Brain tissue volumes in relation to cognitive function and risk of dementia


a Department of Epidemiology, Erasmus MC University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
b Department of Radiology, Erasmus MC University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
c Department of Medical Informatics, Erasmus MC University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
d Department of Neurology, Erasmus MC University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands

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Abstract

We investigated in a population-based cohort study the association of global and lobar brain tissue volumes with specific cognitive domains and risk of dementia. Participants (n = 490; 60–90 years) were non-demented at baseline (1995–1996). From baseline brain MRI-scans we obtained global and lobar volumes of CSF, GM, normal WM, white matter lesions and hippocampus. We performed neuropsychological testing at baseline to assess information processing speed, executive function, memory function and global cognitive function. Participants were followed for incident dementia until January 1, 2005. Larger volumes of CSF and WML were associated with worse performance on all neuropsychological tests, and an increased risk of dementia. Smaller WM volume was related to poorer information processing speed and executive function. In contrast, smaller GM volume was associated with worse memory function and increased risk of dementia. When investigating lobar GM volumes, we found that hippocampal volume and temporal GM volume were most strongly associated with risk of dementia, even in persons without objective and subjective cognitive deficits at baseline, followed by frontal and parietal GM volumes.

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1. Introduction

Several biomarkers for cognitive impairment and dementia have been identified using magnetic resonance imaging (MRI) of the brain. Medial temporal lobe atrophy, including hippocampal atrophy, is closely related to memory impairment and is a strong predictor of dementia even in asymptomatic persons (de Leon et al., 1995; den Heijer et al., 2006; Fox et al., 2001; Jack et al., 2002; Smith et al., 2007). Subcortical vascular disease, as reflected by white matter lesions (WML) and lacunar infarcts, is thought to contribute to the development of dementia by primarily affecting a different cognitive domain than memory, namely information processing speed (Prins et al., 2005; Swan et al., 2000).

Several studies have suggested that persons with whole-brain atrophy also have poorer global cognition and suffer more often from dementia than persons without atrophy (Ertel-Lyons et al., 2006; Jack et al., 2005). However, little is known whether this applies evenly to atrophy of all brain regions and for all cognitive domains. Moreover, few studies distinguished between grey matter (GM) and white matter (WM) atrophy. Previous studies have used visual ratings of sulcal width as an indirect marker of GM atrophy, and ventricular enlargement as an indirect marker of WM atrophy, and found inconsistent results regarding their relationship with specific cognitive domains (Breteler et al., 1994; Longstreth et al., 2000; Mosley et al., 2005; Soderlund et al., 2006).
Recent advances in the analysis of brain MRI-data have opened the way for automated in vivo volumetric quantification of the whole brain, and of GM and WM (DeCarli et al., 2005; Fotenos et al., 2005). The use of these direct volumetric measures of GM and WM atrophy may allow for a better assessment of specific effects on cognition.

Atrophy of the hippocampus, which is a predominantly GM structure, is thought to be one of the first detectable signs of dementia (de Leon et al., 1995). Post-mortem and neuroimaging studies in dementia patients have shown that atrophic changes in GM are present throughout the brain, and that these changes probably develop later in the course of the disease (Blennow et al., 2006; Braak et al., 1993; Delacourte et al., 1999; Halliday et al., 2003; Sonnen et al., 2007). Little is known about whether brain atrophy outside the hippocampus is discernible during the preclinical phase of dementia.

We investigated in a population-based cohort study the association of GM and WM volume with specific cognitive domains and with the risk of dementia. Furthermore, we investigated how atrophy of the different cerebral lobes was related to dementia, and whether lobar atrophy predicted dementia in asymptomatic persons.

2. Methods

2.1. Participants

This study is based on the Rotterdam Scan Study, a large population-based cohort study in the Netherlands, investigating age-related brain changes on MRI (Prins et al., 2005; Vermeer et al., 2003). At baseline (1995–1996), we randomly invited participants (60–90 years) stratified by sex and 5-year age strata from the Zoetermeer Study and the Rotterdam Study to participate in the Rotterdam Scan Study (Hofman et al., 2007; Prins et al., 2005). Individuals who were demented, blind or had an MRI contraindication were excluded from the study. The present study is restricted to participants originating from the Rotterdam Study (n = 563), because their scanning protocol included an additional high-resolution MR sequence. All persons gave written informed consent and the study was approved by the medical ethical committee of the Erasmus Medical Center, Rotterdam.

2.2. MRI measures at baseline

Brain scans were performed on a 1.5-T MRI System (VISION MR, Siemens AG, Erlangen, Germany). We obtained a proton-density, a T2-weighted, and a high-resolution inversion-recovery double contrast 3D HASTE sequence for our multi-spectral volumetry (Vrooman et al., 2007). Among the 563 participants, 52 developed clausrophobia during MRI acquisition and 21 additional datasets were unusable due to various technical reasons (e.g. excessive motion artifacts) leaving a total of 490 participants in our present study.

Image preprocessing and the tissue classification algorithm have been described elsewhere (Ikram et al., 2008; Vrooman et al., 2007). Briefly, preprocessing included co-registration, non-uniformity correction and intensity normalization. Afterwards, we used the k-nearest-neighbor classifier (Anbeek et al., 2005) to classify voxels into cerebrospinal fluid (CSF), GM, normal WM, and WML. To remove non-cerebral tissue, we used non-rigid transformation (Klein et al., 2005; Rueckert et al., 1999) to register to each brain a template scan, in which all non-cerebral tissue was manually masked. Validation methods and results have been described and showed very good to excellent agreement between automated classification and manual classification as reference (Ikram et al., 2008; Vrooman et al., 2007). For an example of the classification result see Ikram et al. (2008).

For measurement of lobar brain tissue volumes, we first created a template scan, in which the lobes were labeled according to a slightly modified version of the segmentation protocol as described by Bokde et al. (2002, 2005). Subsequently, we used a validated non-rigid registration algorithm to map this template to each brain (Klein et al., 2005; Rueckert et al., 1999). Fig. 1 shows an example of this segmentation, which uses anatomical landmarks and cerebral fissures as boundaries to distinguish the four major lobes (frontal, parietal, occipital, and temporal). By combining this lobar segmentation with the tissue classification algorithm we were able to obtain lobar volumes of GM, normal WM and WML separately.

Hippocampal volumes were manually outlined on coronal HASTE slices reconstructed perpendicular to the long axis of the hippocampus (den Heijer et al., 2006). Brain infarcts were rated visually as focal hyperintensities on T2-weighted images, 3 mm in size or larger and with a corresponding prominent hypointensity on T1-weighted images. Intrarater agreement for detection of infarcts was good (κ = 0.80) (Vermeer et al., 2003).

2.3. Cognitive function at baseline

At baseline, participants underwent the following neuropsychological tests: the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the Stroop test (Houx et al., 1993), the Letter-Digit Substitution Task (Lezak et al., 2004), a verbal fluency task (Welsh et al., 1994), and a 15-word verbal learning test (based on Rey’s recall of words) (Bleecker et al., 1988). For each participant, we calculated z-scores for each test separately, except for MMSE (z-score = test score minus mean test score divided by the standard deviation). To obtain more robust outcome measures for cognition, we used the individual neuropsychological test scores to construct compound scores for information processing speed, for executive function, for memory, and for global cognitive function (Prins et al., 2005). The compound score for information processing speed was calculated as the average of the z-scores for the first and second subtask of the Stroop test and the Letter-Digit Substitution Task. The score for exec-
Fig. 1. HASTE odd sequence and the result after segmentation into the various brain lobes using non-rigid registration. Red: left frontal lobe; white: right frontal lobe; dark green: left parietal lobe; light green: right parietal lobe; dark blue: left temporal lobe; light blue: right temporal lobe; yellow: left occipital lobe; purple: central region comprising basal ganglia and corpus callosum. The right occipital lobe is not shown on these cross-sections. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Memory impairment as measured with neuropsychological tests is the first detectable neuropsychological sign of incipient dementia (DeCarli, 2003). Moreover, subjective memory complaints too are thought to be highly predictive of incident dementia (van Oijen et al., 2007). Therefore, we also questioned persons at baseline on subjective memory complaints by asking a single question: “Do you have complaints about your memory performance?” This question has been shown to predict incident dementia (Geerlings et al., 1999).

Executive function was the average of the $z$-scores for the third subtask of the Stroop test, the Letter-Digit Substitution Task, and the verbal fluency task. The compound score for memory was the average of the $z$-scores for the immediate and delayed recall of the 15-word verbal learning test. The compound score for global cognitive function was the average of the $z$-scores for the Stroop test (averaged across the three subtasks), the Letter-Digit Substitution Task, the verbal fluency test, and the immediate and delayed recall of the 15-word verbal learning test (Prins et al., 2005).
2.4. Ascertainment of incident dementia

Assessment and subtyping of dementia cases in the Rotterdam Scan Study followed the protocol of the Rotterdam Study (Ott et al., 1998). We screened all participants for dementia at baseline and at two follow-up examinations (1999–2000, 2001–2002) using a three-step protocol: Two brief tests of cognition (MMSE and Geriatric Mental State schedule (GMS) organic level) were used to screen all participants. Screen-positives (MMSE score < 26 or GMS organic level > 0) underwent the Cambridge examination for mental disorders of the elderly (Camdex) (Roth et al., 1986). Persons who were suspected of having dementia were examined by a neuropsychologist if additional neuropsychological testing was required for the diagnosis.

In addition, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnosis of dementia was made in accordance with internationally accepted criteria for dementia (DSM-III-R). Follow-up for incident dementia was complete until January 1, 2005.

2.5. Covariates

At baseline, information on education and current health status was obtained by interview and physical exam. Smoking status was verified and participants were classified into one of three categories: current smoker, former smoker or never smoked. Blood pressure was measured twice at the right arm with a random-zero sphygmomanometer. The average of the two values measured at one occasion was used. Hypertension was defined as one of the following: a systolic blood pressure of 160 mmHg or higher, or a diastolic blood pressure of 100 mmHg or higher, or current use of blood pressure lowering drugs for the indication of hypertension (Grades 2 and 3 according to the 1999 World Health Organization guidelines) (WHO, 1999). Diabetes mellitus was defined as non-fasting serum glucose level exceeding 11.1 mmol/l or the use of oral blood glucose lowering drugs or insulin. APOE genotype was determined in 420 participants.

2.6. Statistical analysis

All brain tissue volumes were expressed as percentage of intra-cranial volume (=CSF + GM + normal WM + WML) to correct for individual head-size differences. Therefore, a larger relative volume of CSF indicates a smaller whole-brain volume. Total WM was defined as the sum of normal WM and WML. WML were further natural log transformed because of skewness of the untransformed measure. Because initial analyses did not show any consistent differences between left and right lobar volumes, we summed volumes of both sides for further analyses.

With linear regression we investigated the relationship between global brain tissue volumes and cognitive function. With Cox’ proportional hazards model we calculated hazard ratios for dementia per standard deviation increase in global brain tissue volumes. All analyses were adjusted for age, sex, education level, and additionally for cardiovascular risk factors and presence of brain infarcts, and stratified on presence of the APOE ε4-allele. In similar analyses we investigated how lobar brain tissue volumes were related to cognitive function and risk of dementia. We performed these analyses per standard deviation (S.D.) increase in the various volumes in order to be able to compare the magnitude of the effect of these volumes with each other.

Initially, we studied the whole cohort. Subsequently, we investigated whether the relationships between brain tissue volumes and risk of dementia were present even in persons without objective and subjective cognitive problems at baseline. For this, we stepwise excluded persons with increasingly less severe cognitive problems at baseline (den Heijer et al., 2006). We first excluded persons with subjective memory complaints AND z-memory <1.5S.D. of age- and education-specific means (which was calculated by regressing age and education with memory and taking those persons whose standardized residual was lower than 1.5). Secondly, we additionally excluded persons without subjective memory complaints but with z-memory <1.5S.D. of age- and education-specific means. Next, we also excluded persons with z-memory <1.0S.D. of age- and education-specific means. Finally, all persons with subjective memory complaints OR z-memory <1.5 of age- and education-specific means were excluded.

3. Results

Table 1 shows the baseline characteristics of the study population. Table 2 shows the cross-sectional association between global brain tissue volumes and cognitive performance. Larger volumes of CSF and WML were related to a lower MMSE score and all cognitive domains. Larger volumes of total WM and normal WM were related to better performance on the MMSE, higher information processing speed, and borderline with better executive function, whereas larger GM volume was significantly related to better memory function. Investigating lobar brain tissue volumes in relation to cognitive function yielded similar effects for all lobar volumes (data not shown). Adjusting for cardiovascular risk factors and brain infarcts did not change the results.

During a mean follow-up of 5.9 years (standard deviation 1.6; range 0.1–9.0 years), 46 persons developed dementia (incidence-rate 16.0 per 1000 person-years). Table 3 shows the risk of dementia associated with global brain tissue volumes. Larger volumes of CSF and WML were related to an increased risk of dementia. Larger GM volume indicated a decreased risk of dementia, whereas total and normal WM volumes were not related to the risk of dementia.
Table 1
Baseline characteristics of the study population

| N | Age (year) 73.4 (7.9) | Women 249 (51) | Primary education only 149 (30) | Hypertension 250 (51) | Diabetes mellitus 24 (5) | Current smoker 87 (18) | Former smoker 264 (54) | APOE ε4 carriersa 131 (31) | MMSE score 27.7 (2.2) | Brain infarcts 137 (28) | Cerebrospinal fluid (%ICV) 22.6 (3.7) | Grey matter (%ICV) 46.6 (4.1) | Normal white matter (%ICV) 29.5 (6.4) | Total white matter (%ICV) 30.8 (5.7) | White matter lesions (%ICV)b −0.33 (1.26) | Hippocampal volume (%ICV) 0.57 (0.08) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

Values are means (standard deviation) or numbers (%). MMSE: Mini-Mental State Examination; ICV: intra-cranial volume.

a Assessed in 420 persons.
b Natural log transformed.

All relations remained unchanged after adjusting for cardiovascular risk factors and brain infarcts (Table 3). Also, stratification by APOE genotype did not alter the results.

Fig. 2 shows the association of hippocampus volume and GM volume in various lobes with the risk of dementia. Hippocampus volume was most strongly associated with the development of subsequent dementia, followed by volumes of temporal GM, frontal GM and parietal GM, whereas occipital GM volume was not associated with the risk of dementia. As expected, the more people we excluded from the lower end of the memory performance distribution at baseline the weaker the associations became of hippocampus and GM volumes with the risk of dementia, although the overall pattern in strength of the associations remained unchanged (Fig. 2). However, even after excluding persons with z-memory below 1.0 S.D. of age- and education-specific means at baseline, hippocampus volume and temporal GM volume remained significantly associated with dementia (Fig. 2). Only after excluding persons with subjective memory complaints OR z-memory below 1.5 S.D. (which was 33% of the cohort) did the associations of hippocampus and temporal GM with dementia become statistically non-significant.

Of note is that global GM and temporal GM volumes also included hippocampal volume; however, subtracting hippocampal volume from these volumes did not change the results in any way.

In line with our observations on global volumes of normal and total WM, lobar volumes of WM were not associated with the risk of dementia.

4. Discussion

In this population-based cohort study we found that volumes of WM and GM relate differently to specific
Fig. 2. The association of hippocampus volume and grey matter volume in various lobes with the risk of dementia. Symbols represent hazard ratios per standard deviation increase in volume, adjusted for age, sex and education; horizontal error bars represent the 95% confidence interval. Note that the $x$-axis is depicted on a logarithmic scale. S.D. standard deviation.

cognitive domains and to the risk of dementia. Atrophy of WM was related to worse MMSE scores, lower psychomotor speed and worse executive function, but not to risk of dementia. In contrast, GM atrophy was related to worse memory performance and to an increased risk of dementia. When analyzed at the lobar level, hippocampal and temporal GM atrophy were most strongly associated with dementia, followed by frontal GM atrophy and parietal GM atrophy. Occipital GM atrophy was not associated with risk of dementia. Upon stepwise excluding persons with increasingly less severe objective or subjective cognitive deficits at baseline, this pattern remained, although the effect estimates became smaller and ultimately non-significant.

Strengths of our study include the population-based setting, the large sample size, the volumetric quantification of global and lobar brain tissue volumes, and the long and virtually complete follow-up for dementia. Moreover, by taking into account memory complaints and neuropsychological performance at baseline, we were able to also investigate asymptomatic persons. A possible limitation is that in some cases misclassification in diagnosis or subtyping of dementia could have occurred. However, because the diagnosis and subtyping was made blinded for brain tissue volumes at baseline, any misclassification is likely to be non-differential and will lead to an underestimation of the effect we found. Another consideration is that we focused on selected cognitive domains (i.e. memory, information processing speed, and executive function), but did not investigate other cognitive domains such as visuospatial processing, visuoperceptual tasks, or naming. Moreover, we studied global and lobar tissue volumes but not subcortical tissue volumes or volumes of

Table 3
Global brain tissue volumes and the risk of dementia

<table>
<thead>
<tr>
<th>Brain tissue volume</th>
<th>Risk of dementia HR (95% CI)</th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal fluid, %ICV (per S.D.)</td>
<td>2.51 (1.56; 4.06)</td>
<td>2.46 (1.51; 4.01)</td>
<td></td>
</tr>
<tr>
<td>Grey matter, %ICV (per S.D.)</td>
<td>0.66 (0.48; 0.91)</td>
<td>0.66 (0.48; 0.91)</td>
<td></td>
</tr>
<tr>
<td>Total white matter, %ICV (per S.D.)</td>
<td>1.02 (0.71; 1.47)</td>
<td>1.04 (0.73; 1.50)</td>
<td></td>
</tr>
<tr>
<td>Normal white matter, %ICV (per S.D.)</td>
<td>0.88 (0.61; 1.27)</td>
<td>0.90 (0.62; 1.30)</td>
<td></td>
</tr>
<tr>
<td>White matter lesions, %ICV (per S.D.)$^a$</td>
<td>1.52 (1.02; 2.27)</td>
<td>1.57 (1.03; 2.38)</td>
<td></td>
</tr>
</tbody>
</table>


$^a$ Natural log transformed.
specific regions within lobes. Future research using a more extensive test battery coupled with more detailed regional volumes might reveal subtle associations that we could not assess in this study.

Thus far, several imaging studies have shown that whole-brain atrophy is related to poorer cognition and increased risk of dementia (Erten-Lyons et al., 2006; Jack et al., 2004; Jack et al., 2005). In our dataset, this is reflected in the associations of larger CSF volume with poor cognitive function, and with the risk of dementia. However, we went a step further by making a distinction between WM and GM volumes and found that these had different effects on cognitive performance and dementia.

We found that WM atrophy was related to worse MMSE score and information processing speed. In the cerebral WM, the axonal structures are covered by myelin sheets, which are pivotal in increasing the speed of information transfer (Fernando et al., 2006). Damage to myelin may therefore lead to poorer performance on tests measuring information processing speed. These myelin sheets are usually very susceptible to ischemic damage caused by subcortical vascular disease (Bartzokis, 2004; Fernando et al., 2006). Subcortical vascular disease can be seen on structural MRI not only as WML and lacunar infarcts, but also as WM atrophy (Fernando et al., 2006; Scheltens et al., 1995). Moreover, on diffusion-tensor-imaging (DTI) damage to myelin sheets is reflected in loss of microstructural integrity of WM. Our data using structural MRI are in line with studies using DTI that show that a decline in white matter microstructural integrity is related to lower MMSE score, information processing speed and executive function, but not to memory (Deary et al., 2006; Shenkin et al., 2005).

We found that GM atrophy was related to poorer memory performance and an increased risk of dementia. In contrast, Mungas et al. (2001,2005) reported that (change in) GM was related to global cognition, executive function and speed, but not to memory. However, that study was based on a heterogeneous study population including cognitively impaired and demented persons, whereas we focused on persons who were non-demented at baseline. Differences in study population and severity of cognitive impairment might therefore explain these seemingly contradictory findings. This is supported by the fact that exclusion of demented persons in the study by Mungas et al. (2005) attenuated the relation between decrease in GM and decline in executive function.

Memory impairment is a pivotal symptom of dementia, and both are related to neuronal loss (Mortimer et al., 2004), which can be visualized as GM atrophy on MRI (Bobinski et al., 2000). Previously, we did not find an association between increasing age and global GM atrophy in the general non-demented population (Ikram et al., 2008). This suggests that GM atrophy is a process specific to those, who are at an increased risk of dementia. When analyzing the separate lobar tissue volumes we found that atrophy of the hippocampus and temporal GM was most strongly associated with dementia, followed by frontal GM atrophy and parietal GM atrophy. This fits well with several imaging studies that have investigated patterns of GM atrophy in persons with mild cognitive impairment or in persons who are in the early stages of dementia: these studies too have found that the temporal GM is most severely affected, followed by several subregions in the frontal and parietal lobes (Chetelat and Baron, 2003; Killiany et al., 2000; Whitwell et al., 2007; Wolf et al., 2004). This pattern of lobar atrophy has also consistently been confirmed by various post-mortem studies in dementia patients (Braak et al., 1993; Halliday et al., 2003). Moreover, we found this same pattern of lobar GM atrophy even after exclusion of persons with objective or subjective cognitive deficits at baseline. Although we do not separately diagnose mild cognitive impairment in our cohort, persons with subjective memory complaints AND z-memory below 1.5S.D. of age- and education-specific means closely fit the criteria (Jack et al., 1999). Our findings therefore emphasize that dementia has a long pre-clinical phase in which atrophic changes are already taking place without these being clinically apparent, even as mild cognitive impairment (Jack et al., 2005). More importantly, this indicates that the actual moment of clinical diagnosis of dementia and mild cognitive impairment is rather arbitrary and does not accurately reflect the actual disease process, which may have started several years before. Finally, we found that after excluding persons with subjective memory complaints OR z-memory below 1.5S.D. brain atrophy measures were no longer predictive of dementia. Therefore, future studies should also focus on brain changes other than atrophy taking place pre-clinically in those persons, who are cognitively normal at baseline, but do develop dementia during follow-up.

**Conflict of interest**

None of the authors has any actual or potential conflicts of interest related to this manuscript, including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) their work.

**Disclosure**

None of the authors has anything to disclose in relation to this manuscript.

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