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Neurobiology of Aging 33 (2012) 2774–2781

NEUROBIOLOGY OF AGING

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Determinants of cerebellar and cerebral volume in the general elderly population

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Received 21 October 2011; received in revised form 20 January 2012; accepted 11 February 2012

Abstract

In a population-based study of 3962 community-dwelling nondemented elderly we investigated the relation of age, sex, cardiovascular risk factors, and the presence of infarcts with cerebellar volume, and its interrelationship with cerebral volumes. Cerebellar and cerebral gray and white matter were segmented using Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/). We used linear regression analyses to model the relationship between age, sex, cardiovascular risk factors, brain infarcts, white matter lesions (WMLs) and cerebellar and cerebral volume. Smaller cerebellar volumes with increasing age were mainly driven by loss of white matter. Diabetes, higher serum glucose and lower cholesterol levels were related to smaller cerebellar volume. No association was found between hypertension, smoking, apolipoprotein E (ApoE) genotype, and cerebellar volume. Supratentorial lacunar infarcts and WMLs were related to smaller cerebellar volume. Infratentorial infarcts were related to smaller cerebellar white matter volume and total cerebral volume. This study suggests that determinants of cerebellar volume do not entirely overlap with those established for cerebral volume. Furthermore, presence of infarcts or WMLs in the cerebrum can affect cerebellar volume.

Keywords: Cohort study; Cerebellum; Cerebrum; Aging; Brain volume; Magnetic resonance imaging; Cerebrovascular disease; Infarcts; White matter lesions; Cardiovascular risk factors

1. Introduction

The cerebellum is a complex structure, containing more than 50% of all neurons in the brain. It is organized in a different manner than the cerebrum (Kandel et al., 2000; Voogd, 2003). Recently, research has emphasized the role the cerebellum is likely to play in cognitive processing, next to its well-studied contributions to motor skills (Schmahmann, 2010; Stoodley, 2011). It is therefore important to study determinants of cerebellar volume in an elderly population.

Most structural magnetic resonance (MR) imaging studies with large sample sizes have focused on the cerebrum only or the entire brain (DeCarli et al., 2005; Good et al., 2001; Ikram et al., 2008). Studies that specifically assessed the cerebellum showed inconsistent results. Some studies reported that cerebellar volume remains relatively stable with aging (Bergfield et al., 2010; Rhyu et al., 1999; Smith et al., 2007), whereas others found strong effects of age on cerebellar atrophy (Jernigan et al., 2001; Pagani et al., 2008; Raji et al., 2009; Raz et al., 2001, 2010; Walhovd et al., 2005). A histological study of the cerebellum showed that

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10.1016/j.neurobiolaging.2012.02.012

smaller weight and volume were found, and fewer neurons were counted in the cerebellum of older persons than in those of younger persons (Andersen et al., 2003). Drawbacks of this previous work are the relatively small sample sizes and use of preselected populations. An important aspect that is underexposed in current literature is how the cerebellum is affected by cardiovascular factors. Cardiovascular risk factors have extensively been associated with atrophy of the cerebrum (DeCarli et al., 2005; Ikram et al., 2008). Moreover, various studies have shown strong relations of cortical and lacunar infarcts, as well as white matter lesions with cerebral atrophy (DeCarli et al., 2005; Godin et al., 2009; Ikram et al., 2008; Raji et al., 2012). Still, how cardiovascular risk factors and cerebrovascular disease relate to cerebellar volumes, remains unclear. Therefore, there is a need to study cardiovascular risk factors and characteristics of cerebrovascular disease as determinants of cerebellar volume in a population-based elderly population.

The aim of our study was to investigate structural characteristics of the cerebellum with aging, and how cardiovascular factors and cerebrovascular disease affect cerebellar volume. Moreover, we compared determinants of cerebellar volume to determinants of cerebral volume.

2. Methods

2.1. Participants

The study is based on the Rotterdam Study (Hofman et al., 2011), a population-based study in middle-aged and elderly participants that started in 1990, investigating causes and consequences of age-related disease. All participants provided written informed consent for all aspects of the study and the medical ethical committee of the Erasmus MC University Medical Center, The Netherlands, approved of the study. The cohort was expanded in 2000 and 2006. From 2005 onward, standardized brain magnetic resonance imaging (MRI) scanning was implemented in the core protocol of the study (Ikram et al., 2011). From a total of 4898 persons, 30 persons with a diagnosis of prevalent dementia were excluded from the study and 389 persons were considered noneligible for MRI (due to, e.g., pacemakers or claustrophobia). The remaining 4479 persons were invited, of whom 4082 (91%) agreed to participate. Due to physical constraints (e.g., back pain), imaging was not performed or completed in 44 individuals. In total, 4038 complete MRI examinations were obtained.

2.2. MRI acquisition and image analysis

Magnetic resonance imaging of the brain was performed on a 1.5-T MRI scanner (Signa Excite II; General Electric Healthcare, Milwaukee, WI, USA). The MRI protocol included a high-resolution axial T1-weighted 3-dimensional fast radio frequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse (FASTSPGR-IR) sequence (repetition time [TR] = 13.8 ms, echo time [TE] = 2.8 ms, inversion time [TI] = 400 ms, field of view [FOV] = 25 cm^2, matrix = 416 × 256, flip angle = 20°, number of excitations [NEX] = 1, bandwidth [BW] = 12.50 kHz, 96 slices with slice thickness 1.6 mm 0-padded to 0.8 mm). Furthermore a fluid-attenuated inversion recovery (FLAIR) sequence was acquired (TR = 8000 ms, TE = 120 ms, TI = 2000 ms, FOV = 25 × 25 cm^2, matrix = 320 × 224, NEX = 1, BW = 31.25 kHz, 64 slices with slice thickness 2.5 mm) and a proton density-weighted sequence (TR = 12,300 ms, TE = 17.3 ms, FOV = 25 cm [rectangular], matrix 416 × 256, NEX = 1, BW = 17.86 kHz, 90 slices with slice thickness 2.5 mm). All slices were contiguous.

According to our standard acquisition protocol images were resampled to 512 × 512 × 192 voxels (voxel size: 0.5 × 0.5 × 0.8 mm^3) (Ikram et al., 2011).

A nonuniformity correction was performed (Sled et al., 1998). Segmentation and labeling of brain structures was performed by Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/) (Fig. 1) (Fischl et al., 2002). This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information obtained from a manually labeled training set. This yielded intracranial volume (ICV) and gray and white matter volumes for cerebellum and cerebrum. A trained observer inspected a sample of random individuals (n = 192) and all outliers (n = 170) with an intracranial, cerebral, or cerebellar volume outside a range of ± 2.58 SD from the mean, stratified by sex. These scans were blindly rated on segmentation quality. Three scans of the random sample were excluded from the study. Two of these scans contained arachnoid cysts and in 1 scan a large meningioma was present, both interfering with tissue segmentation results. Seventy-three scans of the outlier sample were excluded, because the segmentation quality was insufficient. Problems in the segmentation were due to either technical problems (n = 62, e.g., motion artifacts, susceptibility artifacts due to dental implants) or pathology (n = 11, e.g., large arachnoid cysts, meningiomas) that could influence the volume estimates, resulting in 3962 scans that were included in our analyses. The total of 76 persons that were excluded, were on average older (68.4 ± 12.73 years vs. 60.2 ± 8.58 years) and more often had hypertension (67.1% vs. 54.2%) than those included in the analysis.

The evaluation of infarcts was based on fluid-attenuated inversion recovery, proton density, and T1-weighted sequences, by 5 experienced raters under supervision of a neuroradiologist. The rating protocol has been described elsewhere (Vernooij et al., 2008). Because the primary aim of the study was to investigate the cerebellum as a separate structure, we classified infarcts into 4 mutually exclusive categories. These categories entailed infratentorial infarcts only, supratentorial lacunar only, supratentorial cortical only, or multiple area infarcts. Multiple area infarcts could be supratentorial and infratentorial. Supratentorial white matter lesion volumes were obtained using a k-nearest-

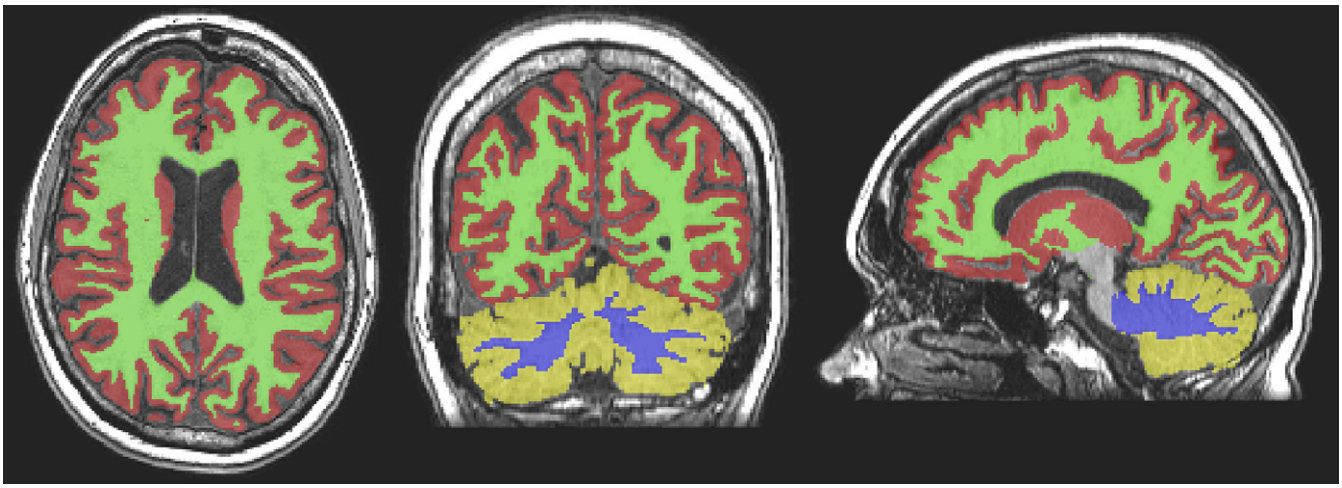

Fig. 1. Example of labeling of brain structures by Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/). Red indicates cerebral gray matter; green, cerebral white matter; yellow, cerebellar gray matter; and blue, cerebellar white matter.

neighbor classifier, according to a protocol previously described elsewhere (de Boer et al., 2009). Infratentorial white matter lesions (WMLs) are rare and in our current protocol these are not automatically quantified.

2.3. Other measurements

Information on health status was collected by interview and physical examination performed during the regular visit of participants to the research center, preceding the MRI visit. Participants were assessed on smoking habits and classified into 1 of 3 categories: current smoker, former smoker, or never smoker. At the research center, blood pressure was measured twice at the right arm with a random-0 sphygmomanometer. The average of the 2 measurements on 1 occasion was used. Besides a continuous measurement of blood pressure, the presence of hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or drug treatment for hypertension at blood pressure assessment. Fasting blood serum was drawn during examination at the research center. The blood was stored at -80 °C in a number of 5-mL aliquots and glucose levels were measured within 1 week of sampling. Diabetes mellitus was defined when fasting plasma glucose was $\geq$ 7 mmol/L, or if a person was taking oral antidiabetics or insulin. Serum total cholesterol and high density lipoprotein (HDL) cholesterol were determined using an automated enzymatic procedure (Hitachi Analyzer, Roche Diagnostics Basel, Switzerland). Apolipoprotein E (ApoE) genotyping was performed on coded genomic DNA samples and was available in 3614 participants. The distributions of ApoE genotype and allele frequencies in this population were in Hardy-Weinberg equilibrium.

2.4. Data analysis

A Pearson's correlation coefficient was computed to quantify the association between cerebellar and cerebral volume. We used linear regression models to investigate associations of age and volumes of cerebellum and cerebrum. In order to standardize differences of volume with age, we calculated z-scores for tissue volumes. To test for sex differences we also included a term for age-sex interaction. We then calculated mean cerebellar and cerebral volumes across different infarct categories. Finally, we investigated the relation between WML volume, cardiovascular risk factors, and volume using linear regression analysis. To aid comparison of the associations between infarcts, WMLs, cardiovascular risk factors and tissue volumes across the cerebellum and cerebrum, all volumetric measures were converted to z-scores. We used analysis of covariance to calculate cerebellar volume for quartiles of systolic and diastolic blood pressure, fasting glucose, total cholesterol and HDL cholesterol levels. All analyses of cardiovascular risk factors, infarcts, and WMLs with tissue volumes were adjusted for age, sex, and intracranial volume to correct for head size differences. All analyses were performed using the statistical software package SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA). Results are presented with 95% confidence interval (CI).

3. Results

Table 1 shows characteristics of the study population. In 295 participants (7.4%), infarcts were present, of whom 62 participants (1.6%) had infratentorial infarcts. Pearson's correlation coefficient between total cerebellar and total cerebral volume was 0.68 ($p < 0.001$).

Table 2 shows that white matter in the cerebellum took up about 20% of total cerebellar volume, whereas in the cerebrum white matter accounted for 51% of total cerebral volume. Mean cerebellar volumes were significantly larger for men (129.7 mL, standard error [SE], 0.25) than for women (126.2 mL; SE = 0.22).

Table 1
Baseline characteristics of the study population

	Total (n = 3962)	Men (n = 1806)	Women (n = 2156)
Age, y	60.1 ± 8.50	60.3 ± 8.52	60.0 ± 8.48
Intracranial volume (mL)	1490.9 ± 156.55	1590.2 ± 133.93	1407.9 ± 121.96
Infratentorial infarcts on MRI	62 (1.6)	34 (1.9)	28 (1.3)
Lacunar infarcts on MRI	131 (3.3)	75 (4.2)	56 (2.6)
Cortical infarcts on MRI	63 (1.6)	39 (2.2)	24 (1.1)
Multiple area infarcts on MRI	39 (1.0)	22 (1.2)	17 (0.8)
White matter lesions on MRI (mL)	4.53 ± 7.3	4.53 ± 7.5	4.52 ± 7.1
Systolic blood pressure (mm Hg)	135.25 ± 19.5	137.54 ± 18.32	133.33 ± 20.25
Diastolic blood pressure (mm Hg)	81.75 ± 10.74	82.61 ± 10.60	81.02 ± 10.81
Hypertension	2071 (53.9)	1012 (57.8)	1059 (50.6)
Diabetes	312 (8.1)	184 (10.5)	128 (6.1)
Fasting serum glucose (mmol/L)	5.54 ± 1.13	5.73 ± 1.28	5.39 ± 0.97
Serum total cholesterol (mmol/L)	5.61 ± 1.04	5.39 ± 1.01	5.78 ± 1.03
Serum HDL cholesterol (mmol/L)	1.44 ± .42	1.25 ± .33	1.59 ± .43
Current smoker	709 (18.0)	291 (16.2)	418 (19.5)
Former smoker	2076 (52.7)	1121 (62.5)	995 (44.5)
Never smoker	1154 (29.3)	383 (21.3)	771 (36.0)
ApoE ε4 carriers[a]	1065 (29.47)	490 (29.59)	575 (29.37)

Values are unadjusted mean ± standard deviation for continuous variables. Values are numbers (percentages) for dichotomous variables.
Key: ApoE, apolipoprotein E; HDL, high density lipoprotein; MRI, magnetic resonance imaging.
[a] ApoE genotypes were available in 3614 participants.

Overall, smaller volumes were found with increasing age for both cerebellar and cerebral gray and white matter. The average decrease in cerebellar volume was 0.35 mL per year increase in age. Regarding cerebellar gray matter, no interaction effect was found between age and sex ($p_{interaction}$ = 0.078). In contrast, cerebral gray matter volume showed a larger yearly decline in men than in women ($p_{interaction}$ < 0.001). Cerebellar white matter volume in men was 0.13 mL smaller per year increase, in women it was reduced by 0.09 mL per year ($p_{interaction}$ < 0.001). Cerebral white matter volume also showed a steeper decline with age in men than in women. Both cerebellar and cerebral white matter volume showed a steeper decline with increasing age than gray matter volumes (Table 3).

Table 4 shows standardized differences in cerebellar and cerebral volumes for several major cardiovascular risk factors. The only relationship found between measures of blood pressure and brain volume was a borderline positive association between diastolic blood pressure and cerebral volume (0.015 [0.003–0.028]). The presence of diabetes was related to smaller volumes of both cerebrum (−0.093 [−0.140 to −0.047]) and cerebellum (−0.260 [−0.341 to −0.179]), however higher glucose levels were only related to smaller cerebellar volume (−0.057 [−0.082 to −0.032]).Supplementary Fig. 1 shows that this association was driven by persons in the fourth quartile of glucose levels. Higher total cholesterol levels were related to a larger cerebellar (0.030 [0.008–0.053]) and cerebral volume (0.037 [0.024–0.050]). Higher HDL cholesterol was related to a larger cerebellar volume. Current smokers had a smaller cerebrum than never smokers (−0.054 [−0.092 to −0.016]). This relation was not found for the cerebellum. No relationship was found between ApoE ε4 carriership and cerebellar or cerebral volume.

In persons with infratentorial infarcts, only the white matter volume of the cerebellum was smaller (−0.19

Table 2
Mean volumes for men and women

	Mean volume ± SE (mL)		Mean difference between men and women (95% CI)
	Men	Women	
Cerebellar volume	129.7 ± 0.25	126.2 ± 0.22	3.54 (2.81–4.28)
Gray matter volume	104.8 ± 0.21	101.0 ± 0.19	3.76 (3.15–4.36)
White matter volume	24.9 ± 0.07	25.15 ± 0.06	−0.21 (−0.42 to −0.01)
Left cerebellar volume[a]	49.7 ± 0.02	49.6 ± 0.02	0.02 (−0.05 to 0.08)
Cerebral volume	895.1 ± 1.06	889.8 ± 0.96	5.29 (2.21–8.37)
Gray matter volume	438.8 ± 0.53	435.7 ± 0.48	3.06 (1.52–4.60)
White matter volume	456.3 ± 0.79	454.1 ± 0.71	2.24 (−0.06 to 4.53)
Left cerebral volume[a]	50.0 ± 0.01	50.0 ± 0.01	−0.06 (−0.10 to −0.02)

Values are adjusted for age and intracranial volume.
Key: CI, confidence interval; SE, standard error of the mean.
[a] Expressed as a percentage of its total volume.

Table 3
Differences per year increase in age of cerebellar volumes

	Men		Women		p Value interaction[a]
	Difference in volume	Difference in volume expressed in *z*-score	Difference in volume	Difference in volume expressed in *z*-score	
Total cerebellar volume	−0.43 (−0.48 to −0.37)	−0.032 (−0.036 to −0.028)	−0.31 (−0.35 to −0.26)	−0.023 (−0.026 to −0.019)	0.006
Cerebellar gray matter	−0.29 (−0.34 to −0.25)	−0.027 (−0.031 to −0.023)	−0.22 (−0.26 to −0.18)	−0.020 (−0.024 to −0.017)	0.078
Cerebellar white matter	−0.13 (−0.15 to −0.12)	−0.039 (−0.043 to −0.035)	−0.09 (−0.10 to −0.07)	−0.025 (−0.029 to −0.022)	< 0.001
Total cerebral volume	−3.13 (−3.35 to −2.90)	−0.032 (−0.034 to −0.029)	−2.00 (−2.19 to −1.82)	−0.020 (−0.022 to −0.018)	< 0.001
Cerebral gray matter	−1.24 (−1.35 to −1.13)	−0.029 (−0.031 to −0.026)	−0.74 (−0.84 to −0.65)	−0.017 (−0.019 to −0.015)	< 0.001
Cerebral white matter	−1.89 (−2.06 to −1.72)	−0.031 (−0.034 to −0.029)	−1.26 (−1.40 to −1.12)	−0.021 (−0.023 to −0.019)	< 0.001

In the first column volumes are expressed in milliliters (95% confidence interval). In the second column volumes are expressed in *z*-scores (95% confidence interval). All values are adjusted for intracranial volume.
[a] *p*Value of age-sex interaction effect.

[−0.38 to 0.00]) compared with persons without any infarct, while in the cerebrum both gray and white matter volumes were reduced in the presence of infratentorial infarcts (Table 5). Participants with supratentorial lacunar infarcts had both smaller cerebellar (−0.13 [−0.25 to −0.01]) and cerebral volumes (−0.12 [−0.19 to −0.05]), with larger effects on white than on gray matter. In contrast, supratentorial cortical infarcts only influenced cerebral volume and not cerebellar volume. Persons with infarcts in multiple locations on average had a smaller cerebellar white matter volume compared with persons without any infarct, but no effect was found on cerebellar gray matter volume. Furthermore, persons with infarcts in multiple areas had smaller cerebral volumes.

Larger WML volume was related to smaller total cerebral volume and total cerebellar volume (Table 4). While in the cerebrum WML volume did relate to both gray (−0.026 [−0.045 to −0.007]) and white matter (−0.049 [−0.068 to −0.029]), in the cerebellum larger WML volume was only related to smaller white matter (−0.095 [−0.126 to −0.065]), but not gray matter volume.

4. Discussion

In a large sample from the general population, we found that increasing age is related to smaller cerebellar volume. There was not a very strong correlation between cerebellar and cerebral volume. The cerebellum contains relatively less white matter than the cerebrum. Decline in cerebellar white matter volume with age was steeper than for gray matter. In our study diabetes, glucose, and cholesterol level appeared as determinants for cerebellar volume, whereas blood pressure, smoking, and ApoE did not. Finally, we showed that the presence of supratentorial lacunar infarcts, as well as WMLs, are related to lower cerebellar volume and that infratentorial infarcts are related to smaller cerebellar white matter and global cerebral volume.

A limitation of this study is that the white matter in the folia of the cerebellum is tightly packed and therefore usually of subvoxel resolution. Therefore, our cerebellar gray and white matter volume measurements reflect the "bulk" anatomy and are not sensitive to subtle changes in the folia structure. To our knowledge, no publicly available brain structure segmentation method exists that can model such partial volume voxels in the cerebellum. Another limitation of this study is the cross-sectional design. Structural age differences observed at a single point in time were used to make inferences about atrophy of the brain with aging. However, it was previously reported that cerebral volumes are strongly correlated between cross-sectional and longitudinal estimates (Resnick et al., 2003). Strengths of this study

Table 4
Cardiovascular factors and cerebellar and cerebral volume

	Cerebellar volume	Cerebral volume
Systolic blood pressure, per SD increase[a]	0.014 (−0.010 to 0.038)	−0.006 (−0.020 to 0.007)
Diastolic blood pressure, per SD increase[a]	0.018 (−0.004 to 0.041)	**0.015 (0.003 to 0.028)**
Hypertension, yes vs. no	0.008 (−0.019 to 0.035)	−0.010 (−0.026 to 0.005)
Diabetes, yes vs. no	**−0.260 (−0.341 to −0.179)**	**−0.093 (−0.140 to −0.047)**
Fasting serum glucose, per SD increase	**−0.057 (−0.082 to −0.032)**	−0.010 (−0.024 to 0.004)
Serum total cholesterol, per SD increase	**0.030 (0.008 to 0.053)**	**0.037 (0.024 to 0.050)**
Serum HDL cholesterol, per SD increase	**0.028 (0.004 to 0.053)**	−0.003 (−0.017 to 0.010)
Smoking, current vs. never	−0.026 (−0.093 to 0.040)	**−0.054 (−0.092 to −0.016)**
Smoking, former vs. never	0.004 (−0.047 to 0.056)	−0.002 (−0.032 to 0.027)
ApoE ε4 carrier vs. noncarrier	−0.013 (−0.062 to 0.037)	0.001 (−0.028 to 0.029)

Values are standardized differences in tissue volumes (95% confidence interval) and adjusted for age, sex, and intracranial volume. Values in bold indicate level $p < 0.05$.
Key: ApoE, apolipoprotein E; HDL, high density lipoprotein.
[a] Additionally adjusted for use of blood pressure-lowering drugs.

Table 5
Infarcts and white matter lesions on MRI related to cerebellar and cerebral volumes

	Cerebellum total volume	Cerebellar GM	Cerebellar WM	Cerebrum total volume	Cerebrum GM	Cerebrum WM
Infratentorial infarcts ($n = 62$)	−0.12 (−0.30 to 0.05)	−0.09 (−0.28 to 0.09)	**−0.19 (−0.38 to −0.00)**	**−0.16 (−0.26 to −0.06)**	**−0.12 (−0.24 to −0.01)**	**−0.18 (−0.30 to −0.05)**
Supratentorial lacunar infarcts ($n = 131$)	**−0.13 (−0.25 to −0.01)**	−0.11 (−0.23 to 0.02)	**−0.17 (−0.31 to −0.04)**	**−0.12 (−0.19 to −0.05)**	−0.06 (−0.14 to 0.02)	**−0.15 (−0.23 to −0.06)**
Supratentorial cortical infarcts ($n = 63$)	−0.09 (−0.26 to 0.09)	−0.10 (−0.28 to 0.08)	−0.03 (−0.22 to 0.16)	**−0.33 (−0.43 to −0.23)**	**−0.28 (−0.39 to −0.16)**	**−0.35 (−0.47 to −0.23)**
Multiple area infarcts ($n = 39$)	−0.06 (−0.29 to 0.16)	0.03 (−0.20 to 0.26)	**−0.35 (−0.59 to −0.11)**	**−0.39 (−0.52 to −0.27)**	**−0.23 (−0.38 to −0.08)**	**−0.48 (−0.64 to −0.33)**
WML volume, per SD increase	**−0.029 (−0.056 to −0.002)**	−0.008 (−0.036 to 0.020)	**−0.090 (−0.119 to −0.061)**	**−0.038 (−0.054 to −0.023)**	**−0.025 (−0.042 to −0.007)**	**−0.046 (−0.064 to −0.027)**

Values represent differences in brain volumes compared with volumes in absence of any infarct. Brain volumes are expressed as z-scores and are adjusted for age, sex, and intracranial volume. Infarct categories are mutually exclusive. In the multiple infarct category persons are included with infarcts seen in at least 2 infarct areas, infratentorial and/or supratentorial. White matter lesion (WML) volumes are natural log transformed, and values are adjusted for age, sex, and intracranial volume. Values in bold indicate level $p < 0.05$.
Key: GM, gray matter; WM, white matter.

include the large sample, population-based design, and automatic quantification of brain volume.

In the cerebrum half of the volume is white matter, whereas in the cerebellum only a fifth of cerebellar volume is white matter. Despite difficulties in comparing studies due to differences in imaging protocols, in general our findings are in line with those of other studies in which brain tissue volumes were reported (Chung et al., 2005; Dimitrova et al., 2006; Paul et al., 2009). Some structural MRI studies have found smaller cerebellar volumes compared with our findings (Acer, et al., 2008; Raz et al., 2010), but these might be attributed to differences in protocols of cerebellar volume estimation.

We found that older age was related to smaller cerebellar volume and that this effect with age was stronger in men than in women (Chung et al., 2005). This effect was mainly driven by stronger reductions in white matter volume. Although, in terms of global cerebellar volume loss in older age, our results are in line with other studies (Good et al., 2001; Jernigan et al., 2001; Raji et al., 2009; Raz et al., 2010; Walhovd et al., 2005), the finding that cerebellar volume loss is stronger for white than for gray matter is in disagreement with several previous imaging studies (Good et al., 2001; Jernigan et al., 2001; Sullivan et al., 2000; Walhovd et al., 2005). A histological study (Andersen et al., 2003), however, also showed that the loss of cerebellar volume was mainly due to white matter loss.

Of the cardiovascular risk factors, we found that diabetes and a lower total cholesterol level were associated with both smaller cerebellar and cerebral volume. Higher fasting glucose and lower HDL cholesterol levels were related to smaller cerebellar volume, but not cerebral volume. Furthermore, smoking and lower diastolic blood pressure were related to the smaller cerebral volume, while these showed no effect on the cerebellum. The association of diabetes and cerebral volume was established previously (de Bresser et al., 2010; Enzinger et al., 2005; Ikram et al., 2008; van Harten et al., 2006), but the strong relationship between diabetes and cerebellar volume in older adults has not been described elsewhere. Related to our findings, other studies did show that glucose metabolism is different in the cerebellum than in cerebral structures (Bingham et al., 2002; Cranston et al., 1998; Herzog et al., 2008). Notably, 1 proton magnetic resonance spectroscopy study showed glucose content was twice as high in the cerebellum as in the cerebrum. Yet, this study also suggested that the cerebellum is better protected from high glucose levels than the cerebrum (Heikkilä et al., 2010), which is in contrast to our findings that serum glucose levels were strongly related to cerebellar volume. The relationship between lower HDL cholesterol and lower brain tissue volume has been demonstrated before (Ward et al., 2010). To our knowledge, our finding that a lower total cholesterol level is related to a smaller cerebellar volume has not been re-

ported before. We did not find any studies relating total cholesterol levels to cerebellar volume. However, there is indirect evidence that lower total cholesterol levels have unfavorable effects on the brain, e.g., hemorrhagic stroke or cerebral microbleeds (Segal et al., 1999; Vernooij et al., 2008). The absence of an association between ApoE ε4 carriership and cerebellar and cerebral volume is in line with other studies in nondemented persons in which ApoE ε4 carriership was not related to global measures of cerebellar and cerebral volume (Enzinger et al., 2005; Lemaître et al., 2005; Raz et al., 2010).

Participants with infratentorial infarcts had both a smaller cerebrum and smaller cerebellar white matter volume compared with participants without any brain infarct. The presence of supratentorial lacunar infarcts, but not supratentorial cortical infarcts, showed effects on both cerebellar and cerebral volume. Lacunar infarcts are 1 of the hallmarks of cerebral small vessel disease (Greenberg, 2006). Therefore, the relation between isolated supratentorial lacunar infarcts and smaller cerebellar volume indicates that the cerebellum is also sensitive to small vessel disease. The finding that isolated infratentorial infarcts are related to smaller cerebral volume is in line with studies suggesting that infratentorial brain damage disrupts connections to supratentorial networks (Grips et al., 2005; Hokkanen et al., 2006; Malm et al., 1998; Ravizza et al., 2006). Accordingly, the finding that supratentorial lacunar infarcts and WMLs are related to smaller cerebellar volume again stresses the importance of interconnectivity between cerebrum and cerebellum.

In conclusion, we presented cerebellar volumes separately for men and women, producing gender specific normative estimates for cerebellar gray and white matter volumes. We found that white matter loss mainly drives the decrease of cerebellar volume with age. This study also shows that it cannot be assumed that determinants of cerebellar volume are the same as those established for cerebral volume. Furthermore, our data suggest that loss of volume in the presence of infarcts or WMLs in the cerebrum can affect cerebellar volume and also that infratentorial infarcts can affect cerebral volume. Follow-up studies should further elucidate the pathways through which cerebellum and cerebrum are differentially affected in aging and how both interrelate.

Disclosure statement

The authors disclose no conflicts of interest. All participants of the Rotterdam Study provided written informed consent for all aspects of the study. The Rotterdam Study was approved by the medical ethical committee of the Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Acknowledgements

The Rotterdam Scan Study was financially supported by the Health Research and Development Council (ZonMW) and the Netherlands Organization for Scientific Research (NWO) (Grants 918-46-615, 904-61-096, 904-61-133). J.N.v.d.G. was supported by the Prinses Beatrix Fonds.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2012.02.012.

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