–85 years ($r = -0.52$, $P < 0.0005$). Because capacity of the cranial vault (head size) is correlated with cerebrum size ($r = 0.42$, $P < 0.005$), we also examined partial correlations between age and cerebral volume after removing variance due to volume of the cranial vault. Normalizing for head size may be more appropriate than raw volumes given that the sample contains both men and women, and the male subjects had significantly larger cranial vaults ($F(1, 46) = 34.2$, $P < 0.0001$) and larger hemispheres than the female ($F(1, 46) = 8.08$, $P < 0.01$). Sex was no longer a significant determinant of cerebral volume when cranial vault was used as a covariate ($F(1, 46) = 2.83$, $P = 0.10$). In addition to reducing the impact of sex, cerebral volume residualized on cranial vault provides a more transparent measure of age-related tissue loss. Fig. 4 (bottom) shows that advancing age continued to be associated with decline in cerebral volume after normalizing for volume of the supratentorial vault ($r = -0.47$, $P < 0.001$). Educational level was not significantly correlated with raw or residual cerebral volume.

4.1.2. White matter signal changes

The number of patchy and punctate abnormalities within the white matter were correlated with each other ($r = 0.32$, $P < 0.05$). Neither variety of signal change increased with age in the elderly sample ($r = -0.12$ and -0.06), nor was there a significant association with educational level. The subjects reporting ischemic heart disease had somewhat more patchy abnormalities than those without heart disease ($F(1, 46) = 4.50$, $P < 0.05$), but the two groups did not differ in prevalence of punctate abnormalities. The subjects reporting hypertension controlled by medication did not differ from those with normal blood pressure in prevalence of either sort of abnormality.

4.1.3. Occipital lobes

As seen in Table 4, the gray matter volume of the occipital lobes was unrelated to age in our elderly sample. Nor were there any significant correlations with educational level.

4.1.4. Temporal lobes

Volumes of most gyri in the temporal lobes showed negative correlations with age after removing variance associated with cranial vault size (Table 4), but these reached statistical significance for only the superior and middle temporal gyri. When gyral measures were combined into more global neocortical (superior, middle and inferior temporal gyri plus fusiform gyrus) and medial cortical (hippocampus plus parahippocampal gyrus) regions in each hemisphere, only the left temporal neocortex showed a significant decline in volume across the 65–85 year age range. None of the temporal lobe measures showed significant associations with educational level.

4.1.5. Frontal lobes

Table 4 shows that only the inferior frontal gyrus showed a significant volume loss across age. However, the sum of superior, middle and inferior gyri also showed negative correlations with age for both the right and left hemispheres, suggesting moderate age-related declines throughout the prefrontal region measured (which did not include the orbital gyrus, cingulate gyus, or gyrus rectus). Volume of the inferior frontal gyrus also showed a positive correlation with years of formal education ($r = 0.32$, $P < 0.05$ for raw volume, partial $r = 0.34$, $P < 0.05$ after cranial vault size); other regions showed no significant association.

4.1.6. Cognitive measures

The present study was not designed to evaluate cognitive changes with age per se, but instead relationships between brain morphometry and cognition in old age. The participants were thus not selected randomly, but rather on the basis of high or low performance on neuropsychological tests of memory and/or tests thought to depend on prefrontal cortex. We thus had no predictions about age and cognitive performance in the selected sample. Indeed, none of the summary cognitive measures were significantly related to subject age: VIQ ($r = -0.06$), PIQ ($r = 0.22$), the factor score for neuropsychological tests thought to depend on the frontal lobe (F-factor, $r = -0.12$), factor score for memory tests (M-factor, $r = -0.13$).

4.2. Predicting IQ from the MR measures

In an initial analysis, all of the raw gyral volumes, hemisphere and cranial vault size, occipital lobe volume, number of WMHs (patchy and punctate summed), age, and educational level were allowed to serve as potential predictors of verbal IQ score in a stepwise regression. Only the volume of the middle temporal gyrus met the minimum F-value of 4.0 to enter the equation, with a simple correlation of $r = -0.31$, $P < 0.05$. No other significant correlations were observed. For performance IQ, there was no significant regression equation nor any significant correlations with individual variables.

4.3. Predicting executive function from the MR measures

The same set of potential predictor variables were entered into an analysis with the F-factor as the dependent variable. Cranial vault size (positive coefficient) and WMHs (negative coefficient) together accounted for 22% of the variance in the F-factor ($F(2, 45) = 6.24$, $P < 0.005$ for the regression, R^2 for vault $= 0.13$, R^2 for WMH $= 0.09$).[2] Remembering that the male subjects had larger cranial vaults than the female, we wondered if the influence of vault size was a sex difference in disguise. However, repeating the analysis on the female brains alone ($n = 33$) produced the same two significant predictors of the F-factor ($R^2 = 0.26$, $F(2, 30) = 5.29$, $P < 0.02$; R^2 for WMH $= 0.15$, R^2 for vault size $= 0.11$). There was no significant regression for the male subjects alone, given the small sample ($n = 15$). Finally, the regression was essentially unchanged when the 13 subjects reporting mild heart disease were excluded ($R^2 = 0.33$, $F(2, 32) = 7.59$, $P < 0.005$ for the regression; R^2 for WMH $= 0.17$; R^2 for vault $= 0.15$).

[2] Because the distribution of WMH counts across brains shows a positive skew from the normal distribution, this analysis was redone using a natural log transform of WMH count. The regression results were essentially unchanged: $F(2, 45) = 6.38$, $R^2 = 0.22$, $P < 0.005$; R^2 for vault $= 0.22$, R^2 for WMH $= 0.09$).

Table 5
Best-fit regression analysis for the memory factor score

Variable	R^2	F-ratio	P-value
ITG volume	0.18	10.04	0.01
MFG volume	0.11	6.79	0.05
Age	0.06	4.09	0.05
White matter hyperintensities	0.06	4.63	0.05
Total	0.41	7.50	0.0005

No significant simple correlations between the frontal gray measures (raw or normalized) and the F-factor score were observed, nor any of the individual tests in the F-factor. The simple correlations for cranial vault size were significant for the overall F-factor ($r = 0.36$, $P < 0.01$), and for two of the tests contributing to the factor (mental arithmetic, $r = 0.33$, $P < 0.05$; mental control, $r = 0.31$, $P < 0.05$).

4.4. Predicting memory performance from the MR measures

Table 5 shows that four of the predictor variables jointly accounted for 41% of the variance in the M-factor score. Smaller gray volumes of the inferior temporal and middle frontal gyri (MFG), older age, and greater number of white matter abnormalities all predicted better memory performance.[3] Note that age was not significantly correlated with memory performance in the simple correlations reported above, but contributed additional predictive value after volumes of the ITG and MFG entered the equation.

4.4.1. White matter hyperintensities

Examination of the simple correlations showed that the memory factor score declined as the number of WMHs increased (patchy: $r = -0.32$, $P < 0.05$; punctate: $r = -0.35$, $P < 0.05$; sum of patchy and punctate: $r = -0.37$, $P < 0.01$).[4] Four of the eight individual memory tests showed

[3] The impact of the estimated measurement error (test–retest discrepancy scores in Table 3) on this result was evaluated by creating four "noise-added" datasets: (a) add 2.4% to the measured volume of the MFG and 8.0% to the ITG for odd-numbered scans, subtract from both for even-numbered scans; (b) subtract from both gyri for odd-numbered scans, add for even-numbered scans; (c) add to the MFG and subtract from the ITG for even-numbered, subtract from the MFG and add to the ITG for odd-numbered; and (d) the converse of (c). Simultaneous regressions on the M-factor then assessed the replicability of the original result, using age, WMH count, and the "noisy" gray matter volumes from the two gyri. All four regressions were significant ($F(4, 43) > 6.34$, $P < 0.0005$, $R^2 > 0.37$); coefficients for each predictor variable were uniformly negative. In each of the four regressions, WMH count and MFG volume made independently significant contributions to the equation. In versions (a) and (d), age showed only a statistical trend toward significance ($P = 0.10$ and 0.12, respectively). ITG volume made an independently significant contribution in three of the analyses; in version (c) it showed only a trend ($P = 0.10$). These analyses suggest that differential measurement error across gyri do influence the results of regression analyses, but also that the observed relationships were fairly resistant to the noise level of the data.

[4] Correlation between natural log of WMH count and M-factor, $r = -0.34$, $P < 0.02$.

negative correlations with the total number of WMHs (visual paired associates I, $r = -0.38$, $P < 0.01$; visual paired associates II, $r = -0.38$, $P < 0.01$; long-delay cued-recall measure of the CVLT, $r = -0.31$, $P < 0.05$; logical memory II, $r = -0.31$, $P < 0.05$). The correlation between poorer memory and more white matter abnormalities remained significant after excluding the 13 subjects with mild heart disease ($r = -0.37$, $P < 0.05$).

4.4.2. Temporal lobe gray volumes

The composite memory score (M-factor) was negatively correlated with volumes of the inferior temporal and fusiform gyri (both $r = -0.34$, $P < 0.05$). When gyral measures were combined into more global neocortical and medial cortical regions, both left and right temporal neocortex showed negative partial correlations with the M-factor (r of -0.34 and -0.30 respectively ($P < 0.05$); sum of left and right, $r = -0.33$, $P < 0.05$), as shown in Fig. 5.

Correlations between individual gyri and individual memory tests are shown in Table 6, both as partial correlations after removing variance accounted by cranial vault size and age, and as simple correlations with raw volumes. This procedure yielded a large number of statistical tests (96 for 12 gyri by eight memory tests), so that a handful of significant correlations–both positive and negative—would be expected by chance alone (some five at an alpha level of $P < 0.05$). Nonetheless, Table 6 shows a large number of significant correlations between individual gyri and individual memory tests (18 partial, 22 simple), and all were negative. The significant correlations spanned seven of the eight memory tests (excepting delayed cued-recall of visual paired associates), and seven of the eight neocortical gyri in the temporal lobe (excepting the left fusiform). There was no obvious differentiation between the immediate and delayed memory tests, nor between those using free- versus cued-recall (note that there was only one recognition test, but it appeared to follow the same general pattern). Within the medial temporal

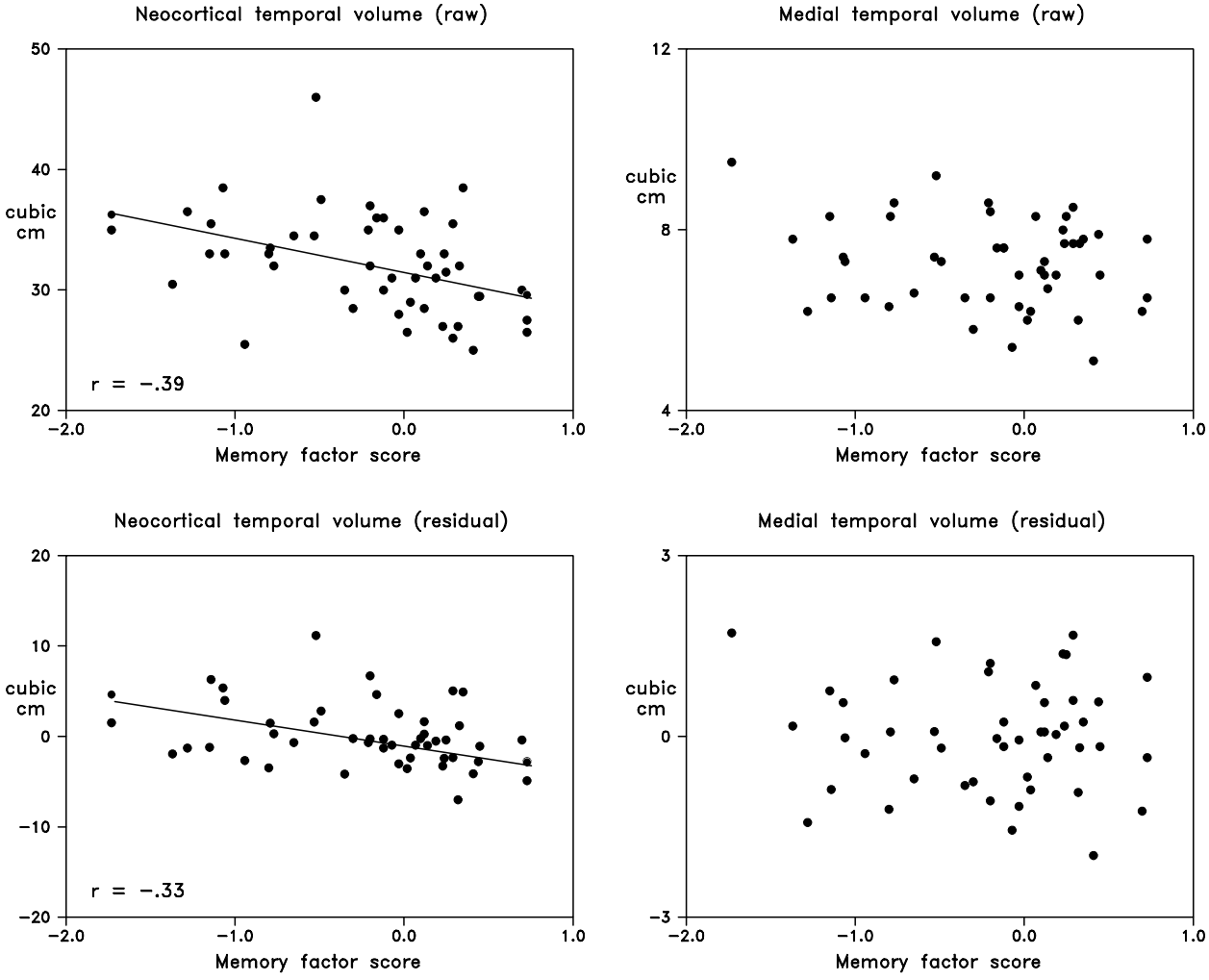

Fig. 5. Top: relationship between volume of left temporal neocortex (sum of superior, middle and inferior temporal gyri plus the fusiform gyrus) and the factor score reflecting performance on five neuropsychological tests of memory. Bottom: residual volume of left temporal neocortex (after removing variance due to cranial vault size and age) is plotted against the memory factor score.

Table 6
Correlations between temporal lobe gyri and memory tests

Gyrus	CVLT		Logical memory I		Logical memory II		Verbal paired association I		Visual paired association II		Visual paired association 1		Visual paired association II		Face recognition I	
L. superior	−0.05	*−0.17*	**−0.35**	***−0.34***	**−0.33**	***−0.36***	0.04	*0.06*	−0.03	*−0.02*	−0.06	*−0.29*	−0.22	*−0.21*	−0.04	*−0.10*
R. superior	**−0.35**	***−0.40***	−0.21	*−0.23*	−0.27	*−0.30*	0.02	*0.05*	−0.19	*−0.14*	**−0.30**	*−0.35*	−0.01	*−0.19*	−0.13	*−0.18*
L. middle	−0.24	***−0.29***	−0.06	*−0.08*	−0.18	*−0.11*	−0.20	*−0.14*	**−0.30**	*−0.23*	−0.22	*−0.26*	0.08	*−0.08*	−0.20	*−0.20*
R. middle	−0.02	*−0.09*	−0.18	*−0.17*	−0.23	*−0.24*	−0.15	*−0.11*	−0.10	*−0.07*	−0.12	*−0.17*	0.14	*0.01*	−0.06	*−0.09*
L. inferior	−0.27	***−0.32***	0.02	*−0.03*	−0.03	*−0.09*	**−0.31**	***−0.31***	**−0.46**	***−0.47***	−0.12	*−0.17*	0.07	*0.01*	**−0.40**	***−0.42***
R. inferior	−0.14	*−0.26*	**−0.35**	***−0.38***	−0.26	***−0.34***	**−0.35**	***−0.32***	**−0.41**	***−0.41***	**−0.30**	*−0.37*	0.25	*0.08*	−0.1	*0.16*
L. fusiform	−0.14	*−0.18*	−0.21	*−0.24*	−0.23	*−0.23*	−0.21	*−0.16*	−0.25	*−0.20*	−0.14	*−0.18*	0.17	*0.05*	−0.25	*−0.25*
R. fusiform	**−0.48**	***−0.52***	**−0.33**	***−0.35***	−0.26	***−0.30***	−0.07	*−0.06*	−0.20	*−0.21*	**−0.34**	***−0.38***	−0.05	*−0.13*	−0.10	*−0.14*
L. hippocampal	−0.19	*−0.22*	−0.20	*−0.18*	−0.16	*−0.18*	−0.17	*−0.12*	−0.21	*−0.17*	−0.27	***−0.29***	−0.09	*−0.18*	0.19	*0.14*
R. hippocampal	−0.27	***−0.30***	−0.21	*−0.21*	−0.26	*−0.19*	−0.04	*−0.02*	−0.18	*−0.16*	−0.23	*−0.26*	−0.16	*−0.24*	0.19	*0.13*
L. parahippocampal	−0.22	*−0.16*	−0.11	*−0.07*	−0.07	*−0.03*	0.07	*0.08*	−0.01	*0.01*	−0.14	*−0.10*	−0.01	*−0.01*	−0.08	*−0.08*
R. parahippocampal	**−0.30**	*−0.15*	0.02	*0.10*	−0.1	*0.01*	−0.16	*−0.16*	**−0.31**	*−0.27*	**−0.37**	*−0.25*	−0.09	*−0.08*	−0.23	*−0.16*

Correlations between gyral gray matter volume and cognitive test score: left columns are partial correlations after removing variance due to cranial vault size and subject age, right columns (italics) are correlations with raw volumes. Bold r are $P < 0.05$, $r > 0.37$ are $P < 0.01$, $r > 0.41$ are $P < 0.005$, and $r > 0.46$ are $P < 0.001$. Note that the "M" factor score is a composite measure based on performance in the CVLT, logical memory I, verbal paired associates I, visual paired associates II, and face recognition I tests.

lobe, the right parahippocampal gyrus demonstrated significant relationships to three of the eight memory tests, but other medial temporal regions yielded no significant *r*. (The combined volumes of left and right hippocampi were negatively correlated with visual paired associates 1, $r = -0.29$, $P < 0.05$, and marginally with the CVLT, $r = -0.28$, $P = 0.07$, but these correlations did not survive correction for vault and age.) Fig. 6 shows correlations between individual memory tests and neocortical temporal volumes. Overall, the individual correlations support the more global analyses in indicating that smaller temporal lobe volumes were associated with better memory performance in this sample.

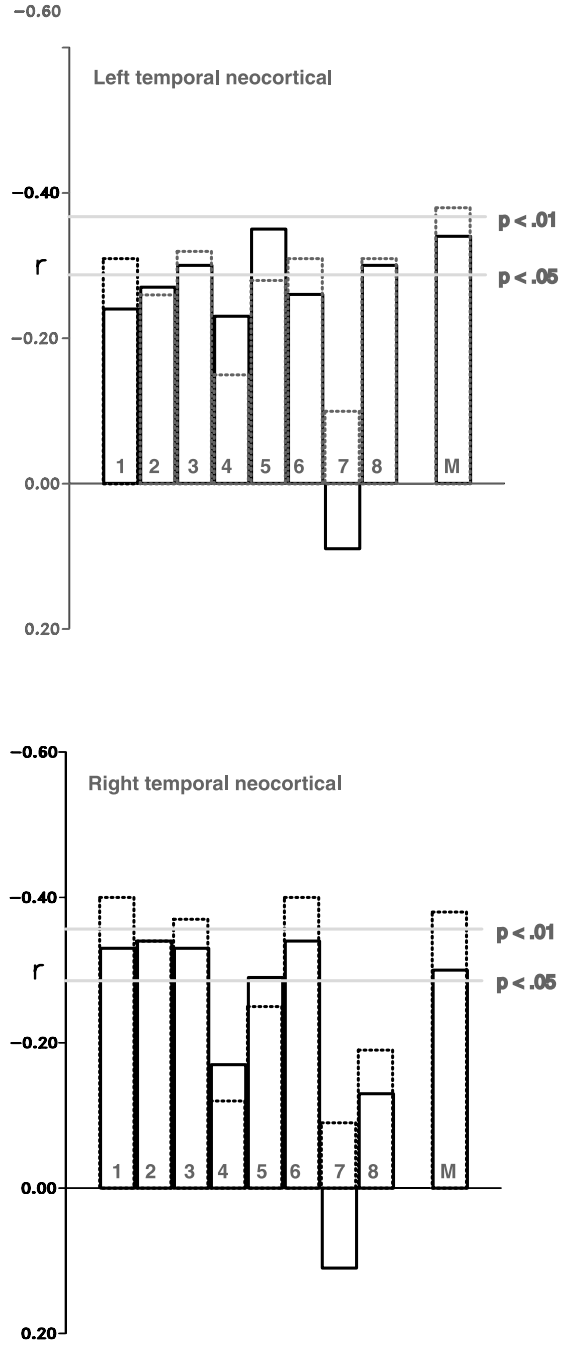

Fig. 6. Correlations between memory tests and gray matter volumes in the temporal lobe. Solid lines are partial correlations after removing variance in volume associated with cranial vault size and subject age. Dashed lines are simple correlations with raw volumes. Test 1 is long-delay cued-recall measure of the California verbal learning test (Delis et al., 1987); Test 2 is logical memory I; Test 3 is logical memory II; Test 4 is verbal paired associates I; Test 5 is verbal paired associates II; Test 6 is visual paired associates I; Test 7 is visual paired associates II; Test 8 is face recognition I (tests 2–8 from the Wechsler memory scale III). "M" is the factor score composite measure of memory performance.

4.4.3. Frontal lobe gray volumes

Like some of the temporal lobe gyri, bilateral volume of the middle frontal gyrus showed a negative partial correlation with the M-factor ($r = -0.42$, $P < 0.005$), shown in Fig. 7. Relationships between individual memory tests and the middle frontal gyri are shown in Table 7.

4.4.4. Occipital lobe gray volume

Occipital volume showed no significant correlations with the M-factor, nor with the F-factor or IQ measures.

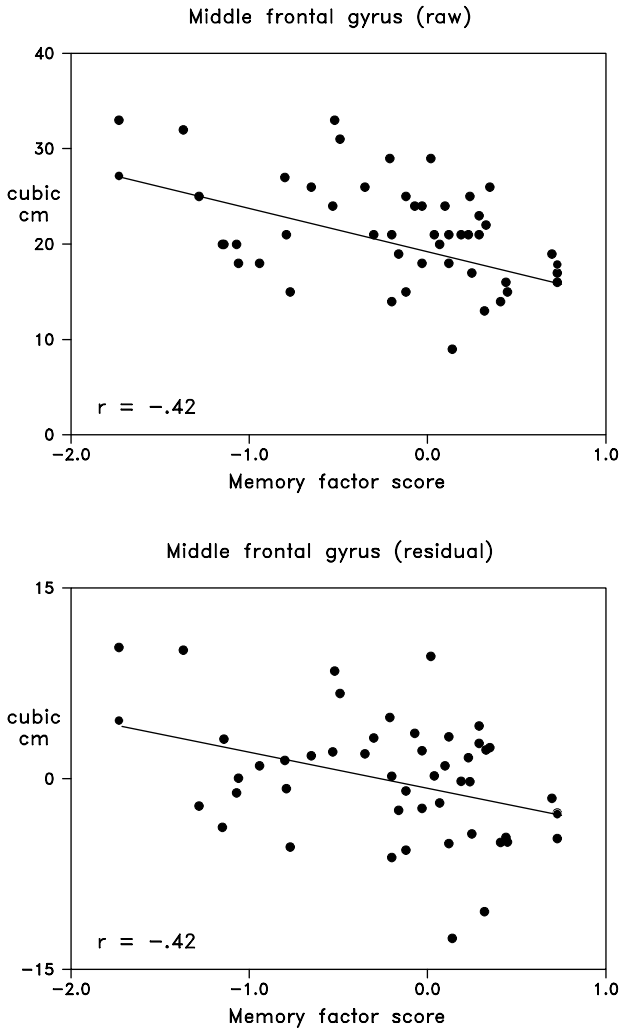

Fig. 7. Top: relationship between volume of middle frontal gyrus and the factor score reflecting performance on five neuropsychological tests of memory (M-factor). Bottom: residual volume after removing variance due to cranial vault size and age.

Table 7
Correlations between individual memory tests and middle frontal gyri

	Left MFG		Right MFG	
CVLT	−0.33*	(−0.34*)	−0.31*	(−0.36*)
Logical memory I	−0.53****	(−0.47****)	−0.51****	(−0.47****)
Logical memory II	−0.39**	(−0.37*)	−0.40**	(−0.40**)
Verbal paired associates I	0.07	(0.09)	−0.10	(−0.06)
Verbal paired associates II	0.06	(0.07)	−0.05	(−0.04)
Visual paired associates I	−0.10	(−0.14)	−0.15	(−0.21)
Visual paired associates II	−0.24	(−0.30*)	−0.18	(−0.28)
Face recognition I	−0.02	(−0.05)	−0.16	(−0.19)
M-factor	−0.36*	(−0.35*)	−0.44***	(−0.45***)

Partial correlations between gyral volume and cognitive test score, after removing variance due to cranial vault size and subject age; correlations with raw volumes in parentheses. CVLT is the long delay cued-recall test of the California verbal learning test (Delis et al., 1987), other tests from the Wechsler memory scale III (Wechsler, 1997). Note that the "M" factor score is a composite measure based on performance in the CVLT, logical memory I, verbal paired associates I, visual paired associates II, and face recognition I tests.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.005$.
**** $P < 0.001$.

5. Discussion

5.1. Age effects on frontal and temporal gray matter

Although the subjects were drawn from a restricted age range of 65–85 years, older age was associated with smaller gray matter volumes in the temporal and frontal lobes. No age effect was observed for occipital gray volume. This differential pattern of loss across lobes is generally consistent with previous reports from subjects across a broad age span (Bigler et al., 1997; Coffey, 2000). For the summed volumes of left and right temporal neocortex, the slopes of the regression lines estimate 7.8 and 7.0% gray matter volume loss per decade, respectively. For the frontal gyri (summed), the slope of the age/volume functions estimate gray matter loss at 8.9% per decade. The magnitudes of these age effects are somewhat larger than previously reported: Courchesne et al. (2000) estimate 5% reduction per decade for whole-brain gray matter, Jernigan et al. (2001) estimate 2.3% for whole-cortex gray, and Raz et al. (1997) estimate 4.9% per decade for prefrontal gray. Our estimates may reflect the participation of only adults over the age of 65, rather than a mix of young, middle-aged and elderly adults as in the previous reports.

Within the frontal lobe, age-related loss of gray matter followed a dorsal/ventral gradient, with the largest effect in the inferior frontal gyrus, similar to Tisserand et al.'s (2002) recent report of a larger age effect in the IFG than MFG. Within the temporal lobe, the largest age effects were observed for the superior and middle gyri, while age differences in the inferior regions were small and non-significant. The age effect for the hippocampus was moderate, and significant only when no correction for cranial vault size was applied. No previous MR studies have evaluated age effects in both superior and inferior regions of the temporal lobe in the same sample, so that the differential impact of age observed here is a novel finding. In studies that have evaluated more than one temporal lobe region, a more typical approach is to contrast age effects in the hippocampus to a single neocortical gyrus, or to the temporal lobe as a whole. These results have been extremely mixed, from reports that hippocampal volumes decline precipitiously across age while neocortical regions experience less volume loss (Golomb et al., 1994; Jernigan et al., 2001), to mild losses in both neocortical and medial regions (Raz et al., 1997), to observations of neocortical but not hippocampal volume loss in healthy subjects (Good et al., 2001; Gur et al., 2000; Sullivan et al., 1995). The present results fall into the category of greater neocortical than hippocampal tissue loss. It remains possible that accelerated atrophy in the medial temporal lobe relative to the rest of the temporal lobe is a sign of incipient dementia, but this issue is hotly debated (Kaye et al., 1997; Ohnishi, Matsuda, Tabira, Asada, & Uno, 2001).

5.2. MR measures and "frontal" cognitive tests

A more central goal of the present study was to relate regional gray matter volumes to cognitive abilities in late life. Our working hypothesis was that age-related decrements in gray matter would lead to decrements in the cognitive abilities served by specific regions. One aspect of the results was disappointing in that no relationships were observed between gyral volumes in the prefrontal cortex and performance in neuropsychological tests thought to be dependent on prefrontal cortex. This may reflect limitations in the regions measured, which did not cover the orbital gyrus, gyrus rectus, or cingulate gyrus. It is also true that the neuropsychological tests comprising the "F-factor" score are diverse, so that high performance is likely to depend on numerous discrete cognitive abilities. Although the individual tests share sufficient variance to be identified as a cohesive factor in a statistical factor analysis (Glisky et al., 1995), their neural substrates may be too widely distributed for performance to correlate with specific frontal gyri. To a lesser degree, this argument also extends to individual tests: the notion of frontal executive function is that prefrontal cortex exerts a modulatory influence on basic processes subserved by posterior cortical regions (Knight, Staines, Swick, & Chao, 1999), so that successful performance depends on the integrity of both frontal and posterior regions and their successful coordination (see Gunning-Dixon & Raz, 2003; for a similar suggestion about working memory).

In the final regression analysis, two MR variables did have predictive value for the F-factor: cranial vault size and prevalence of white matter hyperintensities ($R^2 = 0.22$).

The latter finding is in agreement with Gunning-Dixon and Raz's (2000) recent meta-analysis of WMHs and executive function. If long-distance projections from prefrontal cortex to more posterior regions are the anatomical substrate of executive function, deterioration of fiber tracts would be expected to have a deleterious effect. One limitation of the present study is that WMH counts were global rather than regional; a targeted count of hyperintensities in the white matter underlying the frontal lobe may yield a yet stronger relationship with executive function.

The meaning of the association between cranial vault size and the F-factor is much less clear. Mature cranial capacity is attained at age 12–15 and shows little to no change thereafter (Courchesne et al., 2000; Pfefferbaum et al., 1994). Cranial size in old age thus reflects both genetic factors and conditions during embryonic, neonatal and childhood development, rather than aging. Protein malnutrition early in life, for instance, results in smaller head and brain size in childhood and early adulthood (Oyedeji et al., 1997; Portman, Neuringer, & Alexander, 1987). Two recent studies report negative associations between cranial vault size and physical abuse in childhood (De Bellis, Keshavan, & Clark, 1999; Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002). Some researchers have suggested that large head or cranial vault size is an index of "neural reserve", such that large head sizes are associated with better cognitive function in the healthy elderly (MacLullich et al., 2002; Reynolds, Johnston, Dodge, DeKosky, & Ganguli, 1999), and with reduced risk of meeting the criteria for Alzheimer's disease (Graves et al., 2001; Miller & Corsellis, 1977; Schofield, Logroscino, Andrews, Albert, & Stern, 1997, but see ref. (Edland et al., 2002) for conflicting findings). The simplest version of this theory is that larger intracranial capacity translates to larger remaining brain size and cognitive ability even after aging or AD pathology have taken their toll. By this theory, current brain size would appear to be the critical factor. In the present results however, cerebral volume had a weaker and non-significant relationship with the F-factor as compared to cranial vault size (simple r for cerebral volume and F-factor $= 0.19$, ns; simple r for vault size and F-factor $= 0.36$, $P < 0.02$). We are aware of no other studies that contrast current total brain size and intracranial capacity as determinants of intellectual function in old age, although MacLullich et al. (2002) concluded that intracranial capacity was more important than the current sizes of the frontal or temporal lobes. A more sophisticated version of neural reserve theory might stipulate that instead of merely serving as a proxy for current brain size, large head size reflects favorable conditions during early development that also lead to optimal neural function at the microanatomic level (see Stern, 2002; for discussion of different definitions of "neural reserve"). This idea may be difficult to test in living human subjects.[5] In the present study, the influence of cranial vault size was restricted to the F-factor, and not apparent for memory ability, verbal IQ, or performance IQ, so that support for head size as an indication of "neural reserve" was modest.

5.3. MR measures and memory ability

Significant relationships between memory performance and gray matter volumes of the middle frontal gyrus and most temporal lobe gyri were observed. Within the temporal lobe, memory correlations were more robust for the neocortical gyri than the hippocampus or parahippocampal gyrus, although a small number of correlations between individual memory tests and medial structures were observed. Inferior temporal and middle frontal gray volumes, age, and prevalence of white matter abnormalities jointly accounted for 41% of the variance in memory performance. Although memory encoding and retrieval have more traditionally been associated with temporal cortex, patients with damage to prefrontal cortex show mild memory deficits (Wheeler, Stuss, & Tulving, 1995), and hemodynamic imaging studies frequently report activation of dorsolateral prefrontal cortex (largely composed of the MFG) during memory tasks (Cabeza & Nyberg, 2000). The present correlations linking both temporal and prefrontal cortex to individual memory ability are consistent with the view that normal memory performance is dependent on both temporal and frontal regions.

Because we had adopted the view that gray matter volumes in old age would largely reflect age-related tissue loss, and further that age-related loss is a mild version of the loss that occurs during neurodegenerative diseases like Alzheimer's, we were surprised by the direction of the correlations–that smaller gray matter volumes were associated with better memory performance across a large battery of tests. We initially considered artifactual sources of the negative correlations. Inspections of the scatter plots in Figs. 5 and 7 indicate that the correlations do not reflect undue influence of outlier subjects. Tables 6 and 7, and Fig. 6, indicate that the correlations are not peculiar to one memory measure. The negative correlations did not hinge on the exact statistical procedures: although normalizing for intracranial vault size and age influenced individual correlations, the general pattern of results was much the same for the raw and partial correlations.

Finally, we considered a potential MR artifact specific to the elderly population, namely the possibility that voxels occupied by deteriorating white matter were misclassified as gray matter. The present results, like those of previous studies in the elderly population, showed hyperintense spots that clearly lay within the white matter underlying the cortex and were coded as such by one of the

[5] In non-human primates, manipulations that influence cortical structure at the microscopic level (such as neonatal nutrition) may be associated or dissociated with changes in overall brain size (see Palackal, Kujawa, Moretz, Neuringer, & Sturman, 1991; Palackal, Neuringer, & Sturman, 1993) for examples of a dissociation).

authors. The concern is that additional patches of white matter hyperintensity were coded as gray matter. Jernigan et al. (2001, p. 592) describes this as a potential problem faced by all structural MR studies of older adults: "All tissue segmentation schemes that classify voxels as gray, white, or CSF will misclassify such voxels, since these changes represent the shift of white matter signal values toward, into, and ultimately beyond, the range of signal values characteristic of gray matter". Despite the inherent difficulty of the tissue classification problem, there are several reasons to think that it did not contribute substantial error to the present measurements. First, the segmentation methods incorporated input from human operators who were well aware of the presence of white matter hyperintensities, rather than the more automated methods which Jernigan et al. (2001) pick out as particularly susceptible to gray/white misclassification in elderly brains. By employing the more labor intense method of tissue segmentation based on local (gyri-specific) rather than global (lobe or brain-wide) values, operators were able to make fine adjustments in the segmentation criteria to avoid grouping white matter hyerintensities with gray matter. Second, as Jernigan et al. (2001) also note, the net effect of misclassifying deteriorating white matter as gray is to reduce the estimate of age-related decrements in gray matter volume. The present observation of substantial gray volume decrements across the 65–85 year age range suggests relatively little contribution from misclassified voxels. Finally, the regression equation predicting memory performance from the MR measures (Table 5) indicates that gray matter volumes and the prevalence of identified white matter hyperintensities accounted for independent variance in memory performance. These considerations suggest that the observed correlations between smaller gray matter volumes and better memory performance are unlikely to be artifactual.

The accompanying review paper (Van Petten, in press) indicates that negative correlations between MR volumetric and memory measures are not especially rare across published studies, so that it is worth revisiting our initial assumption that gray matter volumes in the elderly largely reflect tissue loss in late life. A more complete view is that the brain of an adult in late life will reflect developmental processes, any brain changes that occur in early and mid-adulthood, and finally any processes that are specific to late life, which may include pathology. MR morphometry studies of children and adolescents indicate that cortical gray matter volume (relative to brain or cranial vault size) increases from birth through early childhood (6–9 years of age), then declines across later childhood and teenage years (Courchesne et al., 2000; Pfefferbaum et al., 1994; Sowell, Trauner, Gamst, & Jernigan, 2002). This developmental decline in gray matter volume is likely to reflect regressive events in cortical development described in both monkey and human studies, such as the pruning of ineffective synapses (Cowan, Fawcett, O'Leary, & Stanfield, 1984; Huttenlocher, 1993; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986), and occurs during a period of obvious expansion in cognitive abilities. A recent MR study makes this connection more directly. Sowell and colleagues (Sowell, Delis, Stiles, & Jernigan, 2001) observed a direct relationship between smaller gray matter volumes and better performance in both verbal and nonverbal memory tests in subjects aged 7–16 years. Their nonverbal memory test additionally yielded a negative correlation with medial temporal gray matter volume.

Studies of healthy young adults (18–31 years) have similarly reported negative correlations between memory performance and MR volumes of medial temporal lobe structures (Chantôme et al., 1999; Foster et al., 1999; these studies did not measure the neocortical gyri additionally reported here). Foster et al. (1999, p. 715) interpreted the adult volumes as the residue of developmental processes, specifically that "insufficient pruning of the hippocampus during childhood and adolescence (following adequate growth) may lead to reduced mnemonic efficiency". The pruning part of this hypothesis is speculative; one can imagine other factors that might influence both volumetric measures and neural efficiency, such as neuron/glia ratios. But the results from young adults are of interest because they reflect intrinsic individual differences in mnemonic ability, uncontaminated by declines that might occur in late life. As a thought experiment, we can wonder what would happen if Foster's (or Chantome's) subjects were rescanned in 50 years. Would smaller volumes still be associated with better memory? Or would cerebral atrophy in late life cause a reversal of the relationship?

This particular experiment is unlikely to take place, but considering the alternative outcomes forces consideration of the fact that gray matter volumes in late life reflect an individual's entire lifespan. During development, gray matter reduction appears to have a positive influence on memory ability (see also; Van Petten, in press), while later reductions may be deleterious. Which of these determinants of gray matter volume proves dominant is likely to be highly variable across elderly individuals. Participants with Alzheimer's disease are one extreme, for whom small volumes of temporal lobe structures have been clearly linked to impaired memory (Deweer et al., 1995; Köhler et al., 1998; Petersen et al., 2000; Wilson et al., 1996). Similar observations have been made for elderly subjects diagnosed with mild cognitive impairment or age-associated memory impairment (Golomb et al., 1996; Soininen et al., 1994). In contrast, the participants in the present experiment can be described as "successfully aging"; mean verbal IQ, performance IQ, and index scores from the Wechsler memory battery (WMS-3) were more than a standard deviation above those of normative age groups. The same description can be offered for the elderly samples in two other recent reports of negative correlations between cortical volumes and memory ability. Salat et al. (Salat, Kaye, & Janowsky, 2002) observed negative correlations between working memory measures and prefrontal gray matter volumes in older adults (aged 72–94) who scored substantially above the age norms for multiple

tests from the Wechsler memory and intelligence batteries.[6] Köhler et al. (1998) observed negative correlations between hippocampal volumes and both immediate and delayed verbal recall in an elderly sample with mini-mental state scores that also appear to be above the normative mean.

Our supposition is thus that, in cognitively superior elderly samples, variation in memory ability across individuals may be largely determined by pre-existing differences rather than differential degrees of age-related decline. When such intrinsic individual differences dominate measures of memory ability, the relationships between gray matter volumes and memory measures will tend to resemble those observed in young adults, which have frequently consisted of negative correlations (Chantôme et al., 1999; Foster et al., 1999; Van Petten, in press). When age-related decline or neuropathology dominate tests of current memory ability, positive correlations will be observed. The hypothesis that developmental versus late-life changes in gray matter volumes exert opposing influences on memory function is speculative, but offers a unified account for the variable outcomes observed across published studies.

In addition to the relative dominance of pre-existing versus age-related influences on current memory ability, another source of variability in the relationship between gray matter volumes and memory performance will be the degree of age-related atrophy across cortical regions. In the present cross-section of the 65–85 year age range, regional estimates of gray matter loss ranged from essentially zero in occipital cortex to over eight percent per decade for the middle temporal and inferior frontal gyri. The gray matter volumes which showed the strongest negative correlations with memory performance were in regions with non-significant age effects (inferior temporal, fusiform, and middle frontal gyri), consistent with the view that these regional measures were more strongly influenced by developmental influences than by late-life atrophy. Similarly, Salat and colleagues (Salat et al., 2001; Salat et al., 2002) report negative correlations between working memory and a region of prefrontal cortex (orbital) that showed the least age-related change in volume.

In contrast to what we have suggested is an inherent ambiguity in the interpretation of gray matter volumes in cognitively intact older adults, white matter changes may be a more specific reflection of the negative aspects of aging. In contrast to the apparently continuous decline in gray volume beginning in late childhood, white volume is reported to increase across early adulthood and plateau in midlife; when declines are observed, these are reported to begin only after the age of 60 (Courchesne et al., 2000; Jernigan et al., 2001; Paus et al., 2001; Pfefferbaum et al., 1994). The present study did not quantify white matter volumes, but instead the prevalence of hyperintense spots in the WM underlying the cortex. These are rarely observed in the brains of healthy individuals prior to age 50 (Jernigan et al., 2001), and were associated with poor performance in both of the cognitive domains examined here. If, as generally thought, WMHs in MR scans indicate degenerating myelin (and possibly the underlying axons), these may be early signs of a loss of cortical connectivity. Like executive function, episodic memory may be especially reliant on coordinated activity among cortical regions, and thus vulnerable to even subtle disruptions of connectivity in cognitively intact older adults.

[6] Differences among elderly samples may also be relevant for relationships between prefrontal gray volumes and cognitive measures. In a recent report (Gunning-Dixon & Raz, 2003) of a negative correlation between prefrontal gray (superior, middle, inferior and orbital) and perseverative errors in the WCST, the number of such errors appears to be high for the age range tested (29.4, as compared to mean of 12, S.D. of 11 in the Heaton (2004) norm). In contrast, the number of perseverative errors for the current sample is about average for the version of the WCST used here (4.75 as compared to 4.1, S.D. 4.8 in the Hart et al. (1988) norm).

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Appendix A. Definition of regions-of-interest

A.1. Cerebrum

Cerebral volumes were extracted from axial SPGR images. The original images included one hundred and twenty-four 1 mm thick slices. This number was reduced by summing every 10 consecutive slices, starting with the lowest slice on which the temporal lobes were visible. The cerebral volumes were estimated from the resulting composite slices. Previous work (Plante, Uecker, Senkfor, & Gmitro, 1998) indicated that sampling as few as 1 in 10 MRI slices produced accurate volume estimates of objects with regular shapes.

An operator traced between the cerebrum and skull, and between the cerebrum and cerebellum to extract the cerebrum from other parts of the image.

The operator identified “seed” voxels within the extracted composite slice that corresponded to gray matter, white matter, and cerebral spinal fluid. A Matlab-based program (Qi, 1999) was used to classify the remaining pixels into these tissue types based on the values of the seed voxels previously identified.

Voxels classified as either gray matter or white matter were summed over consecutive composite slices to produce the area of brain tissue within the cerebrum. This was converted into a volume by multiplying by the slice thickness of the composite slices measured.

A.2. Cerebral vault

The cerebral vault measure was extracted from the axial SPGR images. The original 1 mm slices were rotated orthogonally into the sagittal plane. The midline sagittal image was selected for segmentation.

An operator traced along the inner edge of the skull, between the cerebellum and cerebrum along the tentorium, and across the brainstem in a straight line from the most superior edge of the tentorium to the base of the frontal lobe. This area was extracted from the remaining portions of the image.

Numerical values for voxels corresponding to brain tissue and CSF within the extracted region were displayed and a value that accurately separated these two types of voxels was selected. The image was then thresholded above this value and the number of voxels corresponding to brain tissue and CSF were summed to produce an area value for the midline cerebral vault.

A.3. Frontal gyri

Frontal measurements were derived from the axial SPGR images. The original 124 axial images were reduced by summing every four consecutive slices, starting with the lowest slice on which the frontal lobes were visible. ROIs were obtained from the resulting composite slices. This sampling rate has been shown previously to result in acceptable accuracy for volume estimates of irregularly shaped objects (Plante et al., 1998).

Frontal ROIs included the superior frontal gyrus, the middle frontal gyrus and the inferior frontal gyrus. These were extracted together from the composite slices. The medial border of the SFG was the cingulate sulcus. When this sulcus included two branches (common anteriorly), the most anterior branch of this sulcus was used. The lateral border of the SFG was the superior frontal sulcus. This sulcus was also the anterior border of the MFG. Its posterior border was the inferior frontal sulcus, which also formed the anterior border of the IFG. The posterior border of the IFG was the precentral sulcus.

Extraction of each ROI began at the most inferior composite slice on which the orbital gyrus was no longer visible and continued superiorly until the gray matter could not be distinguished from the meningies on the most superior slice, or until the gyrus was no longer visible (in the case of the IFG).

Operators extracted each frontal ROI from the remaining image by tracing along the midline of each anterior or medial defining sulcus and around the outer edge of the cortex, and along the midline of each posterior defining sulcus. Tracings included some supra-gyral CSF and white matter between the sulci that formed the borders of the ROIs.

The operator identified "seed" voxels within the extracted composite slice that corresponded to gray matter, white matter, and cerebral spinal fluid. A Matlab-based program (Qi, 1999) was used to classify the remaining pixels into these tissue types based on the values of the seed voxels previously identified.

Voxels classified as gray matter were summed over consecutive composite slices to produce the slice area of brain tissue within each ROI. This was converted into a volume by multiplying by the slice thickness of the composite slices measured.

A.4. Temporal gyri

Temporal lobe measurements were made on coronal obliqued Spin Echo images. These T2-weighted images included 32 contiguous 3 mm slices from which the ROIs were obtained. The slice angle was standardized to fall perpendicular to the long axis of the left hippocampus. This standardization minimized measurement error due to intersubject variations in slice angle. This method of slice placement was preferred to rotating the axial SPGR images, because non-orthogonal rotations introduce interpolation error (Plante et al., 1998), the degree of which would vary from subject-to-subject. We wished to minimize any such sources of error variance that might reduce statistical power. T2-weighting was used for this set of images to facilitate identification of white-matter anomalies (see below) without having to obtain additional images which may have stressed older subject's capabilities to comply with scanning procedures.

Temporal ROIs included the superior temporal gyrus, the medial temporal gyrus, the inferior temporal gyrus, the fusiform gyrus, the parahippocampal gyrus (PHG), and the hippocampus (Hi). The superior border of the STG was the lateral sulcus. The superior temporal sulcus was the inferior border of the STG, as well as the superior border of the MTG. The middle temporal sulcus formed the inferior border of the MTG and the superior border of the ITG. When a bifurcated branch was visible between the MTG and ITG, the superior portion was included with the MTG and the inferior portion included with the ITG. The inferior temporal sulcus delineated the boundary between the ITG and the fusiform gyrus. The medial border of the fusiform gyrus was the collateral sulcus. This sulcus was also the inferior border of the PHG. The lateral superior borders of the Hi were defined by the inferior horn of the lateral ventricle. The inferior border of the Hi was the superior edge of the white matter of the PHG.

Extraction of the PHG and Hi began at the most anterior slice on which both the elongated inferior horn of the lateral ventricle and the characteristic coiled shape of the Hi were visible. The parahippocampal gyrus merges with the temporal pole and this general region contains several cortical fields by cytoarchitectonic criteria (not available in MR); the PHG measure used here can be assumed to include both entorhinal and perirhinal cortex as well as portions of the posterior parahippocampal gyrus, but not temporopolar cortex (see Insausti et al., 1998a,b). Extraction of the remaining

ROIs began at the most anterior slice on which the inferior horn of the lateral ventricle and amygdala were visible. Extraction for all ROIs continued posteriorly until the trigones of the lateral ventricles were clearly visible.

With the exception of the Hi, an operator extracted each temporal ROI from the remaining image by tracing along the midline of each superior or lateral defining sulcus and around the outer edge of the cortex, and along the midline of each inferior or medial defining sulcus. The Hi was extracted by tracing along the midline of the elongated inferior horn of the lateral ventricle and along the superior border of the white matter of the PHG. Tracings included some blood vessels, supra-gyral cerebral spinal fluid, and white matter between the sulci that formed the border of the ROIs. Where possible, tracings excluded areas of apparent demyelinization.

Operators identified numerical values for voxels within the extracted slice that corresponded to gray matter, white matter and CSF. A value that accurately separated the CSF and gray matter was selected, and a value that accurately separated the gray matter and white matter was selected. These values were used to quantify the voxels corresponding to gray matter. Note that this thresholding procedure was used because the range of values for the T2-images, the narrow gyri within the temporal lobe, and the presence of white matter abnormalities combined to make the procedure used with other ROIs less stable and accurate with temporal lobe ROIs. Thresholding was completed using a customized program that used Khoros software.

Voxels quantified as gray matter were summed over consecutive slices to produce the slice area of brain tissue within each ROI. This was converted into a volume by multiplying by the slice thickness of the slices measured.

A.5. Occipital lobes

Occipital lobes were extracted from the axial SPGR images. The original 124 axial images were reduced by summing every four consecutive slices, starting with the lowest slice on which the occipital lobes were visible. ROIs were obtained from the resulting composite slices.

An operator extracted the occipital ROI from the remainder of the image by tracing around the occipital lobes at lower slice levels, where they appear detached from the rest of the brain in the axial view, or between the occipital lobes and cerebellum at slightly higher levels.

At higher levels, the occipital lobes are contiguous with the temporal lobes. These two lobes were separated by identifying the occipitotemporal sulcus (at or near the preoccipital incisura). This sulcus constituted the anterio-lateral border of the occipital ROI. This sulcus was followed superiorly over consecutive composite slices. The anterio-medial border was the most anterior edge of the gray matter adjacent to the posterior edge of the brainstem.

Extraction was discontinued at the level of the splenium of the corpus callosum because of the loss of the occipito-temporal sulcus as the anterior landmark around this level.

The operator identified "seed" voxels within the extracted composite slice that corresponded to gray matter, white matter, and cerebral spinal fluid. A Matlab-based program (Qi, 1999) was used to classify the remaining pixels into these tissue types based on the values of the seed voxels previously identified.

Voxels classified as gray matter were summed over consecutive composite slices to produce the slice area of brain tissue within the cerebrum. This was converted into a volume by multiplying by the slice thickness of the composite slices measured.

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