

Regional White Matter and Neuropsychological Functioning across the Adult Lifespan

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Background: *The current study utilized magnetic resonance imaging (MRI) to more fully elucidate the relationship among age, regional white matter, and neuropsychological functioning.*

Methods: *One hundred ninety-nine neurologically healthy adults received MRI and standardized neuropsychological assessment. MR images were spatially normalized and segmented by tissue type; relative white matter values in each of the four cerebral lobes in each hemisphere were computed. Subjects were divided into Younger (ages 21–30), Middle (ages 31–54), and Older (ages 55–79) age groups.*

Results: *The Older group had significantly less overall relative white matter than the Middle group, who had significantly less overall relative white matter than the Younger participants ($F(2, 193) = 5.42, p = 0.005$). Differences in frontal lobe white matter were of largest magnitude, followed by temporal lobe ($F(6, 579) = 3.32, p = 0.003$). Age and frontal and temporal lobe white matter were primarily associated with performance on neuropsychological tests of executive functioning and memory. Mediation analysis suggested that frontal lobe white matter mediated the relationship between age and performance on tasks of executive functioning and memory.*

Conclusions: *The results confirm age-associated decline in frontal and temporal white matter, and age-related cognitive decline in several domains. Decline in neuropsychological functioning is, in part, mediated by a relative age-related reduction in frontal white matter.*

Key Words: Normal aging, structural MRI, white matter, cognition, memory, executive functioning

In an effort to better characterize brain changes across the lifespan, there has been recent increased focus on the examination of brain morphology in healthy elderly individuals using structural magnetic resonance imaging (MRI) protocols. Findings from these studies have generally demonstrated age-associated reduction in total brain volume. However, there has been a paucity of studies that has related these structural changes to age-related decline in neuropsychological functioning. The purpose of this study was to comprehensively examine relative white matter changes across the adult lifespan and to determine the interrelationship among age, relative white matter, and cognitive functioning.

Cross-sectional and longitudinal MRI studies that have examined whole-brain changes across the lifespan have demonstrated a decline in total brain volume in later life (Courchesne et al 2000). Our previous study, using voxel-based morphometry, revealed an average loss of $2.5 \pm .5$ mL (approximately .3%) per year in global brain volume across eight decades (Grieve et al 2005). In a longitudinal analysis, Resnick et al (2003) demonstrated that tissue loss was particularly pronounced ($5.4 \pm .3$ cm³

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annually, approximately 1.6%) in healthy individuals over age 60. This finding replicated an earlier study (Tang et al 2001) that found an annual decrease of $2.1\% \pm 1.6\%$ total brain volume in healthy adults in their 70s and 80s. Other large-scale studies have shown linear age-related decline in brain volume throughout adulthood in research samples (Courchesne et al 2000; Good et al 2001; Resnick et al 2000) and in population-based studies (Decarli et al 2005). Thus, there is a culmination of evidence in the extant literature supportive of age-associated total brain volume decline.

While studies that examine total brain volume are important in establishing gross anatomical changes across the lifespan, investigation of regional changes can help establish specific functional or neurobiologic systems that selectively decline with age. Indeed, several investigators have reported selective regional changes across the lifespan. Structural imaging studies in both animals (e.g. Tapp et al 2004) and humans (e.g. Decarli et al 2005; Pfefferbaum et al 1998; Raz et al 1997; Salat et al 2001, 2004) show consensus that the greatest age-associated decline in volume occurs in the frontal lobe. Some studies also report substantial tissue loss in the temporal lobe (Decarli et al 2005), using voxel-based morphometry we have found marked loss in the parietal lobe (Grieve et al 2005). There is relatively little age-related change reported in occipital lobes. Results from early postmortem aging studies would suggest that these changes are due to neuronal loss (e.g. Brody 1955); however, more recent analyses indicate a maintenance in the number of neurons across the adult lifespan, with greater evidence of neuronal shrinkage and synaptic density loss, particularly in anterior brain regions (Haug and Eggers 1991). Thus, age-related morphological changes could be the consequence of synaptic or connectivity degradation rather than a reflection of widespread neuronal apoptosis.

When examining age-related brain changes with MRI, relatively few studies have considered white and gray matter separately. Age-associated white matter loss may reflect myelin degeneration (Peters 2002) and would be consistent with the idea that the aging brain is associated with a reduction in efficient

neuronal connectivity (Albert 1993). Guttmann et al (1998) reported significant age-associated reduction in cortical white matter across the adult lifespan, in the absence of a significant decrease in total gray matter. Although other investigators have shown age-related decline in gray matter volume (Coffey et al 1992), the negative association between age and total white matter volume may be greater than that between age and total gray matter volume (Courchesne et al 2000; Resnick et al 2000), as there is some evidence that the longitudinal rate of decline for white matter is greater than for gray matter (Bartzokis et al 2003; Resnick et al 2003).

Bartzokis and colleagues (Bartzokis 2004; Bartzokis et al 2003) have proposed that regional age-related white matter decline recapitulates white matter development. During brain maturation, myelin-producing oligodendrocytes that are operative during later stages of brain development are particularly vulnerable to insult because of qualitative differences in the axons they myelinate and decreases in their ability for myelin repair (Hildebrand et al 1993). As anterior brain regions are the last to fully myelinate (Nieuwenhuys 1999; Paus et al 2001), they may be the most vulnerable to age-related decline. Indeed, MRI studies using morphometric techniques have demonstrated selective age-associated anterior white matter decline (Bartzokis et al 2003; Good et al 2001; Raz et al 2005; Resnick et al 2000; Salat et al 2001) and increased white matter abnormalities (Jernigan et al 2001).

Although several studies have demonstrated sex differences in brain morphology, with men possessing significantly larger brains than women (Raz et al 2004), it is less clear what the exact regional distribution of these differences is and how they may interact with age. Some (Coffey et al 1998; Raz et al 2004; Xu et al 2000), but not all (Murphy et al 1996) reports demonstrate consistently greater age-associated volume loss in men than women. Examinations of sexual dimorphism with MRI have generally been limited to either undifferentiated tissue or to gray matter alone. Similarly, though it has been well-established that globally the right cerebral hemisphere is larger than the left hemisphere, there is less consistency in reported specific asymmetrical regions as well as how cerebral asymmetry may interact with age and sex (Raz et al 2004).

The reported changes in white matter in older adulthood may have particular relevance to cognitive outcome. While the exact neurobiological underpinnings of changes in neuropsychological functioning across the lifespan remains somewhat elusive, one compelling, though controversial (Band et al 2002; Greenwood 2000) theory (West 1996) proposes that cognitive functions mediated by anterior brain systems are most vulnerable to the effects of age and selectively decline in normal, healthy aging. Although cognitive functions supported by more posterior regions clearly decline in normal aging (Greenwood 2000), the theory postulates that there is greater magnitude of decline for processes mediated by anterior systems (West 2000). There is an emerging consensus that white matter pathological markers of vascular disease (i.e., white matter hyperintensities) are associated with neuropsychological impairment (e.g. Gunning-Dixon and Raz 2000, 2003), but the effect of regional age-related relative white matter loss on cognition has been understudied in normal adults.

In the current study, regional white matter was examined in a large cohort of neurologically healthy adults across the lifespan. Our focus was on the impact of age on the relative distribution of lobar white matter; thus regional white matter was considered in the context of global white matter volume, as opposed to total brain volume or gray matter volume. Participants received a set

of standardized neuropsychological tests. Aging, sex, and hemispheric effects were examined for regional relative white matter and the relationship between variability in neuropsychological test performance and regional white matter was determined. We investigated whether a relationship between regional white matter and neuropsychological functioning exists independent of aging effects and whether aging accounts for variability of neuropsychological functioning independent of regional white matter changes. We predicted a selective age-associated white matter reduction in anterior brain regions and that variability in anterior white matter would be significantly associated with decreases in performance on neuropsychological tests implicated in normal aging, particularly those mediated by more anterior regions of the brain, such as executive functioning and memory.

Methods and Materials

Subjects

Subjects in the current study were participants in a large multi-site study of brain functioning across the lifespan (Brain Resource International Database; Gordon 2003; Gordon et al 2005). Each participant was carefully screened for medical or psychiatric conditions that could potentially interfere with brain or cognitive functioning. Screening was completed via a comprehensive web-based questionnaire examining personal and family history of medical and psychiatric disorders. Participants were excluded if they reported a positive personal or first-degree family history of psychiatric illness (e.g., attention deficit hyperactivity disorder, schizophrenia, bipolar disorder, other Axis I disorder); neurological disorder (e.g., Parkinson's disease, epilepsy, Alzheimer's disease, multiple sclerosis); serious medical disorder (e.g., human immunodeficiency virus, hepatitis, hypertension, diabetes, thyroid disease); visual, hearing or movement disorder; and current or past addiction to drugs or alcohol. The Somatic and Psychological Health Report (SPHERE; Hickie et al 2001) screen was used to exclude individuals with Axis-I disorders. The SPHERE is a 12-item questionnaire that was designed to screen for undiagnosed common psychiatric disorders and has been validated against DSM-III-R and DSM-IV (Hickie et al 2001). Six questions assess psychiatric symptoms and six assess somatic symptoms. Furthermore, subjects were evaluated with a structured interview to rule out anxiety or depressive disorders (Hickie et al 1998). For the current study, adult subjects receiving identical assessment with structural MRI (acquisition parameters described below) were drawn from the database. Magnetic resonance imaging data were acquired from two imaging sites in Australia (Westmead Hospital in Sydney and Wakefield Imaging in Adelaide); a previous structural MRI study found similar results when findings were compared between the two sites (Grieve et al 2005). All participants gave written informed consent, approved by local institutional ethics committees.

Data from 199 adults, ranging in age from 21 to 79 years, were used for the current study. Imaging data from these participants were used in two previous reports (Grieve et al 2005; Zimmerman et al, unpublished data). To facilitate cross-sectional aging analyses, the subjects were divided into three groups; age boundaries that ensured relatively equal distribution of the number of subjects in each group were selected. The first group ($n = 77$) was composed of individuals ranging in age from 21 to 30 years; the second group ($n = 82$) contained subjects ranging in age from 31 to 54 years; and the third group ($n = 40$) comprised subjects between the ages of 55 and 79. Demographic

Table 1. Subject Demographics

	Younger (21–30) <i>n</i> = 77	Middle (31–54) <i>n</i> = 82	Older (55–79) <i>n</i> = 40	Total (21–79) <i>n</i> = 199
Age Mean (SD) ^a	25.18 (2.89)	43.73 (7.27)	63.18 (6.94)	40.46 (15.29)
Education Mean years (SD) ^b	14.74 (3.90)	14.17 (3.64)	12.15 (2.91)	13.98 (3.72)
% Right handed	89	89	92	89
% Men	38	54	58	48
Height Mean cm (SD)	171.09 (11.48)	173.06 (11.16)	168.92 (9.10)	171.48 (10.98)
Weight Mean kg (SD)	70.34 (14.04)	75.79 (19.81)	74.00 (15.32)	73.32 (16.99)

^aOlder > middle > younger (all $p < .001$).

^bOlder < younger ($p = .00030$), older < middle ($p = .0042$).

data for the three groups and the entire sample are presented in Table 1. As expected, the three groups significantly differed in age ($F(2, 196) = 569.35$, $p < .001$). The number of years of formal education also differed among groups ($F(2, 196) = 6.936$, $p = .0012$), with Older subjects having significantly less years of education than the Younger group ($p = .0003$) and the Middle group ($p = .0042$). Height ($F(2, 193) = 1.939$, $p = .194$), handedness ($\chi^2(4) = .167$, $p = .996$), and sex ($\chi^2(2) = 5.788$, $p = .055$) distributions did not significantly differ among groups.

MRI Scan Acquisition

The MR image acquisition protocol was identical at the two imaging sites. A 1.5 Tesla Siemens (Erlangen, Germany) Vision Plus system was used at Westmead Hospital and a 1.5 Tesla Siemens (Erlangen, Germany) Sonata was used at Wakefield Imaging. A 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time [TR] = 9.7 msec; time to echo [TE] = 4 msec; Echo train: 7; Flip Angle = 12°; inversion time [TI] = 200 msec; NEX = 1) was used to acquire 3D T1-weighted partitions in the sagittal plane. A total of 180 contiguous 1 mm slices were acquired in a 256×256 matrix (in-plane resolution of 1 mm \times 1 mm, isotropic voxels).

MR Image Analysis

A clinical radiologist reviewed each MRI scan and confirmed that there was no clinically significant neuropathology for any of the subjects. MR image post processing and analysis was conducted using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London; <http://www.fil.ion.ucl.ac.uk/spm>), running on MATLAB 6.5 (MathWorks, Natick, Massachusetts). Images were first normalized to a Brain Resource International Database-specific T1-weighted template, which was made using 255 subject images that had previously been normalized to the International Consortium for Brain Mapping (ICBM) 152 template (Montreal Neurological Institute). This procedure facilitated data averaging by normalizing brains to standardized stereotactic space. Standard T1 templates of segmented images provided by SPM were used to create customized gray and white matter template images. Based on a cluster analysis method that separates pixels based on the distribution of intensities and a priori knowledge of spatial tissue distribution patterns in normal subjects (Friston et al 1996), images were segmented into gray, white, cerebrospinal fluid (CSF), and nonbrain tissues. A correction was made to preserve quantitative tissue volumes following the normalization procedure (Ashburner and Friston 2000). These voxel based morphometry procedures are based on established techniques, presented in greater detail elsewhere (Ashburner and Friston 2000; Good et al 2001).

For the normalized and segmented images, lobe-based anatomical assignments were made with reference to the standard-

ized anatomical parcellation derived by Tzourio-Mazoyer et al (2002). For the purposes of the current study, we focused on the parcellation of white matter to derive values for the left and right hemispheres in the frontal lobe, temporal lobe, parietal lobe, and occipital lobe. Consistent with Tzourio-Mazoyer's neuroanatomical parcellation (Tzourio-Mazoyer et al 2002), an anatomically-based mask was created with the following steps. The corpus callosum and internal capsule ROIs were first defined; the external borders of these two internal ROIs were used to limit the internal aspects of the frontal, parietal, and temporal lobes. The occipito-parietal border was interpolated from the borders of the superficial occipital and parietal lobes to the cuneus-precuneus border. The temporo-occipital border was similarly defined by the previously parcellated borders of the occipital and temporal lobes. The frontal lobe border followed the central sulcus superficially, with the internal border defined as anterior to the putamen and caudate at the level of the anterior commissure, and as anterior to the amygdala inferiorly. The white matter ROI template is presented in Figure 1 superimposed on a segmented and normalized white matter image.

The normalization, segmentation, and volume correction procedures used to generate segmented white matter images in MNI space are described in detail and have been extensively validated (Ashburner and Friston 2000; Good et al 2001). The accuracy of using template derived ROIs to determine lobe volumes is subject to the level of precision of the coregistration and normalization process, which, for the methodology described here, has been estimated at between a maximum of 8 mm and as little as 1.5 mm in the medial temporal lobe (Salmond et al 2002). For ROIs encompassing entire lobe volumes, this represents a more than acceptable level of precision (Tisserand et al 2002).

In the current study, the absolute volumes of the left and right frontal, temporal, parietal, and occipital lobes were divided by the global white matter volume to derive relative values. Relative regional values were considered in all statistical analyses.

Neuropsychological Evaluation

Participants were evaluated with a set of tests from 'Brain Resource Cognition', a highly standardized, computer-administered neuropsychological battery. This battery has been utilized in a number of studies (Brickman et al 2005; Clark et al 2004; Gordon 2003; Paul et al 2005a; Paul et al in press) and its validity (Paul et al 2005b) and reliability (Williams et al 2005) have been demonstrated. Tests are administered to the participant via a computerized touch-screen interface and voice recordings, to ensure that performance is not influenced by lack of mouse or keyboard familiarity. To ensure task instructions are standardized and understood, they are presented through headphones, as well

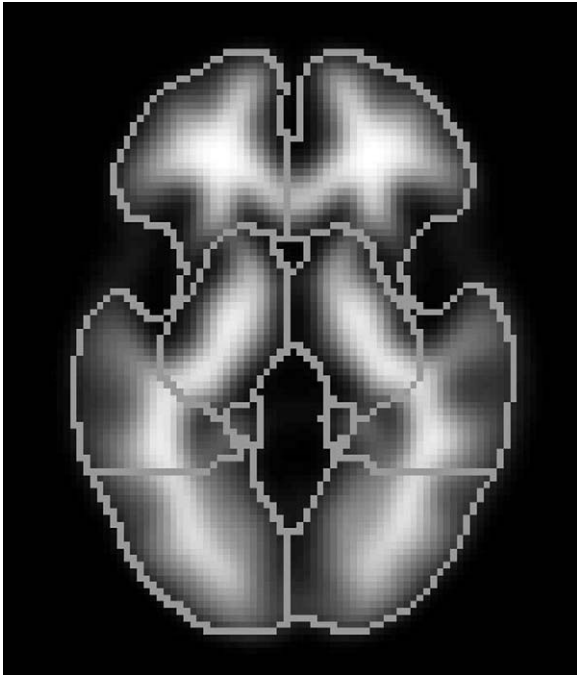


Figure 1. White matter region of interest (ROI) template superimposed on a segmented and normalized white matter image.

as in text on the touchscreen, and practice trials are included for each test.

For the purposes of the current study, the following tasks and dependent variables were used:

1. Choice Reaction Time. This is a task of simple reaction time (RT) in which participants are required to attend to the computer screen as one of four target circles is illuminated in pseudo random sequence over a series of trials. The subject is required to touch the illuminated circle as quickly as possible following presentation. The dependent variable is the mean reaction time across twenty trials.

2. Digit Span. In this test of basic attention, a series of digits, of increasing length over trials, is presented visually on the computer screen. Following presentation, the subject is asked to enter the digits on a numeric keypad on the touch screen. On the first part of this test, subjects are required to recall the digits in a forward order (digits forward); in the second part subjects recall the digits in reverse order (digits backward). The dependent variable is the maximum number of digits successfully recalled for each part.

3. Verbal Interference. This task is similar to the Stroop Test (Golden 1978), a standard neuropsychological test that examines the ability to inhibit automatic response. Color words (e.g., “red”) are presented in incongruent colors (e.g., the word “red” presented in a blue-colored font). The test has two parts. In part 1, the subject is required to name, as quickly as possible, the name of each word. In the second part, the subject is required to name the color of the font each word is presented in, rather than read the word. The number of correct responses is the dependent variable for each part.

4. Verbal List Learning. In this test of verbal learning and memory, a 12-word reading list is presented over four trials and subjects are asked to recall as many words possible after each presentation. A 12-word distractor list, consisting of novel words, is then presented, and the subject is asked to recall items from the

first list afterwards (short delay recall). A long delay free recall trial is completed following a 20 min delay period. For the purposes of this study, the number of words correctly recalled on the delayed free recall trial was considered for analyses.

5. Verbal Fluency. Fluency, or the ability to rapidly produce verbal responses to a pre-determined demand characteristic, is assessed in both phonemic and semantic domains. For the former, participants are required to generate as many words as possible beginning with F, A, and S during a 60-sec trial for each letter. The dependent variable is the total number of correct responses across trials. For the semantic domain, participants name as many animals as quickly as possible in a 60-sec trial. Total number of correct responses is the dependent variable.

6. Switching of Attention. This test of concept formation and mental flexibility is a computerized adaptation of the Trailmaking Test (Army Individual Battery 1944). In the first part, the subject is presented with 25 encircled numbers presented pseudo-randomly on the computer touch screen. The subject is asked to “connect” the numbers by pressing them in ascending numerical order as quickly as possible. On the second part of the test, the subject is presented with 13 numbers (1–13) and 12 letters (A–L) presented pseudo-randomly about the screen. The subject is required to connect the stimuli by alternating between numbers and letters in ascending sequential order (i.e., 1 A 2 B 3 C etc.). The dependent variable for each part is the time to completion in sec.

Statistical Analysis

A mixed design repeated measures analysis of variance (ANOVA) was used to examine the effect of age and sex on regional relative white matter volume. For this analysis, Age Group (3: younger, middle, older) and Sex (2: male, female) were treated as between-subjects factors. Cerebral Lobe (4: frontal, temporal, parietal, occipital) and Hemisphere (2: left, right) were within-subjects factors. Follow up ANOVAs, with Age Group and Sex as between subjects factors and Hemisphere as a within subjects factor, were conducted on each lobe separately to identify the greatest sources of variance on the omnibus analysis. An ANOVA design was chosen to facilitate the examination and display of interactions with Sex, Lobe, and Hemisphere.

As some studies have suggested that the effects of age on cerebral white matter are nonlinear (e.g. Raz et al 2005; Scahill et al 2003; Walhovd et al 2005a, 2005b), secondary regression analyses examined linear and quadratic effects of age on left and right relative white matter values in each of the four lobes. First, Age (as a continuous variable) was used as a predictor variable and each of the imaging variables were used as criteria variables. The regression analyses were repeated with Age² as a second predictor to test nonlinear quadratic effects.

To comprehensively examine the relationship among age, white matter volume, and neuropsychological functioning, an omnibus multivariate test of the associations was conducted. Specifically, the associations between age and the regional measures of white matter volume (entered together) and all of the neuropsychological performance variables were examined with canonical correlations. Following statistical significance of the omnibus test, follow-up bivariate correlations between age, regional white matter volumes, and neuropsychological test performance variables was examined with Pearson Product Moment correlations. We identified which regions and neuropsychological tests evidenced the greatest associations between each other and with age; to examine whether age-related

changes in neuropsychological abilities was mediated by age-related changes in brain morphology, a mediational model was conducted following Baron and Kenny (1986). Testing mediation followed a four-step process. Step 1 involved establishing the simple association between age and the neuropsychological tests. Next, the simple associations were demonstrated between age and the identified brain regions (Step 2) and between the identified brain regions and the neuropsychological tests (Step 3). Finally, multiple regressions with age and the identified brain regions predicting performance on the neuropsychological tests were conducted (Step 4). Steps 1 through 3, which were carried out with the bivariate correlations described above, confirmed that the zero-order relationships among the variables existed. Step 4 explicitly tested the mediation. With this approach, if age no longer significantly predicted neuropsychological test performance, the finding was consistent with full mediation. If both age and white matter still predicted neuropsychological test performance, then the finding supported partial mediation (Baron and Kenny 1986).

Results

Older participants had less overall white matter than the two younger groups (significant main effect of Age Group, $F(2, 193) = 5.4186$, $p = .00513$; see Figure 2). Post-hoc analysis using the LSD test demonstrated that the Older participants had significantly less relative white matter than the Middle group ($p = .018416$) and the Younger group ($p = .0006674$), but the two latter groups were statistically similar to each other ($p = .176779$). The main effect of Age Group was modified by a significant interaction between Age Group and Lobe ($F(6, 579) = 3.3224$, $p = .00317$; see Figure 3). The pattern of age-related differences (i.e., Younger > Middle > Older) was greatest in the frontal and temporal lobes, but of much smaller effect size in parietal and occipital lobes. Follow up ANOVAs on each lobe separately confirmed this pattern on the omnibus test. That is, for frontal lobe, a significant main effect of Age Group ($F(2, 193) = 4.7739$, $p = .00947$) demonstrated that the Oldest group had significantly reduced relative frontal lobe white matter compared to the Youngest group ($p = .000309$); although the Middle group was intermediate between the other

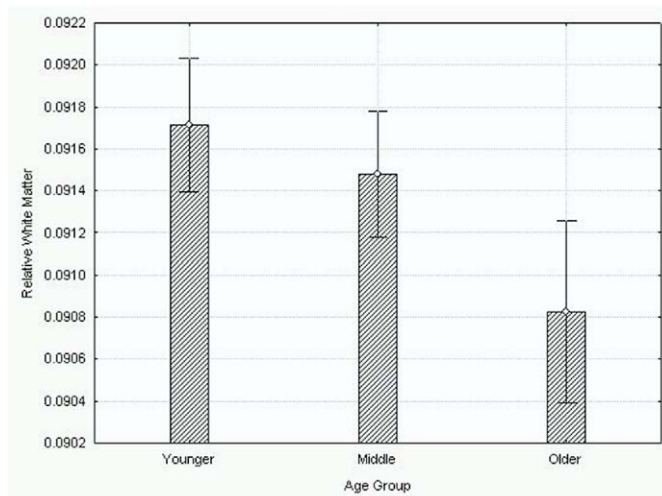


Figure 2. Significant main effect of Age Group, $F(2, 193) = 5.4186$, $p = .00513$. Error bars represent .95 confidence intervals. The values are relative (regional white matter volumes divided by global white matter volumes, collapsed across lobe, hemisphere, and sex).

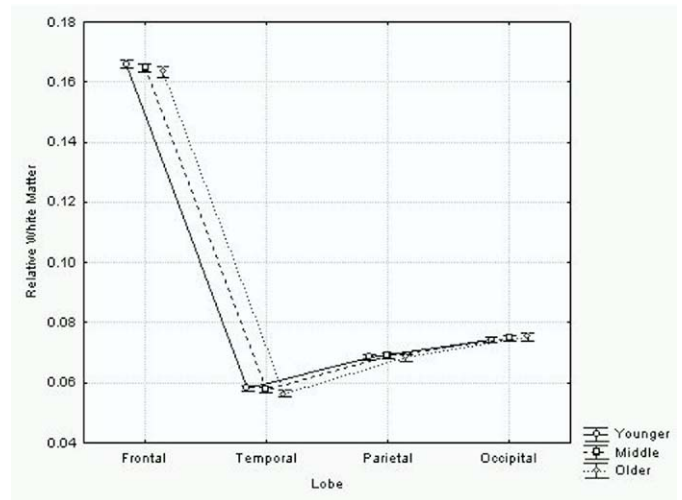


Figure 3. Age by Lobe interaction, $F(6, 579) = 3.3224$, $p = .0037$. Bars represent .95 confidence intervals. Values are volume relative to global white matter, collapsed across hemisphere and sex.

two, it was only statistically different from the Younger group ($p = .010914$; $p = .111656$ for comparison with the Oldest group). For the temporal lobe, follow-up tests for the significant main effect of Age Group ($F(2, 193) = 6.2168$, $p = .00242$) revealed that the Oldest group and Middle groups had significantly less white matter than the Youngest group ($p = .000309$ and $p = .010914$, respectively). The three age groups did not significantly differ in parietal lobe ($F(2, 193) = 1.2979$, $p = .27546$) or occipital lobe ($F(2, 193) = 1.2695$, $p = .28330$) relative white matter.

Analysis of Sex effects indicated that men have less relative frontal lobe white matter than women (significant Sex by Lobe interaction ($F(3, 579) = 12.865$, $p < .00001$)), which was more pronounced in the left hemisphere (significant Sex by Lobe by Hemisphere interaction ($F(3, 579) = 6.2893$, $p = .00033$)). Follow up analyses on each lobe separately confirmed the significant main effect of Sex ($F(1, 193) = 11.471$, $p = .00086$) and significant Sex by Hemisphere interaction ($F(1, 193) = 6.3894$, $p = .01228$) in the frontal lobes. This pattern was also evident in the parietal lobes (significant Sex by Hemisphere interaction ($F(1, 193) = 4.7825$, $p = .02995$)). In the occipital lobes, men had significantly more white matter than women (significant main effect of Sex ($F(1, 193) = 19.956$, $p = .00001$)), particularly in the left hemisphere (significant Sex by Hemisphere interaction ($F(1, 193) = 5.9030$, $p = .01603$)).

There was a significant Age Group by Sex by Lobe by Hemisphere interaction ($F(6, 579) = 2.2268$, $p = .03917$). On follow-up testing within each lobe, the Age Group by Sex by Hemisphere interaction was only significant for the occipital lobes ($F(2, 193) = 3.6857$, $p = .02686$) and seemed to indicate that differences between men and women were greater in the left hemisphere, particularly in the Middle group.

Not surprisingly, there were significant main effects of Lobe ($F(3, 579) = 39531.0$, $p < .00001$) and Hemisphere ($F(1, 193) = 38.175$, $p < .00001$, $L < R$). The main effect of Sex was not statistically significant ($F(1, 193) = 1.6877$, $p = .19545$), as regional white matter was relative to total white matter values (i.e., systematic differences in total white matter volume between men and women were controlled).

Results from the regression analyses were consistent with the

Table 2. Regression Equations for the Linear Effects of Age on Relative Values for Left and Right Lobar Regions

Dependent Measure	Beta	F	p-Value	R ²	R ² with Age ²	Quadratic p-Value
Frontal Left	-6.689	6.636	.011	.033	.033	.039
Frontal Right	.00	27.913	<.001	.124	.150	<.001
Temporal Left	-3.342	6.875	.009	.034	.047	.009
Temporal Right	-3.940	10.171	.002	.049	.059	.003
Parietal Left	-1.212	.011	.918	.000	.038	.021
Parietal Right	-1.151	1.068	.303	.005	.017	.193
Occipital Left	3.220	2.731	.100	.014	.015	.236
Occipital Right	3.896	5.054	.026	.025	.034	.033

The R² change and significance values for the tested quadratic effects are included.

ANOVA results. Significant linear effects were noted for left and right frontal lobe, left and right temporal lobe, and left and right occipital lobe. Significant quadratic effects were found for left and right frontal lobe, left and right temporal lobe, left parietal lobe, and right occipital lobe. Regression equations, significance values, and the R² change values when the quadratic effect of age was tested are presented in Table 2. Plots of the regressions with significant linear and quadratic trends are displayed in Figure 4.

Age and Neuropsychological Correlates

The omnibus canonical correlation examining the relationship between age and the regional white matter volumes and performance on the neuropsychological tests was statistically significant (Canonical $R = .800$, $\chi^2(99) = 137.60$, $p = .0063$). Follow-up bivariate coefficients calculated with Pearson Product Moment correlations are displayed in Table 3. Age was significantly correlated with performance on all of the neuropsychological measures, except FAS, a letter fluency task. Correlation coefficients were all in the predicted direction and effect sizes were generally moderate to large. Consistent with the results of the ANOVA above, there were also significant inverse relationships between Age and relative white matter of the left and right frontal and temporal lobes. Of note, there was a significant positive relationship between Age and right relative occipital white matter. As the white matter values are relative values, this finding most likely reflects age-related white matter stability in occipital lobe in the context of white matter loss in the rest of the brain.

In terms of structural brain correlates of neuropsychological test performance, right frontal relative white matter yielded the most consistent relationships. Correlations indicated that greater amounts of white matter were associated with better performance on neuropsychological tests. Correlation coefficients for these comparisons are displayed in Table 3. The largest effect sizes were noted for the relationship between frontal white matter and tasks of learning/memory and executive functioning. Similar relationships, though of smaller magnitude, were noted for the right temporal lobe. Left frontal and temporal values accounted for a significant amount of variance only in the tasks of memory and category fluency.

As the greatest associations were for age, frontal lobe and temporal white matter, and tasks of executive functioning (i.e., Switching of Attention part 2) and memory list recall (i.e., Memory test delay free recall trial), a more detailed examination of the interrelationships among these variables was conducted. Results from the correlational analyses confirmed the zero-order relationships among age, frontal lobe and temporal white matter, and

performance on Switching of Attention part 2 and the Memory test delay free recall trial (Steps 1 through 3 of the mediational analysis (Baron and Kenny 1986)). Results of the multiple regression analysis, in which age and left and right frontal white matter or left and right temporal lobe white matter predicted performance on the executive functioning or memory test are presented in Table 4. The findings demonstrate that both left and right frontal lobe white matter partially mediated the relationship between age and performance on the memory test and left frontal lobe white matter partially mediated the relationship between age and performance on the test of executive functioning. Neither left nor right temporal lobe white matter emerged as a mediator of the relationship between age and performance on these tests.

Discussion

The current study provides additional evidence for a relative age-related decline in anterior white matter and neuropsychological functioning. Quantitative image analysis of frontal, temporal, parietal, and occipital lobe white matter and a comprehensive computerized neuropsychological evaluation were conducted with a sample of 199 neurologically healthy individuals across the adult lifespan. Relative white matter, particularly in the frontal and temporal lobes, was significantly reduced as a function of age. Regression analyses indicated that quadratic effects were operative for left and right hemispheres with a steeper decline beginning the early 50s. Men had significantly less relative frontal lobe white matter, with specific decreases noted in the left hemisphere. As expected, increasing age was associated with worsening performance on all neuropsychological tests, except for a task of letter fluency, with the largest effects noted on tasks of executive functioning and learning/memory. Similarly, relative frontal white matter, particularly in the right hemisphere, was significantly associated with tasks of memory and executive functioning. Relative frontal lobe white matter was a partial mediator of the relationship between age and performance on a task of declarative memory. Taken together, the findings demonstrate a relationship between relative frontal lobe white matter and neuropsychological functioning that is strongly moderated by age.

These findings are consistent with the hypothesis that age-related changes in brain volume recapitulate neurodevelopment (Bartzokis et al 2003) and are in line with results from a number of studies that have demonstrated volumetric reduction of anterior brain regions across the adult lifespan (Bartzokis et al 2003; Decarli et al 2005; Good et al 2001; Resnick et al 2000). As postmortem studies have demonstrated that normal aging is not particularly associated with neuronal cell death (Haug and Eggers 1991), the observed relative decline in white matter may reflect faulty neural transmission efficiency and a decline in normal synaptic functioning. Age-related white matter changes, thus, may indicate a decline in interregional connectivity that could have secondary effects on gray matter structure and have obvious implications for maintenance of normal neuropsychological functioning in later life.

Indeed, the results from the current study suggest that age-related decline in neuropsychological functioning is, in part, mediated by age-related reduction in relative white matter. That is, variability in frontal and temporal lobe white matter was highly related to age, and, that variability was significantly related to performance on tasks of executive and memory functioning. Although the correlations between relative frontal and temporal

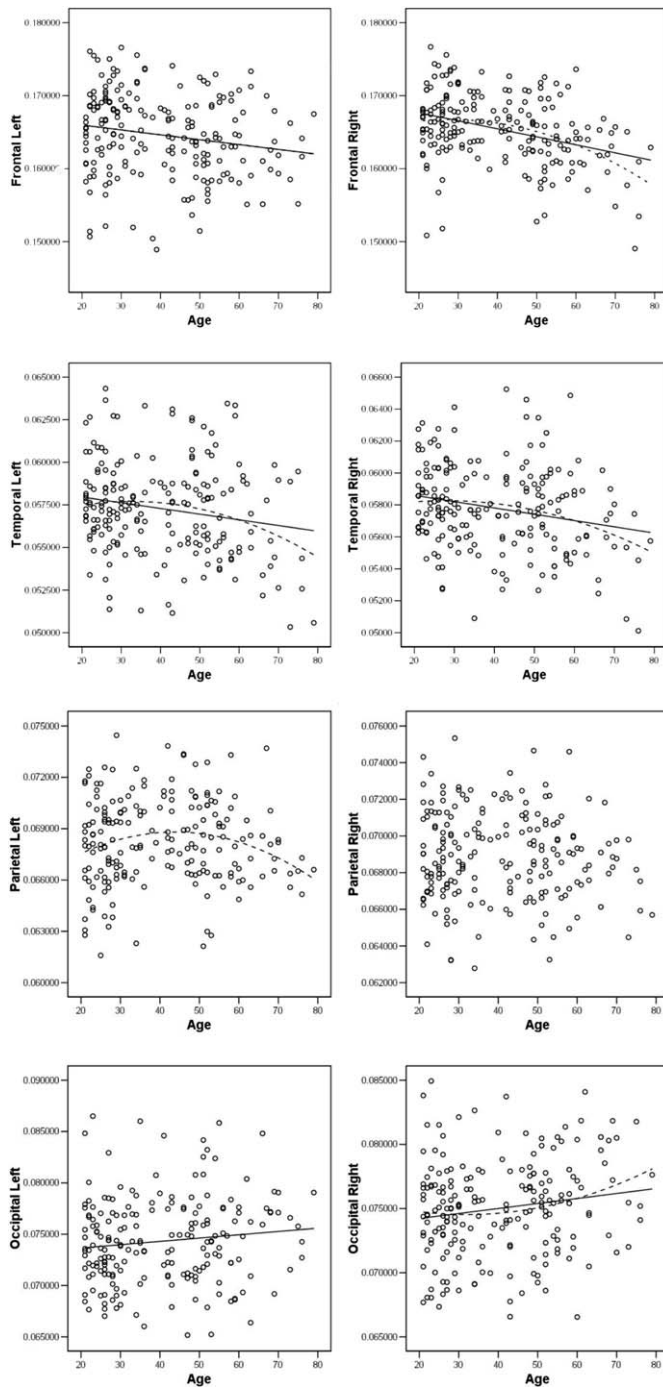


Figure 4. Plots of the regression equations examining the relationship between Age and regional white matter values. Trend lines for significant linear and quadratic trends are included.

white matter and performance on the neuropsychological tests were of small-to-medium effect sizes, they were consistent and in the predicted direction. Explicit mediational analyses demonstrated that left and right frontal lobe white matter partially mediated performance on a test of memory and that left frontal lobe white matter partially mediated performance on the test of executive functioning. It is likely that other factors not related to relative white matter volume (e.g., metabolism, cerebrovascular effects, gray matter integrity) are additional mediators.

Few previous studies have examined the interrelationship among age, brain structure, and neuropsychological functioning in normal, healthy adults (Cook et al 2002; Rodrigue et al 2005; Schretlen et al 2000). In one study, Gunning-Dixon and Raz (2003) used path analysis to demonstrate that age-related variability in perseveration errors on a task of executive functioning was mediated by the volume of the prefrontal cortex. The current study extends these findings by examining regional white matter separately and its relationship to performance on a more comprehensive battery of neuropsychological tests. That the most systematic relationships were observed among age, relative frontal and temporal white matter, and executive and memory functioning suggests that fronto-temporal circuitry may underlie the pronounced age-related decline in neurocognitive processes.

Relationships between age, neuropsychological functioning, and relative white matter were most notable in the right cerebral hemisphere. Theories of selective normal age-associated decline in right hemisphere functioning have been reported in the extant literature for decades (e.g. Brown and Jaffe 1975). More recent work by Cabeza and colleagues (Cabeza 2002; Dolcos et al 2002) suggests hemispheric asymmetry reduction in older adults (i.e., HAROLD); the theory postulates that, with normal aging, there is a reduction in lateralized functioning of the frontal lobes. The HAROLD model is supported by a number of functional imaging studies employing cognitive tasks that have demonstrated a reduction in lateralization in older healthy subjects (see Dolcos et al 2002 for review). However, to our knowledge, the theory has not been evaluated in the context of structural changes that occur with aging. The current study suggests a relatively greater decline in right frontal lobe white matter, which could contribute to the reported decline in functional asymmetry with normal aging.

In the current study, men had less white matter volume than women, particularly in the left frontal lobe. This finding is similar to that of a recent study by DeCarli et al (2005), who reported relatively reduced frontal lobe volume in men, but did not examine hemispheric effects. Consistent with some past studies (Guttmann et al 1998; Resnick et al 2003), differential aging effects as a function of sex were unremarkable, although others (Gur et al 1991; Murphy et al 1996) have suggested greater age-associated total volume loss in men than women. Studies that have examined sex-related differential aging effects in brain morphology have generally considered total brain volume and/or regional volumes without differentiation of gray and white matter.

It is important to note that findings from the current study pertain to relative lobar white matter values and that the regional values used were calculated relative to total white matter volume as opposed to total brain volume. We decided to use this approach a priori because the hypotheses were specific to lobar distribution of white matter. We felt that by correcting for total brain volume, we would not have been able to test the specific relative relationships within white matter alone. In the current sample, total gray matter volume and total CSF were significantly associated with age ($r = -.390, p < .001$ and $r = .496, p < .001$, respectively), but total white matter volume was not ($r = .017, p = .812$). Therefore, the examination of relative regional white matter volumes correcting for total brain volume would have been contaminated by the larger age-associated effects of gray matter. That total white matter volume did not significantly decline with age is somewhat inconsistent with some (Resnick et al 2000), but not all (Tisserand et al 2004) previous reports. Discrepancies among studies could be due, in part, to methodological differences in spatial normalization protocols, sample size differences, and tissue segmentation protocols. The validity

Table 3. Correlations Among Age, Regional White Matter, and Neuropsychological Test Performance

	Age	Choice RT	Digits Forward	Digits Backward	List Learning	Verbal Interference	FAS	Animal Naming	Switching of Attn.1	Switching of Attn. 2
Age		.42 ^a	-.20 ^a	-.33 ^a	-.48 ^a	-.62 ^a	-.10	-.51 ^a	.48 ^a	.57 ^a
Frontal Left	-.18 ^a	-.09	.05	.08	.34 ^a	.14	.02	.10	-.07	.02
Frontal Right	-.35 ^a	-.28 ^a	.07	.16 ^a	.44 ^a	.29 ^a	.17 ^a	.24 ^a	-.20 ^a	-.25 ^a
Temporal Left	-.18 ^a	-.02	.04	.00	.15 ^a	.12	.03	.18 ^a	.05	-.02
Temporal Right	-.22 ^a	-.07	.06	.12	.20 ^a	.15 ^a	.17 ^a	.24 ^a	-.15 ^a	-.07
Parietal Left	-.01	.01	-.05	-.08	-.03	.07	-.06	.02	-.08	-.04
Parietal Right	-.07	.07	-.01	-.08	.00	.05	-.15 ^a	-.05	-.01	.00
Occipital Left	.12	-.08	.08	.19 ^a	-.02	-.06	.14	-.10	-.01	.00
Occipital Right	.16 ^a	.00	-.06	.00	-.14	-.22 ^a	.04	-.19 ^a	.14	.14

RT, reaction time; FAS, beginning letters for verbal fluency test words.

^a*p* < .05.

of tissue segmentation protocols, particularly in older subjects, has not been well evaluated and spatial normalization approaches have come under scrutiny for potentially containing systematic biases (Bookstein 2001). In the current study, we attempted to address these issues by creating a sample-specific normalization template. Although the total white matter volume was not significantly associated with age, the findings highlight the impact of age-associated changes in the regional distribution of white matter.

Limitations for the current study include the cross-sectional nature of the analyses. As with many cross-sectional studies of normal aging, there is the possibility that cohort effects are influencing the findings. However, there is now a culmination of both cross-sectional and longitudinal findings suggesting robust regional changes with age and it is unlikely that cohort effects are accounting for the large observed effects. Further, all subjects in the current analyses were well screened for medical and psychiatric histories and it is, therefore, unlikely that changes seen in older participants reflect some underlying neurodegenerative process, such as dementia. Nonetheless, that the participants in the current study were well screened may have accounted for the smaller age-related effects we observed for change in white matter. The pattern of the findings, however, is consistent with

large-scale, population-based studies (Decarli et al 2005), whose inclusion criteria were, by definition, not as stringent.

Future research in this area should focus on potential mediators and moderators of the age-related changes observed in the current study. Two levels of analyses warrant further investigation. First, the identification of factors that might mediate the relationship between normal aging and morphological change is essential. For example, there is a possibility that subclinical vascular load or other health-related phenomena could be contributing to changes in regional white matter. To this end, quantification of white matter hyperintensities and its relationship to age, cardiovascular risk factors, and neuropsychological functioning (e.g. Paul et al 2005a) should be considered in the context of volumetric change. Second, potential mediational factors of the relationship between morphological change and neuropsychological functioning should be identified. For example, the concept of cognitive reserve (Stern 2002, 2003) has been postulated as a potential mechanism that modulates the relationship between brain change or damage and the clinical or cognitive manifestation of that change. Understanding the role of cognitive reserve in cognitive correlates of age-related change in brain morphology is an important line of research. Both levels of analyses could lead to the elucidation of potentially treatable

Table 4. Results of Multiple Regression Analyses Explicitly Testing Whether Left and Right Frontal or Temporal White Matter Mediates the Relationship Between Age and Performance on Tests of Executive or Memory Functioning

Model							
Predictors	DV	F	R ²	p	Effect	p	Mediation
Age	SWOA2	43.261	.340	<.001	Age	<.001	Trend
Frontal L					Frontal L	.063	Partial
Age	SWOA2	41.211	.329	<.001	Age	<.001	No
Frontal R					Frontal R	.391	
Age	Memory	18.067	.260	<.001	Age	<.001	Trend
Frontal L					Frontal L	.052	Partial
Age	Memory	20.715	.287	<.001	Age	<.001	
Frontal R					Frontal R	.006	Partial
Age	SWOA2	42.041	.334	<.001	Age	<.001	No
Temporal L					Temporal L	.175	
Age	SWOA2	41.445	.330	<.001	Age	<.001	No
Temporal R					Temporal R	.306	
Age	Memory	15.860	.235	<.001	Age	<.001	No
Temporal L					Temporal L	.492	
Age	Memory	15.899	.236	<.001	Age	<.001	No
Temporal R					Temporal R	.466	

SWOA2, Switching of Attention Task part 2; L, left; R, right.

(e.g., subtle vascular disease) or adaptable (e.g., cognitive reserve) constructs that could improve cognitive aging. Finally, more detailed structural and functional (e.g. Brickman et al 2003) methodological approaches could be useful in understanding the physiological mechanisms underlying normal cognitive aging. Parcellation of specific brain regions (e.g., Brickman et al, unpublished data) and utilization of other structural sequences (e.g., diffusion tensor imaging, Nusbaum et al 2001) can complement more global regional approaches.

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