Controversy persists regarding whether Alzheimer's disease (AD) is a distinct entity or instead exists on a continuum with nondemented aging. To explore this issue, volumetric analyses of callosal and hippocampal regions were performed on 150 participants aged 18–93 years. Group-level analyses revealed that nondemented age-related differences were greater in anterior than posterior callosal regions and were not augmented by early-stage AD. In contrast, early-stage AD was associated with substantial reduction in hippocampal volume. Examination of the 100 older adults using regression analyses demonstrated age-associated differences in callosal volume that were similar in demented and nondemented individuals. Early-stage AD was again characterized by a marked reduction in hippocampal volume whereas age alone induced only mild differences in hippocampal volume. As a final analysis, the formal double dissociation was confirmed by comparing the effects of age directly against the effects of dementia. These results suggest a multiple-component model of aging. One process, associated with AD, manifests early and prominently in the medial temporal lobe. A separate process, ubiquitous in aging, affects brain white matter with an anterior-to-posterior gradient and may underlie the executive difficulties common in aging.

Keywords: corpus callosum, dementia, MCI, MRI, white matter

Introduction

Resiliency and decline characterize the effects of advancing age on neuronal structure and function (Kemper, 1994; Raz, 2000). Alzheimer’s disease (AD), which increases in prevalence in the later stages of life, is a major determinant of impairment in the aged. AD is associated with a characteristic histopathology, including neurofibrillary tangles and amyloid plaques, and cognitive dysfunction (Braak and Braak, 1991; Hauw and Duyckaerts, 2001). Yet, uncertainty regarding how AD relates to aging persists because the pathologic changes, together with changes in mnemonic function, are seen in a substantial proportion of “normal” aged individuals (Huppert and Brayne, 1994; Albert, 1998; Price et al., 2001; Whalley, 2002). Based on such observations, it has been argued that AD and normal aging exist on a continuum with no clearly discernible boundaries (Huppert and Brayne, 1994; Whalley, 2002). On the other hand, differences between AD and nondemented aging have been recognized (Morrison and Hof, 1997; Albert, 1998; Morris, 1999; Price et al., 2001; Uylings and de Brabandere, 2002).

The degenerative changes in AD begin in medial temporal lobe structures and later involve adjacent temporal, parietal and frontal neocortex (Braak and Braak, 1991; Price et al., 2001). Magnetic resonance image (MRI) studies of AD consistently reveal marked volume reductions in the hippocampus using cross-sectional and longitudinal approaches (e.g. Jack et al., 1992, 1997; Convit et al., 1993; Killiany et al., 1993). In contrast, structural MRI (Salat et al., 1999; Raz, 2000) and diffusion tensor imaging (DTI) cross-sectional studies (O’Sullivan et al., 2001; Head et al., 2004) suggest that atrophy in nondemented aging may be relatively greater in anterior regions (gray and white matter) and striatal structures. With respect to cognitive function, the hallmark of early-stage AD is memory impairment (Albert, 1998; Storandt et al., 2002) possibly accompanied by deficits in attentional control (Balota and Faust, 2001). In contrast, the cognitive change in nondemented aging is mostly in executive control (Moscovitch and Winocur, 1995; Craik and Grady, 2002) accompanied by memory problems related more to executive dysfunction than rapid forgetting (Albert, 1998; Storandt et al., 2002).

Here we provide direct evidence that nondemented aging and AD are distinct entities by demonstrating an anatomical double dissociation. The structures selected for study were the hippocampus (HC) and the corpus callosum (CC). Although neuropathological investigations (Braak and Braak, 1991) suggest that AD-related changes may begin in the entorhinal cortex and subsequently spread to the hippocampus, we elected to measure the hippocampus as the MRI-based procedures for hippocampal delineation are better established than for the entorhinal cortex and there is a substantial literature on AD- and nondemented age-related effects on the hippocampus (for reviews, see Jack and Petersen, 2000; Raz et al., 2000). The CC is topographically organized, with anterior and posterior portions connecting anterior and posterior lobar regions, respectively (de Lacoste et al., 1985; Pandya and Seltzer, 1986). Studies in nondemented aging reveal a trend for anterior regions to exhibit greater atrophic effects than posterior regions (e.g. Weis et al., 1991; Abboitz et al., 1996; Janowsky et al., 1996; see also O’Sullivan et al., 2001; Head et al., 2004), which is similar to the anterior-to-posterior gradient observed for white matter lobar regions (Head et al., 2004). In contrast, early-stage AD may differentially affect posterior regions of the CC (Jack and Petersen, 2000). Later stages of AD include more widespread effects (Braak and Braak, 1991) and anterior portions of the CC may then be involved (e.g. Pantel et al., 1999; Teipel et al., 1999; Hensel et al., 2002). We first obtained measurements in 25 young adults, 25 nondemented older adults and early-stage AD was again characterized by a marked reduction in hippocampal volume while age alone induced only mild differences in hippocampal volume. As a final analysis, the formal double dissociation was confirmed by comparing the effects of age directly against the effects of dementia. These results suggest a multiple-component model of aging. One process, associated with AD, manifests early and prominently in the medial temporal lobe. A separate process, ubiquitous in aging, affects brain white matter with an anterior-to-posterior gradient and may underlie the executive difficulties common in aging.
and 25 individuals with very mild-to-mild dementia of the Alzheimer type (DAT) (Table 1). The two older groups were matched for age and gender. Then, measurements were repeated in a second, independent sample that was age- and gender-matched to the initial cohort. A final set of analyses combined data across the two cohorts and formally explored the double dissociation between aging and early-stage AD.

Materials and Methods

Participants

Young adults were undergraduate students at Washington University screened for neurologic illness or injury and use of psychoactive medications. Older adults were recruited from the Washington University Alzheimer’s Disease Research Center (ADRC) screened for neurologic illness, head injury, current depression, use of psychoactive medications and medical conditions that might produce cognitive impairment (e.g. cerebrovascular disease and Parkinson’s disease). All participants were right-handed native English speakers. Older adults were classified as demented or nondemented based on the Washington University Clinical Dementia Rating (CDR, Morris, 1993). This a validated, interview-based measure that examines the participant’s abilities in memory, orientation, judgement and problem solving, community affairs and functions in the home, hobbies and personal care (Morris et al., 1988). Separate interviews are conducted with the participant and a collateral source. The clinical distinction between ‘nondemented’ (CDR = 0) and ‘demented’ (CDR > 0.5) has been validated by neuropsychological examination (Berg et al., 1998), including at the very mildest (CDR = 0.5) stages of dementia (Morris et al., 2001). All participants consented to participation in accordance with guidelines of the Washington University Human Studies Committee. Demographic characteristics of participants are listed in Table 1.

MR Acquisition

All imaging was performed using a Siemens 1.5 Tesla Vision scanner (Erlangen, Germany). Cushions and a thermoplastic mask were used during scanning to reduce head movement. A scout image (TR = 15 ms, TE = 6 ms, flip angle = 30°, 2.34 × 1.17 × 8 mm resolution) was acquired first in order to center the field of view on the brain. Four T1-weighted sagittal MP-RAGE (Mugler and Brookeman, 1991) scans (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, T1 = 20 ms, T2 = 200 ms, 1 × 1 × 1.25 mm resolution) were acquired in each subject. Inter- and intra-scan motion correction and averaging were accomplished off-line. All raw MRI data are available to research investigators.

Image Processing

Image processing prior to regional analysis included several image registration steps ultimately resulting in registered structural data resampled to 1 mm³ voxels in the atlas space of Talairach and Tournoux (1988). The following describes the image registration steps carried out for each individual. First, a 12-parameter affine atlas transform was computed for one MP-RAGE. The atlas representative target image included 12 (six female) young adult and 12 (nine female) nondemented old (mean age 75 years) subjects (Buckner et al., 2000). Results from our laboratory indicate that atlas normalization, when using this young-old target atlas, is equivalent to normalization based on intracranial volume (r = 0.93) and is minimally biased by global atrophy typical of aging and dementia (Buckner et al., 2004). For each participant, the remaining MP-RAGE images were registered to the first (allowing 3D stretch). Atlas transforms for all MP-RAGE images were computed by transform composition (matrix multiplication). Each participant’s averaged, atlas-transformed MP-RAGE image was then produced using a single interpolation per scan. Intensity inhomogeneity was corrected using an algorithm minimizing intensity variation within continuous regions with the bias field modeled as a general second-order polynomial in x, y, z (10 free parameters) (Styner, Brechbuhler, Szelke and Gerig, 2000). MP-RAGE images were segmented into gray matter, white matter and cerebrospinal fluid using fuzzy-class means. These segmented images in conjunction with the unsegmented T1-weighted images were used to manually obtain regional measurements of the corpus callosum.

Regions-of-Interest Measurement Procedures

The following measurement procedures were conducted using Analyze software (Version 4.0, Mayo Clinic). Images were displayed on an 18-inch interactive display monitor and each region-of-interest (ROI) was manually outlined on the screen with the accompanying grip pen. One operator (D.H.), blind to participants’ exact age, gender and cognitive status, manually outlined the ROIs. Intrarater reliability was assessed on 10 randomly selected brains measured on two occasions separated by two weeks. All reliability coefficients, with intraclass correlations presuming random selection of raters [ICC(2); Shroot and Fleish, 1979], exceeded 0.90. One nondemented older adult participant was replaced because their data for several measurements were >3 SD above the mean.

Corpus Callosum

The entire corpus callosum (CC) was measured on segmented images in the sagittal plane. The T1-weighted nonsegmented image was also displayed during measurement to allow for exclusion of large blood vessels and the fornices. Measurements were made on the midsagittal slice and five slices lateral to the midsagittal slice in both hemispheres, giving a total of 11 slices. The midsagittal slice was determined primarily by the clarity of the cerebral aqueduct, using the septum pellucidum as a second landmark when the cerebral aqueduct was less clearly visualized. As in previous studies (Janowsky et al., 1996; Pantel et al., 1999), the CC was separated into five subregions, each 20% of the rostro-caudal length: genu and rostrum (CC1), rostral body (CC2), midbody (CC3), isthmus (CC4) and splenium (CC5). Examples of the tracings of the ROIs are depicted in Figure 1a.

Hippocampus (HC)

Measurement procedures were similar to those employed in previous work on hippocampal volume in aging and AD (Jack et al., 1992; Killiany et al., 1993). The hippocampus (HC) was measured on 23–30 coronal T1-weighted nonsegmented images aligned perpendicular to the long axis of the left hippocampus post-acquisition. Images were resampled to 0.5-mm-thick slices and measurements were made on every third slice, i.e. on sections separated by 1.5 mm. The most anterior slice on which the HC emerged inferior to the amygdala formed the rostral border. The caudal border was the slice on which the fornices are seen as they rise after leaving the fimbria. Measured volumes included the hippocampal formation, dentate gyrus, alveus, fimbria and portions of the subiculum. Examples of the tracings of the ROIs are depicted in Figure 1b.

Bias

When using MRI measurements of volume there is always the potential for bias because tissue parameters change with age (Seong et al., 1997) and also because tissue boundaries are influenced by voxels that contain multiple tissue classes. This issue was approached here by tracing outlines based on our best estimate of where the anatomy of

Table 1 Demographics for full sample

<table>
<thead>
<tr>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 1</th>
<th>Sample 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
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<td>22 ± 4</td>
<td>22 ± 6</td>
<td>22 ± 6</td>
<td>24 ± 4</td>
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<tr>
<td>Age range (years)</td>
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<td>18-30</td>
<td>69-88</td>
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<td>69-87</td>
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<td>18/7</td>
<td>18/7</td>
<td>17/8</td>
</tr>
<tr>
<td>Mean education (years)</td>
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<td>n/a</td>
<td>15 ± 3</td>
<td>15 ± 3</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>CDR</td>
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<td>n/a</td>
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<td>0</td>
<td>0.5(14); 11(11)</td>
</tr>
<tr>
<td>MMSE</td>
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<td>n/a</td>
<td>29±1</td>
<td>29±2</td>
<td>25±5</td>
</tr>
<tr>
<td>MMSE range</td>
<td>n/a</td>
<td>n/a</td>
<td>26-30</td>
<td>25-30</td>
<td>15-30</td>
</tr>
</tbody>
</table>

CDR = Clinical Dementia Rating, where CDR 0 = no dementia, CDR 0.5 and 1 = very mild and mild dementia, respectively, MMSE = Mini-Mental State Exam (Folstein et al., 1975), where the range from best to worst performance is 30-0; AD = Alzheimer’s disease; F = females; M = males; n/a = not available/applicable.
structure began and ended, using knowledge of structure shape across adjacent sections as a guide. In ambiguous cases, such as low-intensity voxels (likely including partial contributions of CSF) that were adjacent to clear tissue-containing voxels, we conservatively included these voxels in the region being traced.

**Results**

Age- and dementia-related effects on the volumes of the HC and five subregions of the corpus callosum [CC1 (anterior)--CC5 (posterior)] were examined with a series of mixed general linear models. Group (young, nondemented old and early-stage AD) and sex were categorical variables and brain region (CC1--CC5 or left HC and right HC) was a within-subject variable.

**Regional Variability in Age- and Dementia-related Effects**

Anterior portions of the CC showed aging effects independent of dementia (Fig. 2). This was supported by a significant group × brain region interaction \(F(8,284) = 3.34, P = 0.001\). Follow-up, independent samples \(t\)-tests revealed all subregions of the CC were significantly smaller in nondemented older adults compared with young adults [CC1: \(t(48) = 4.65, P < 0.0001\); CC2: \(t(48) = 6.45, P < 0.0001\); CC3: \(t(48) = 4.55, P < 0.0001\); CC4: \(t(48) = 2.82, P < 0.01\); CC5: \(t(48) = 2.34, P < 0.05\)]. However, the age differences were greater in CC1 compared with CC5 as indicated by a significant group (young versus nondemented old) by brain region (CC1 versus CC5) interaction \(F(1,48) = 9.85, P < 0.01\). There were no significant differences between the nondemented and demented older adults for any of the sub-regions (all \(P > 0.12\)). The main effect of sex was not significant \((F<1)\). However, there was a significant sex × brain region interaction \(F(4,284) = 2.63, P < 0.05\). Follow-up, independent samples \(t\)-tests did not reveal significant sex differences in any subregions (all \(P > 0.19\)), but the interaction appeared to reflect numerically larger volumes in males in CC1, CC2, CC3 and CC4, but a larger CC5 volume in females.

In contrast to the CC, hippocampal volume showed robust effects of AD that were not significant in aging. There was a significant main effect of group \(F(2,71) = 34.10, P < 0.001\). HC volumes were bilaterally smaller in the demented adults compared with nondemented older adults [left HC: \(t(48) = 6.17, P < 0.0001\); right HC: \(t(48) = 6.10, P < 0.0001\)]. There were no significant HC differences between the young adults and nondemented older adults (left HC: \(t < 1\); right HC: \(t < 1\)).
Figure 2. Group differences in corpus callosum and hippocampus volumes for sample 1. Effects of aging in the corpus callosum and early-stage AD in the hippocampus are depicted. Bars indicate the mean regional volumes for each group for (a) CC1, (b) CC5, (c) left hippocampus (HC) and (d) right HC regions. Young, white bars; nondemented older adults, gray bars; and early-stage AD individuals, black bars. Error bars indicate standard error of the mean.

Neither the main effect of sex \((F < 1)\) nor the sex \(\times\) region interaction \([F(1,71) = 2.7, \text{ns}]\) was significant.

Thus, age-dependent volume differences were present in all regions of the CC, but greater in anterior than posterior regions. There were no effects of early-stage AD compared with age-matched controls in the CC. In direct contrast, significant AD-related effects were apparent bilaterally in the HC.

Replication of the Anatomical Double Dissociation between Nondemented Aging and AD

The above-noted differential effects of aging and AD on anatomic structures are strongly suggestive of distinct mechanisms underlying nondemented aging and AD. The results are consistent with previous findings of HC volumetric reduction in AD (for a review, see Jack and Petersen, 2000) and a recent report of greater atrophy in hippocampus/amygdala compared with CC area in AD (Teipel et al., 2003). However, other studies have reported AD-specific effects in the CC, including CC1 (e.g., Janowsky et al., 1996; Pantel et al., 1999; Teipel et al., 1999), and mild-to-moderate age effects in the HC (Raz, 2000; Salat et al., 1999). Measurement of the second sample was therefore undertaken to substantiate the dissociation observed in the first sample (Table 1).

Analyses of the second sample confirmed the initial findings in all critical particulars (Fig. 3). The group \(\times\) brain region interaction was again significant \([F(8,284) = 4.56, P < 0.0001]\) for the CC. Follow-up, independent samples t-tests indicated significant nondemented age-related differences in CC1 \([t(48) = 3.24, P < 0.01]\) and the three truncal regions \([\text{CC2}: t(48) = 4.71, P < 0.0001; \text{CC3}: t(48) = 2.79, P < 0.01; \text{CC4}: t(48) = 2.07, P < 0.05]\), but not in CC5 \((t < 1)\). There were no significant AD-related effects on the volume of the CC subregions compared with nondemented older adults \((P > 0.15)\). There also was a significant main effect of sex \([F(1,71) = 6.36, P = 0.01]\), but the sex \(\times\) brain region interaction was not significant \([F(4,284) = 1.78, \text{ns}]\). For the hippocampus, there was a main effect of group \([F(2,71) = 15.82, P < 0.0001]\). The nondemented age-related volume differences in the HC were more pronounced in this sample, but still nonsignificant \([\text{left HC}: t(48) = 1.51, P = 0.14; \text{right HC}: t(48) = 1.32, P = 0.19]\). In contrast, AD status was associated with significant HC volume differences compared with nondemented older adults \([\text{left HC}: t(48) = 3.53, P < 0.001; \text{right HC}: t(48) = 3.62, P < 0.001]\). Neither the main effect of sex \((F < 1)\) nor the sex \(\times\) brain region interaction \([F(1,71) = 2.19, \text{ns}]\) was significant.

Anatomical Effects of Age and Dementia Status in the Combined Cohorts of Older Adults

Additional analyses were conducted to examine the influence of aging in the 100 older individuals in the combined cohorts (nondemented and early-stage AD). This analysis is independent of the earlier analyses, as variance within the older individuals did not contribute to the group effects described above. However, the impact of advancing age in the early-stage AD group should be interpreted with caution as this is a cross-sectional design and the most appropriate assessment of aging effects on AD progression requires a longitudinal design. Again, analysis of the CC revealed a marked effect of age with an anterior-to-posterior gradient. A mixed general linear model with age as a continuous variable, group (early-stage AD versus nondemented) and sex as between-subjects variables and brain region (CC1 versus CC5) as a within-subjects variable was conducted (Fig. 4a). Nonsignificant interaction terms in the full linear model were removed. In the reduced model, the
age × brain region interaction was significant \[F(1.96) = 3.96, P < 0.05\]. This interaction reflected a larger effect of age on CC1 [Pearson’s \(r(100) = -0.44, P < 0.0001\)] than CC5 [\(r(100) = -0.29, P < 0.01\)]. Based on the regression equations, there is an estimated loss of 1.01% and 0.60% per year in the anterior and posterior regions of the CC, respectively, in the older adults (nondemented and early-stage AD). Neither the main effect of group \((F < 1)\), the group × age interaction \((F < 1)\) nor the group × brain region interaction \([F(1.96) = 1.35, \text{ns}]\) was significant, indicating no significant differences in CC1 or CC5 volume between the early-stage AD adults and the nondemented older adults.

In contrast, hippocampal volume showed marked differences in early-stage AD with mild differences in aging (see Fig. 4b). A mixed general linear model with age as a continuous variable, group (early-stage AD versus nondemented) and sex as between-subjects variables and brain region (left and right HC combined) as a within-subjects variable was conducted. There was a trend for age-related volume loss in the hippocampus [main effect of age: \(F(1.96) = 3.54, P = 0.06\)]. Within the nondemented older adults, this trend reflected an estimated 0.43% volume difference per year. The volume of the hippocampus was markedly smaller in the early-stage AD adults compared with nondemented older adults [8.11% difference; main effect of group: \(F(1.96) = 48.90, P < 0.0001\)]. The age × group interaction was not significant \((F < 1)\).

In order to further examine the relationship between nondemented aging and early-stage AD, the combined sample of older adults was split into subgroups based on whether they were above or below an age criterion of 77 years and their dementia status (e.g. ≤77-nondemented, >78-nondemented, ≤77-demented and >78-demented; see Table 2 for demographics). The logic of this analysis is that it allows exploration of the formal double-dissociation between effects of aging and AD by contrasting the ≤77-demented group and the >78-nondemented group. In this manner, the two effects (aging and dementia) are structured to oppose one another. Thus, the effect of dementia on the hippocampus must significantly exceed the effect of aging and, separately, the effects of aging on the anterior corpus callosum must significantly exceed any effect of dementia status. This analysis represents a conservative balance between the desire to directly test the two predictions of the double dissociation and the constraint that the current study has insufficient power to explore a three-way interaction.

The volumes of the hippocampus and the anterior corpus callosum were compared across these subgroups using independent samples \(t\) tests. Figure 4c,d shows the results. The >78-nondemented individuals had smaller anterior corpus callosum volumes than the ≤77-demented individuals \([t(47) = -2.74, P < 0.01]\), indicating that age group, and not dementia status, determined anterior corpus callosum volume. By contrast, the ≤77-demented individuals had smaller hippocampus volumes than the >78-nondemented individuals \([t(48) = 3.96, P < 0.001]\), indicating that dementia status, and not age group, determined hippocampus volume.

**Discussion**

The present study provides direct evidence differentiating nondemented aging from early-stage AD. Whereas individuals with dementia show substantial reduction in hippocampal volume, only mild effects are present in nondemented aging. In contrast, nondemented age-related effects include significant reductions in callosal volume with an anterior-to-posterior gradient. Moreover, anterior (frontal) callosal differences are not accelerated by early-stage AD, suggesting they are unlikely to contribute to initial stages of AD. These results suggest a multiple-component model of aging (e.g. Buckner, 2004; Hedden and Gabrieli, 2004). One process, associated with AD, influences the medial temporal lobe early in its course. A separate process, ubiquitous in aging, affects white matter regions with a frontal bias and may underlie the executive difficulties that are common in the elderly.

Across two independent samples, the magnitudes of nondemented age-related differences were greatest in the most anterior portions of the CC (genu and rostrum) than in the

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**Table 2**

Demographics for combined sample of older adults

<table>
<thead>
<tr>
<th></th>
<th>Nondemented old</th>
<th>Early-stage AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤77 years</td>
<td>≥78 years</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>65-77</td>
<td>78-93</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>16/8</td>
<td>20/6</td>
</tr>
<tr>
<td>Mean education (years)</td>
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</tr>
<tr>
<td>Education range</td>
<td>10-20</td>
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<tr>
<td>CDR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MMSE</td>
<td>29 ± 1</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>MMSE range</td>
<td>26-30</td>
<td>25-30</td>
</tr>
</tbody>
</table>

CDR = Clinical Dementia Rating, where CDR 0 = no dementia, CDR 0.5 and 1 = very mild and mild dementia, respectively. MMSE = Mini-Mental State Exam (Folstein et al., 1975), where the range from best to worst performance is 30-0; AD = Alzheimer’s disease; F = females; M = males; n/a = not available/applicable.
splenium. There were no additional reductions in callosal subregions associated with AD status, suggesting that this was entirely an aging phenomenon. The pattern of macrostructural volume loss observed in the current study likely parallels findings apparent at the microstructural level. Recent studies assessing white matter microstructure with diffusion tensor imaging note differential age-associated degeneration of anterior corpus callosum and lobar regions (O’Sullivan et al., 2001; Head et al., 2004). The cellular basis of the losses observed in these neuroimaging studies is uncertain. Post-mortem investigations document decreases in length and diameter of myelinated fibers and loss of small diameter myelinated fibers in subcortical white matter with advancing age (Tang et al., 1997). Subcortical white matter damage in nondemented older adults, as evidenced by white matter hyperintensities, may contribute to callosal atrophy (Pantel et al., 1999). Critically, the present study strongly suggests that the anatomical changes associated with normal aging and AD are due to distinct mechanisms.

It is possible that the regional atrophy of the CC observed here is related to regional neocortical degeneration (Pandya and Seltzer, 1986; Teipel et al., 2003). The distribution of age-related callosal differences is consistent with a tendency for greater vulnerability of anterior compared with posterior regions of the cortex (Kemper, 1994; Raz, 2000). It has been reported that gray matter losses may precede white matter changes followed by acceleration of white matter degeneration (Miller et al., 1980; Jernigan et al., 2001). However, the temporal sequence and functional relationship of gray and white matter changes require further investigation. It is also possible that white matter is preferentially vulnerable to age-associated processes, such as hypertension, that influence cortical functioning indirectly.

The temporoparietal association cortices are affected by AD prior to other neocortical sites (Braak and Braak, 1991; Price and Morris, 1999). As the splenium contains fibers from these regions, it was expected to be particularly affected by AD. Previous reports have noted atrophy of posterior callosal regions in early-stages of AD (Teipel et al., 1999) that may be similar in magnitude to medial temporal atrophy, even in early-stage AD (Teipel et al., 2003). In the current study the AD group was not significantly different from the nondemented group in splenial atrophy. The present sample consisted of very mildly to mildly demented individuals, with a preponderance of very mildly demented. It is possible that neocortical degeneration sufficient to result in callosal effects may be present in later stages of AD. There were nonsignificant trends for mildly demented individuals (CDR = 1) to show reductions in splenial volume compared with very mildly demented (CDR = 0.5) individuals and from age-matched controls.

As expected from the substantial literature (Jack and Petersen, 2000), hippocampal volume was considerably reduced in AD individuals. The volume reductions likely correspond to well-known neuropathological effects (Jack et al., 2002). Conversely, nondemented older adults did not have significantly smaller hippocampal volumes compared with younger adults, although there was a 0.47% per year age-associated volume reduction within the nondemented older adults (aged 65–93 years). The nature and degree of nondemented age-related volume loss in the hippocampus remains unsettled. A recent quantitative review of 15 cross-sectional studies revealed a median age by hippocampus correlation of $r = -0.27$, with a range of $r = -0.03$ to $r = -0.63$ (Raz, 2000). Reasons for such variability include intrinsically high variance of the $r$ statistic, inconsistent screening for pre-clinical dementia or other health-related problems that may impact the hippocampus, and disparate rules for regional demarcation. In addition, our morphometric methods conservatively estimate volume decline because ambiguous voxels are often included within the structure (such as occur at the juncture between CSF and hippocampus and increase with age). Recent longitudinal studies converge on an -1–2% annual age-related hippocampal decline (Jack and Petersen, 2000; Cardenas et al., 2003; Raz et al., 2004). The decline may be characterized by a constant slope during younger ages and accelerated decline in later life (Raz et al., 2004). Such a pattern might explain the present findings and also failures to find significant age effects in samples with restricted age ranges. Our results, and those reported in the literature, all imply that hippocampal volume loss in AD is prominent and disproportionate to that observed in nondemented aging (Jack and Petersen, 2000; Cardenas et al., 2003).

The present results complement a growing body of literature reporting differences in the effects of nondemented aging and AD. Ohnishi et al. (2001) noted differences in hippocampal and entorhinal regions in AD and also age-related differences in frontal, temporal and parietal cortex. Differential effects have also been observed within the hippocampus. Nondemented aging affects the dentate gyrus and subiculum whereas AD is particularly associated with CA1 and entorhinal cortex changes (Small et al., 2000, 2002; Uylings and de Brabandender, 2002). At the behavioral level, memory problems in AD present as rapid forgetting whereas in nondemented aging the memory problems may relate more to executive dysfunction secondary to impairments in prefrontal cortical function (Albert, 1998; Storandt et al., 2002).

The possibility that AD represents accelerated aging has been based in part on the observation of hippocampal atrophy in both nondemented aging and AD. However, the present data in aggregate lead to the conclusion that at least one of the mechanisms underlying nondemented aging disproportionately affects anterior regions of the cerebrum and is independent of AD. Furthermore, although mild hippocampal atrophy may occur in nondemented aging, there appears to exist a separate pathologic mechanism that results in substantial hippocampal volume loss at the very earliest stages of AD (e.g. CDR = 0.5/1). The double dissociation implies that AD and nondemented aging are separable entities and provides strong support for a multiple-component model of brain aging: certain aspects of aging and AD reflect distinct underlying processes.

Notes

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