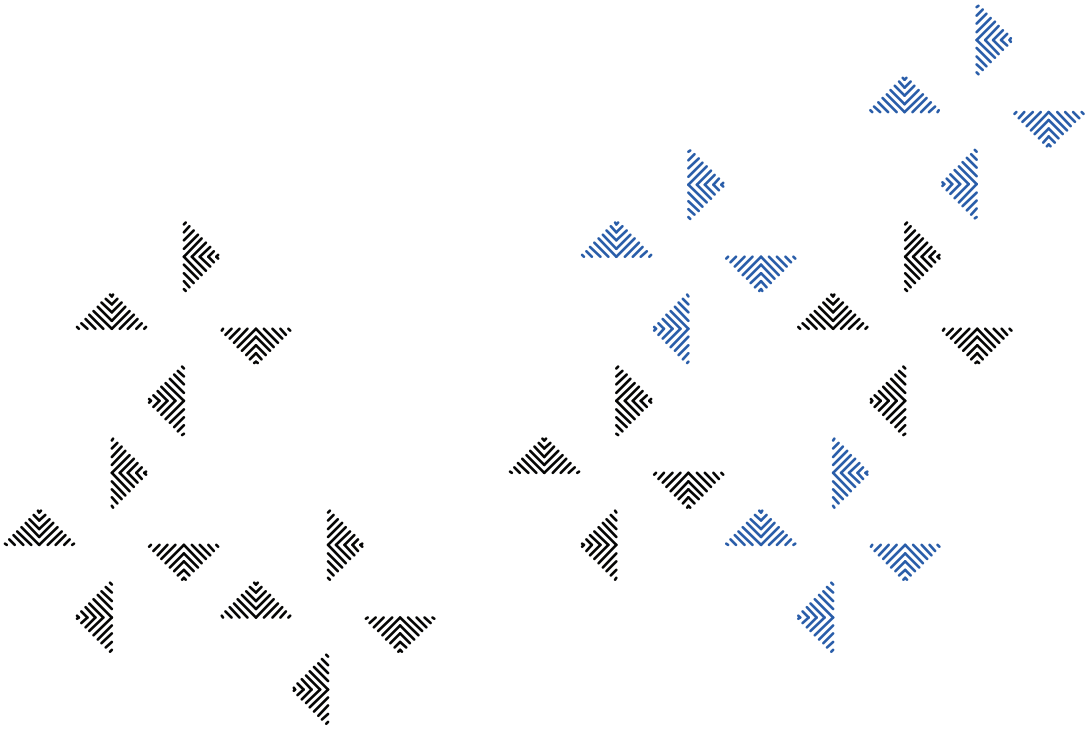
The Role of **Brain Aging** in **Cognition** and **Motor Function**



Yoo Young Hoogendam

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The Role of Brain Aging in Cognition and Motor Function

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Chapter 1

Introduction

Aging of the population is accompanied by many challenges, such as the maintenance of health and quality of life during older age.[1] An important aspect of living longer is that old age is related to disease and loss of functions.[2] The loss of brain functions poses a large problem in older age. Changes that occur in the brain can already be visualized when no symptoms or clinical disease are apparent.[3, 4] Magnetic resonance imaging (MRI) is often used to visualize subtle brain changes. The subclinical brain changes can however be used as markers of future clinical disease.[5, 6] Furthermore, subclinical, subtle changes in brain function can cause considerable discomfort in daily living.[7]

Importantly, cognitive decline is a function of the brain that is the most feared feature of getting older.[8] Especially, many people are afraid of getting dementia. Although memory decline is a hallmark of dementia, other domains of cognition are often affected as well.[9] While many studies focus on persons in preclinical stages of dementia, i.e. mild cognitive impairment, these studies are not generalizable to the many community-dwelling elderly who also face possible decline of cognitive functions. Still, cognitive aging has been investigated extensively outside the context of dementia and mild cognitive impairment, and age effects on a variety of cognitive domains, such as spatial orientation, inductive reasoning, memory, verbal and number skills, have been documented in different populations.[10, 11] However, rates of cognitive decline across cohorts have shown inconsistencies, and age effects on cognition can alter over time due to changes in a population with regard to factors such as education, environment, health or employment.[12, 13] Motor function, is another function controlled by the brain that is essential in maintaining quality of life, and is also affected by age. Motor functions, such as gait and fine motor skills are important in many daily activities. Although a part of the deterioration in motor function can be ascribed to musculoskeletal functioning, decreased motor function has also been related to age-related brain changes.[14, 15] Increasing life expectancy insures an accumulation of problems not only in cognitive function, but also in motor function. Nonetheless, population-based studies, have been relatively less concerned with describing effects of brain aging on motor functions.[15-17]

Admittedly, an abundance of literature exists on brain aging, cognitive aging and decrease of motor function. However, the majority of brain aging studies have focused on changes in cerebral structures. For example, the role of temporal lobe or hippocampal atrophy has been studied extensively. The infratentorial-situated cerebellum plays an important role in motor function.[18] Over the last decades, the role of the cerebellum in cognitive function has also been widely studied.[19, 20] No consensus has yet been reached about the role of cerebellar atrophy in aging and its effects on different cognitive domains. Yet, despite the growing amount of studies investigating the role of the cerebellum in cognition, not many studies have focused on the contribution of both cerebellar and cerebral volume to multiple cognitive domains. Furthermore, even though cerebellum and cerebrum are connected and both are involved in cognitive and motor function, the contribution of cerebellar and cerebral volumes in declining motor functions, have not often been studied simultaneously.

The overall aim of this thesis is to assess age effects on multiple aspects of cognition and motor function and to further explore the relation between cerebral and cerebellar volumes with cognition and motor function in a population of middle-aged and elderly persons.

The studies described in this thesis are part of the Rotterdam Study, a large prospective population-based cohort study among people of 45 years and older in Ommoord, a district of Rotterdam, The Netherlands. The large number of people in Ommoord who participated in the extensive and in depth investigations provided a database to study effects of aging on multiple cognitive tests, and relate multiple MRI correlates to measures of cognitive and motor function.

Chapter 2 of this thesis gives a description of determinants of cerebellar and cerebral volume. We looked at different cardiovascular risk factors in relation to cerebellar and cerebral grey and white matter volumes. Furthermore we looked at the effects of white matter lesions on both brain regions.

Chapter 3 describes effects of age and brain volumes on cognitive function in older persons. **Chapter 3.1** focuses on the relation between older age and decline of a variety of cognitive tests, representative of multiple cognitive domains in a non-demented population of more than 3000 persons. **Chapter 3.2** explores the contribution of cerebellar and cerebral volumes to various cognitive domains. In **chapter 3.3** the relation between the cerebral lobes, cerebellum, supratentorial white matter lesions and visuospatial ability is described. Furthermore, the association between visuospatial ability and dementia is explored.

Chapter 4 presents data on motor function, measured by an electronic version of the Archimedes spiral-drawing test, and gait patterns, measured on an electronic walkway in an older population. **Chapter 4.1** presents patterns of gait in persons of 50 years and older. We explored different aspects of gait and how age affects different gait factors. In **chapter 4.2** the relation between older age and several aspects of fine motor function is presented. Also, the association between cerebellar and cerebral volume and fine motor function are discussed. In **chapter 4.3**, results of participants of the Rotterdam Study were used as reference values, against which results of chemotherapy-exposed breast cancer survivors were tested. Since late effects of chemotherapy on fine motor skills are relatively unexplored, we investigated the relation between adjuvant chemotherapy treatment for breast cancer twenty years before and fine motor skills.

Finally, **chapter 5** summarizes the main findings of this thesis and it discusses implications and suggestions for future investigations.

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Chapter 2

Determinants of cerebellar and cerebral volume in the general elderly population

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Abstract

In a population-based study of 3962 community-dwelling non-demented 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 grey and white matter were segmented using Freesurfer. 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, 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.

Introduction

The cerebellum is a complex structure, containing more than 50 percent of all neurons in the brain. It is organized in a different manner than the cerebrum.[1, 2] Recently, research has emphasized the role the cerebellum is likely to play in cognitive processing, next to its well-studied contributions to motor skills.[3, 4] It is therefore important to study determinants of cerebellar volume in an elderly population.

Most structural MR imaging studies with large sample sizes have focused on the cerebrum only or the entire brain.[5-7] Studies that specifically assessed the cerebellum showed inconsistent results. Some studies reported that cerebellar volume remains relatively stable with aging,[8-10] whereas others found strong effects of age on cerebellar atrophy.[11-16] A histological study of the cerebellum showed that smaller weight and volume were found, and fewer neurons were counted in the cerebellum of older persons than in those of younger persons.[17] Drawbacks of this previous work are the relatively small sample sizes and use of pre-selected 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.[5, 6, 18] Moreover, various studies have shown strong relations of cortical infarcts, lacunar infarcts as well as white matter lesions with cerebral atrophy.[19-22] 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.

Methods

Participants

The study is based on the Rotterdam Study,[23] a population-based study in middle-aged and elderly participants that started in 1990, investigating causes and consequences of age-related disease. The cohort was expanded in 2000 and 2006. From 2005 onwards, standardized brain MRI scanning was implemented in the core protocol of the study.[24] From a total of 4898 persons, 30 persons with a diagnosis of prevalent dementia were excluded from the study and 389 persons were considered non-eligible 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. backpain), imaging was not performed or completed in 44 individuals. In total, 4038 complete MRI examinations were obtained.

MRI acquisition & 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 three-dimensional fastradio frequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse (FASTSPGR-IR) sequence (TR = 13.8 ms, TE = 2.8 ms, TI = 400 ms, FOV= 25 cm^2, matrix = 416x256, flip angle = 20°, NEX= 1, BW= 12.50 kHz, 96 slices with slice thickness 1.6mm zero-padded to 0.8 mm). Furthermore a fluid-attenuated inversion recovery (FLAIR) sequence was acquired (TR= 8000 ms, TE= 120 ms, TI= 2,000 ms, FOV=25x25 cm^2, matrix= 320x224, 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 416x256, 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 512x512x192 voxels (voxel size: 0.5x0.5x0.8 mm3).[24]

A non-uniformity correction was performed.[25] Segmentation and labeling of brain structures was performed by FreeSurfer (Figure 1).[26] 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 grey 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 one 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 artefacts, susceptibility artefacts due to dental implants) or pathology (n = 11; e.g. large arachnoid cysts, meningioma's) 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

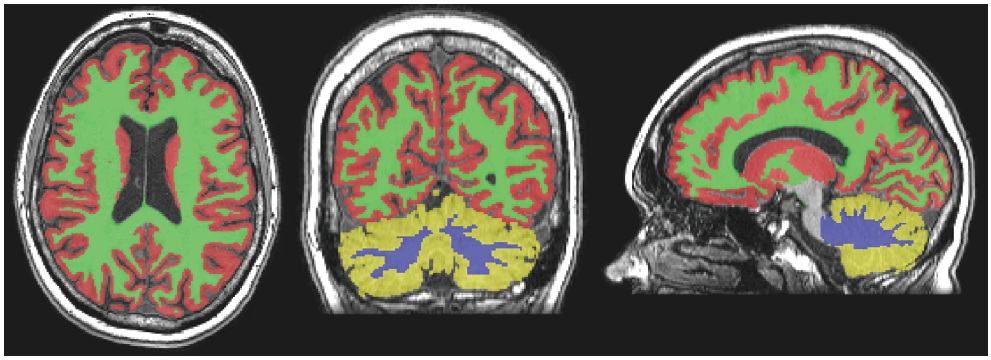


Figure 1. Example of labeling of brain structures by Freesurfer. Red = cerebral grey matter; green = cerebral white matter; yellow = cerebellar grey matter; blue = cerebellar white matter

average older (68.4 ± 12.73 versus 60.2 ± 8.58) and more often had hypertension (67.1% versus 54.2%) than those included in the analysis.

The evaluation of infarcts was based on FLAIR, proton density- and T1-weighted sequences, by five experienced raters under supervision of a neuroradiologist. The rating protocol has been described elsewhere.[27] Because the primary aim of the study was to investigate the cerebellum as a separate structure, we classified infarcts into four 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-neighbor classifier, according to a protocol previously described elsewhere.[28] Infratentorial white matter lesions (WMLs) are rare and in our current protocol these are not automatically quantified.

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 one of three categories: current smoker, former smoker, or never smoker. At the research center, blood pressure was measured twice at the right arm with a random-zero sphygmomanometer. The average of the two measurements on one occasion was used. Besides a continuous measurement of blood pressure, the presence of hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥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 ≥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). 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.

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 (Chicago, IL, USA), version 19.0 for Windows. Results are presented with 95% confidence intervals (CI).

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 percent of total cerebellar volume, whereas in the cerebrum white matter accounted for 51 percent of total cerebral volume. Mean cerebellar volumes were significantly larger for men (129.7 mL, SE = 0.25) than for women (126.2, SE = 0.22).

Table 1. Characteristics of the study population

	Total (n = 3962)	Men (n = 1806)	Women (n = 2156)
Age (year)	60.1 ± 8.50	60.3 ± 8.52	60.0 ± 8.48
Intra-cranial 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 (mmHg)	135.25 ± 19.5	137.54 ± 18.32	133.33 ± 20.25
Diastolic blood pressure (mmHg)	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 means ± standard deviation for continuous variables. Values are numbers (percentages) for dichotomous variables.

HDL = high density lipoprotein; MRI = magnetic resonance imaging. [a]ApoE genotypes were available in 3614 participants.

Table 2. Mean volumes for men and women

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

Values are adjusted for age and intracranial volume.

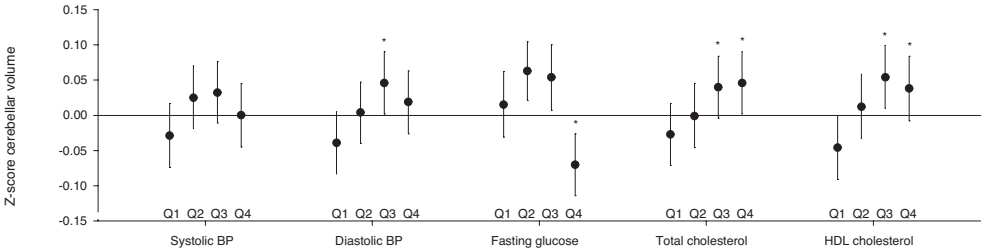
[a] Expressed as a percentage of its total volume. CI = confidence interval; SE = standard error of the mean.

Overall, smaller volumes were found with increasing age for both cerebellar and cerebral grey and with matter. The average decrease in cerebellar volume was 0.35 mL per year increase in age. Regarding cerebellar grey matter, no interaction effect was found between age and sex ($p_{interaction}$ = 0.078). In contrast, cerebral grey 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 grey matter volumes (Table 3).

Table 3. Differences per year increase in age of cerebellar volumes

	Men		Women		p-Value interaction*
	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; -0.37)	-0.032 (-0.036; -0.028)	-0.31 (-0.35; -0.26)	-0.023 (-0.026; -0.019)	0.006
Cerebellar grey matter	-0.29 (-0.34; -0.25)	-0.027 (-0.031; -0.023)	-0.22 (-0.26; -0.18)	-0.020 (-0.024; -0.017)	0.078
Cerebellar white matter	-0.13 (-0.15; -0.12)	-0.039 (-0.043; -0.035)	-0.09 (-0.10; -0.07)	-0.025 (-0.029; -0.022)	< .001
Total cerebral volume	-3.13 (-3.35; -2.90)	-0.032 (-0.034; -0.029)	-2.00 (-2.19; -1.82)	-0.020 (-0.022; -0.018)	< .001
Cerebral grey matter	-1.24 (-1.35; -1.13)	-0.029 (-0.031; -0.026)	-0.74 (-0.84; -0.65)	-0.017 (-0.019; -0.015)	< .001
Cerebral white matter	-1.89 (-2.06; -1.72)	-0.031 (-0.034; -0.029)	-1.26 (-1.40; -1.12)	-0.021 (-0.023; -0.019)	< .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 ICV. * P-value of age-sex interaction effect.



Supplementary figure 1. Quartiles of cardiovascular factors and cerebellar volume

BP = blood pressure. HDL = high density lipoprotein. The x-axis shows cardiovascular factors divided into quartiles. The y-axis shows cerebellar volume expressed in a z-score. Values are adjusted for age, sex and intracranial volume. Systolic and diastolic blood pressure are additionally adjusted for blood pressure lowering drugs. Error bars represent standard errors of the mean. * $p < 0.05$ compared to quartile 1.

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 to 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 figure 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 to 0.053)) and cerebral volume (0.037 (0.024 to 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 e4 carriership and cerebellar or cerebral volume.

Table 4. Cardiovascular factors and cerebellar and cerebral volume

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

Values are standardized differences in tissue volumes (95% confidence interval) and adjusted for age, sex and intracranial volume.

[a] Additionally adjusted for use of blood pressure lowering drugs.

SD = standard deviation. HDL = high density lipoprotein. Values in bold indicate level $p < 0.05$.

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

Values represent differences in brain volumes compared to 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 two infarct areas, infratentorial and/ or supratentorial. White matter lesion volumes are natural log transformed, and values are adjusted for age, sex and intracranial volume. GM = grey matter; WM = white matter. Values in bold indicate level $p < 0.05$.

In persons with infratentorial infarcts, only the white matter volume of the cerebellum was smaller (-0.19 (-0.38 to 0.00)) compared to persons without any infarct, while in the cerebrum both grey 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 grey 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 to persons without any infarct, but no effect was found on cerebellar grey 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 grey (-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 grey matter volume.

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 grey 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 sub-voxel resolution. Therefore, our cerebellar grey 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.[29] Strengths of this study include the large sample, population-based design and automatic quantification of brain volume.

In the cerebrum half of the volume constitutes of white matter, whereas in the cerebellum only one 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.[30-32] Some structural MRI studies have found smaller cerebellar volumes compared to our findings,[33, 34] 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.[32] 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,[7, 15, 16, 35, 36] the finding that cerebellar volume loss is stronger for white than for grey matter is in disagreement with several previous imaging studies.[7, 15, 36, 37] A histological study,[38] 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,[22, 39-41] 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.[42-44] Notably, one 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,[45] 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.[46] To our knowledge, our finding that a lower total cholesterol level is related to a smaller cerebellar volume has not been reported 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.[27, 47] The absence of an association between ApoE e4 carriership and cerebellar and cerebral volume is in line with other studies in non-demented persons in which ApoE e4 carriership was not related to global measures of cerebellar and cerebral volume.[33, 39, 48]

Participants with infratentorial infarcts had both a smaller cerebrum and smaller cerebellar white matter volume compared to 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 one of the hallmarks of cerebral small vessel disease.[49] 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.[50-53] 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 grey 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.

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Chapter 3

Brain aging and cognitive function

Chapter 3.1

Patterns of cognitive function in aging. The Rotterdam Study

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Abstract

Cognitive impairment is an important hallmark of dementia, but deterioration of cognition also occurs frequently in non-demented elderly individuals. In more than 3000 non-demented persons, aged 45 – 99 years, from the population-based Rotterdam Study we studied cross-sectional age effects on cognitive function across various domains. All participants underwent an extensive cognitive test battery that tapped into processing speed, executive function, verbal fluency, verbal recall and recognition, visuospatial ability and fine motor skills. General cognitive function was assessed by the g-factor, which was derived from principal component analysis and captured 49.2% of all variance in cognition. We found strongest associations for age with g-factor (difference in z-score -0.59 per 10 years; 95%CI -0.62 to -0.56), fine motor skill (-0.53 per 10 years; 95% CI -0.56 to -0.50), processing speed (-0.49 per 10 years; 95% CI -0.51 to -0.46), and visuospatial ability (-0.48 per 10 years; 95% CI -0.51 to -0.45). In contrast, the effect size for the association between age and immediate recall was only -0.25 per 10 years (95%CI -0.28 to -0.22), which was significantly smaller than the relation between age and fine motor skill ($p < 0.001$). In conclusion, in non-demented persons of 45 years and older, general cognition deteriorates with aging. More specifically, fine motor skill, processing speed and visuospatial ability, but not memory, are affected most by age.

Introduction

Normal aging, as well as various clinical diseases, such as for example dementia, are accompanied by a deterioration of cognitive function. Even though memory decline is a hallmark of dementia, other cognitive domains, like executive function and processing speed are also often affected.[1] Many studies focus on persons in pre-clinical stages of dementia, i.e. mild cognitive impairment, and therefore are not always generalizable to community-dwelling elderly.[2-4] Still, cognitive aging has also been investigated extensively outside the context of dementia. Age effects have been documented on several cognitive domains, such as spatial orientation, inductive reasoning, memory, verbal and number skills, and in a variety of populations.[5, 6] However, different rates of cognitive decline across cohorts have also been reported and age effects on cognition could be altered over time due to changes in a population with regard to, for example, education, environment, health factors, or employment.[7-9] Therefore, more contemporary data on aging effects on cognition are needed.

In order to gain a comprehensive understanding of cognitive function in non-demented elderly, it is essential to study a broad range of cognitive domains in unselected community-dwelling persons. Furthermore, in addition to studying separate domains, it is equally important to investigate global cognition. The rationale for this is that cognition consists of a general underlying construct that is domain-independent and reflects an individual's general cognitive function. This construct is linked to intelligence and can be quantified as a general cognitive factor, or g-factor. The g-factor is a stable concept, comprising the shared variance between cognitive tests, and can be interpreted as a common underlying factor to a variety of cognitive domains.[10-12] The g-factor has even been shown to be independent of cognitive test batteries used, and can therefore be easily generalized to other studies.[13]

The aim of this study was to investigate patterns of cognitive function in middle-aged and elderly community-dwelling persons. We specifically studied both general cognition, using the g-factor, as well as specific cognitive domains.

Methods

Setting

The study is embedded within the Rotterdam Study, a population-based cohort study in middle-aged and elderly participants that started in 1990 and aims to investigate frequency, causes and determinants of chronic diseases.[14] The initial cohort encompassed 7,983 persons and was expanded by 3,011 persons in 2000 and by 3,932 persons in 2005. In-persons examinations take place every 3 to 4 years and consists of home interview and 3 center visits. The institutional review board of Erasmus MC approved the study and participants gave written informed consent.

Study population

Table 1 shows the number of participants from each cohort used in this study. Also, age at time of invitation to the study, sex and if available level of education are given for participants and non-participants to the study (Supplementary table 1). Additionally, we show age and sex of participants by year (Supplementary Table 2). The current cross-sectional study focuses on the period from January 1st 2008 onwards, because only then the full cognitive test battery in its current format was implemented. From the persons who responded to the invitation to participate in the study (n = 7,963), persons with a stroke (n = 325) or prevalent dementia (n = 73) were excluded from the sample used in this study. Sixteen persons had both a stroke and dementia and were excluded. For dementia, this is based on a two-step procedure, which has been published before.[15] It involves screening by MMSE, additional work-up by CAMDEX, informant interview, additional neuropsychological assessment, imaging, and final diagnosis in a consensus meeting led by a neurologist. For stroke, the assessment is based on self-report, family doctor files, and files of medical specialists, which are all discussed in a consensus panel led by a neurologist.[16] Also, neuroimaging is used if required.

Table 1. Participation to the current study presented per cohort

	RSIII-1	RS-II-3	RS-I-5	Total
Time period of invitations for participation	Jan 2008 – Feb 2012	Dec 2008 – Sep 2011	Dec 2008 – Nov 2010	Jan 2008 – Feb 2012
Females, (%)	55.7%	56.3%	59.9%	57.5%
Mean age in years (standard deviation)	60.0 (8.1)	72.4 (5.2)	79.5 (4.8)	71.9 (9.7)
Total number of living persons invited for the current study	6027	2322	2952	11301
Refusal	1074	344	597	2015
Incapable to participate	10	38	92	140
Incapable to participate due to self-reported dementia	0	25	62	87
Non-response	1017	23	56	1096
Total number of responders to invitation & interview	3926	1892	2145	7963
Number of participants to any cognitive test	1132	1639	1651	4422
Number of participants to all cognitive tests	764	1189	1068	3021

Note that for cohort RSIII-1 there is a remarkably large difference between the amount of persons that participated in the interview and the amount of persons that participated in any of the cognitive tests. This large difference can be explained by the fact that the included sample (n = 1,132) was selected from the point at which the Design Organization Test was included in the study. This test was only fully introduced into the Rotterdam Study in January 2008. Sex and mean age are based on the number of participants to any cognitive test (n = 4,422).

Supplementary table 1. Demographic factors for participants and non-participants

	RSIII-1		RSII-3		RS-I-5	
	Participants	Non-participants	Participants	Non-participants	Participants	Non-participants
	n = 1132	n = 4895	n = 1639	n = 683	n = 1651	n = 1301
Age of entering the Rotterdam Study (SD)	59.5 (8.1)	57.0 (7.9)	61.9 (5.2)	66.0 (8.2)	61.9 (4.7)	65.3 (5.9)
Females, (%)	55.8%	55.6%	56.3%	61.9%	59.9%	68.5%
Primary education only, (%)	10.9%	unknown	4.9%	13.5%	24.5%	36.4%

SD = standard deviation.

Supplementary table 2. Cognitive testing per year for participants to any cognitive test

	2008	2009	2010	2011	2012
Mean age	60.0 (8.1)	79.7 (5.4)	76.9 (5.5)	72.7 (5.3)	74.5 (6.5)
Females, (%)	55.7%	65.6%	57.5%	53.2%	55.1%
Number of participants in any cognitive test	1132	917	1022	1262	89

Table 2. Description of cognitive tests

Cognitive test	Test demand	Latent skills
Mini Mental State Examination [17]	30 item test (range 0 – 30)	Global cognitive function
Stroop task [18]		
Reading subtask	Reading color names aloud (time taken)	Speed of reading
Color naming subtask	Naming colors (time taken)	Speed of color naming
Color-word interference subtask	Naming colors of color names printed in incongruous ink color (time taken)	Interference of automated processing and attention
Letter-digit substitution task [19]	Writing down numbers underneath corresponding letters (range 0 – 125)	Processing speed, executive function
Verbal fluency test [20]	Mentioning as many animals possible in 1 min	Efficiency of searching in long-term memory
15-Word learning test [21]		
Immediate recall	Immediate recall of 15 words directly after visual presentation (range 0 – 15)	Verbal learning
Delayed recall	Delayed recall of words 10 min after visual presentation (range 0 – 15)	Retrieval from verbal memory
Recognition	Correctly recognize words that were shown 10 min before (range 0 – 15)	Recognition of verbal memory
Design Organization Test [22]	Reproduce designs using a numerical code key (range 0 – 56)	Visuospatial ability
Purdue Pegboard both hands [23]	In 30 seconds, place as many pins in parallel rows of holes using left and right hand simultaneously (range 0 – 25)	Dexterity and fine motor skill

Until February 29th 2012, cognitive tests were performed in 3,706 up to 4,176 persons. In case of technical problems, refusal of participation, physical limitations, or deviation from instructions, test results were excluded. This explains the range in number of subjects that performed various cognitive tests. The number of persons in the study who completed a valid cognitive test result on any of the tests used was 4,422 (Table 1). The complete cognitive test battery was available in 3,021 persons.

Cognitive test battery

During two separate center visits a cognitive test battery was administered, which included Mini-Mental State Examination (MMSE),[17] Stroop test,[18] Letter-Digit Substitution Task (LDST),[19] verbal fluency test,[20] 15-word verbal learning test (15-WLT),[21] Design Organization Test (DOT) [22] and Purdue pegboard test.[23] A description of the cognitive tests, test demands and latent skills measured is given in Table 2. Level of education was obtained and categorized into seven levels, ranging from primary to university education. Higher scores indicate a better performance on all cognitive tests, except for the Stroop task in which a higher score indicates a worse performance. Scores for the Stroop task were thus inverted for better comparison to other tests. The DOT is a test which is based on and highly correlated to WAIS-III Block design, but is administered in two rather than ten

Table 3. Characteristics of the study population

	Men (n = 1880)	Women (n = 2542)	P-value sex difference*
Age, years	71.5 ± 9.5	72.2 ± 9.8	0.02
Primary education only, (%)	9.5%	16.8%	< 0.01
Cognitive tests			
Mini Mental State Examination, test score	27.6 ± 2.3	27.6 ± 2.2	0.02
Stroop reading subtask, seconds	17.8 ± 3.7	18.0 ± 3.7	0.97
Stroop color naming subtask, seconds	24.8 ± 5.4	24.2 ± 4.9	< 0.01
Stroop interference subtask, seconds	54.3 ± 20.2	54.4 ± 21.3	0.11
Letter digit substitution task, number of correct digits	27.6 ± 6.8	27.7 ± 7.7	< 0.05
Verbal fluency test, number of animals	21.8 ± 5.7	21.2 ± 5.9	0.46
15-Word learning test immediate recall, number of correct answers	20.8 ± 6.0	22.9 ± 6.3	< 0.01
15-Word learning test delayed recall, number of correct answers	6.5 ± 2.7	7.5 ± 2.9	< 0.01
15-Word learning test recognition, number of correct answers	13.0 ± 2.1	13.5 ± 1.9	< 0.01
Design Organization Test, number of corrects	25.6 ± 9.8	23.0 ± 10.3	< 0.05
Purdue Pegboard test, number of pins placed	9.4 ± 1.8	9.9 ± 1.8	< 0.01

Values are unadjusted means ± standard deviation. *P-values for cognitive tests comparing values of men and women are adjusted for level of education.

minutes and is less dependent on motor skills than the Block Design test.[22] Test score on the DOT has a range from 0 to 56 points for each subject.

G-factor [12]

To calculate a general cognitive factor (g-factor) we performed a principal component analysis incorporating Color-word interference subtask of the Stroop test, LDST, verbal fluency test, delayed recall score of the 15-WLT, DOT and Purdue Pegboard Test. For tests with multiple subtasks we chose only one subtask in order to prevent highly correlated tasks distorting the factor loadings. Principal component analysis was performed on complete case data of 3,021 persons. The g-factor was identified as the first unrotated component of the principal component analysis and explained 49.2% of all variance in the cognitive tests. This is a typical amount of variance accounted for by the g-factor.[12]

Statistical analysis

To aid comparison across cognitive tests we first calculated Z-scores for cognitive test scores. The MMSE score was not standardized due to its skewed nature. We used analysis of covariance to compare scores between men and women, adjusting for level of education. We used linear regression models to investigate the continuous association between age and cognitive test score, corrected for level of education. In additional analyses we used subcohort as an extra covariate to the linear regression model to test for cohort effects. We used Z-tests to formally test differences of age effects between cognitive tests. We tested interaction effects between age and sex and explored non-linear effects of age on cognition. All analyses were performed using the statistical software package SPSS version 20.0 for Windows. Results are presented with 95% confidence intervals (CI).

Supplementary table 3. Correlations across all cognitive tests

	Mini Mental State Examination	Stroop reading	Stroop naming	Stroop interference	Letter-digit substitution task	Verbal fluency test	15-WLT immediate recall	15-WLT delayed recall	15-WLT recognition	Design Organization Test	Purdue Pegboard Test
Mini Mental State Examination	1										
Stroop reading	0.28	1									
Stroop naming	0.27	0.67	1								
Stroop interference	0.32	0.44	0.52	1							
Letter-digit substitution task	0.38	0.47	0.46	0.52	1						
Verbal fluency test	0.31	0.35	0.37	0.39	0.44	1					
15-WLT immediate recall	0.37	0.29	0.31	0.33	0.38	0.34	1				
15-WLT delayed recall	0.32	0.23	0.26	0.28	0.34	0.32	0.79	1			
15-WLT recognition	0.25	0.14	0.14	0.18	0.22	0.18	0.50	0.52	1		
Design Organization Test	0.38	0.36	0.35	0.50	0.62	0.41	0.32	0.31	0.20	1	
Purdue Pegboard Tests	0.15	0.27	0.30	0.34	0.43	0.27	0.22	0.20	0.10	0.37	1

Values represent Pearson r coefficients, and were calculated based on complete cases (n = 3,021).

Results

Mean age was 71.9 years (SD = 9.7), with 57.5 % women (Table 3). Men scored better than women on the DOT, whereas women scored better on Stroop color naming, immediate recall, delayed recall and recognition parts of the 15-WLT, and Purdue Pegboard test (Table 3). Pearson correlation coefficients between all cognitive test scores are shown in Supplementary table 3.

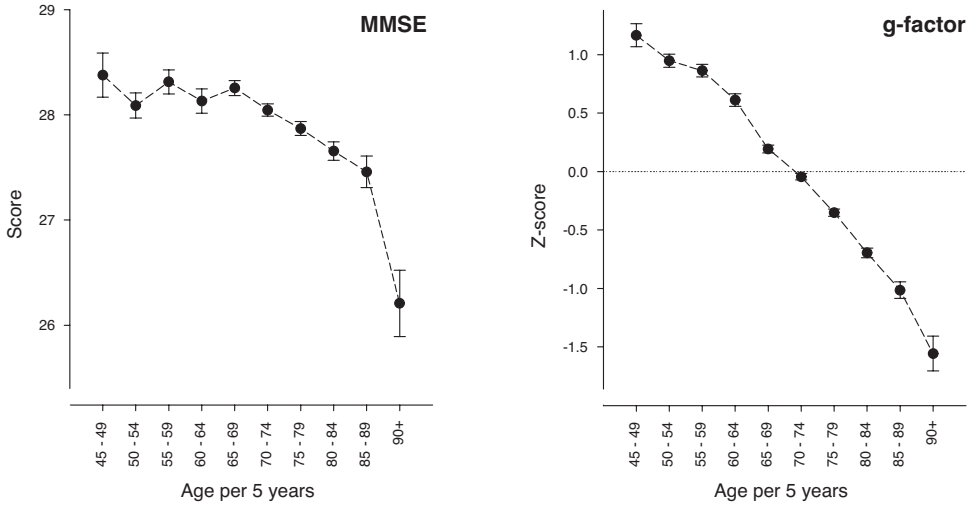

Figure 1. Age effects on global cognitive scores. The x-axis represents age per 5 years and the y-axis represents the MMSE-score or z-score of the g-factor. Error bars represent 95% confidence intervals. Estimates are adjusted for level of education. MMSE = Mini Mental State Examination; g-factor = general cognitive factor

Figure 1 illustrates MMSE score and g-factor in 5-year strata of age. MMSE score stayed stable until age 70 and then showed a rapid decline. In contrast, the g-factor showed decline in scores already from age 45 onwards. The mean decline in g-factor per 10-year increase in age was -0.59 (95%CI -0.62 to -0.56). For both MMSE score and g-factor we also found a quadratic effect of age (Table 4).

Figure 2 shows mean test scores in 5-year strata of age. We found the strongest decline for Purdue Pegboard, LDST, DOT and Stroop interference task (Table 5). In contrast, smaller effects of age were found for 15-WLT immediate recall (-0.25 per 10 years; 95%CI -0.28 to -0.22), delayed recall (-0.23 per 10 years; 95%CI -0.26 to -0.20) and recognition (-0.09 per 10 years; 95%CI -0.12 to -0.05). These differences in age effects between the memory subtasks versus Purdue Pegboard, LDST, DOT and Stroop were confirmed by formal statistical testing (Z-tests). For example, the age effects on the Purdue Pegboard test or DOT were both significantly larger than the effect on im-

Table 4. Association of age with global cognitive function

N = 3,021	Total	Men	Women	$P_{interaction}$ *	$P_{quadratic}$ **
MMSE	-0.24 (-0.30; -0.18)	-0.30 (-0.39; -0.22)	-0.19 (-0.28; -0.10)	0.11	< 0.01
g-factor	-0.59 (-0.62; -0.56)	-0.60 (-0.64; -0.56)	-0.58 (-0.62; -0.54)	0.73	< 0.01

Values represent differences in MMSE score and g-factor per 10 year increase, adjusted for level of education. MMSE = Mini Mental State Examination; g-factor = general cognitive factor. *P-value for interaction between age and sex. **P-value for quadratic effect of age on cognition for total sample.

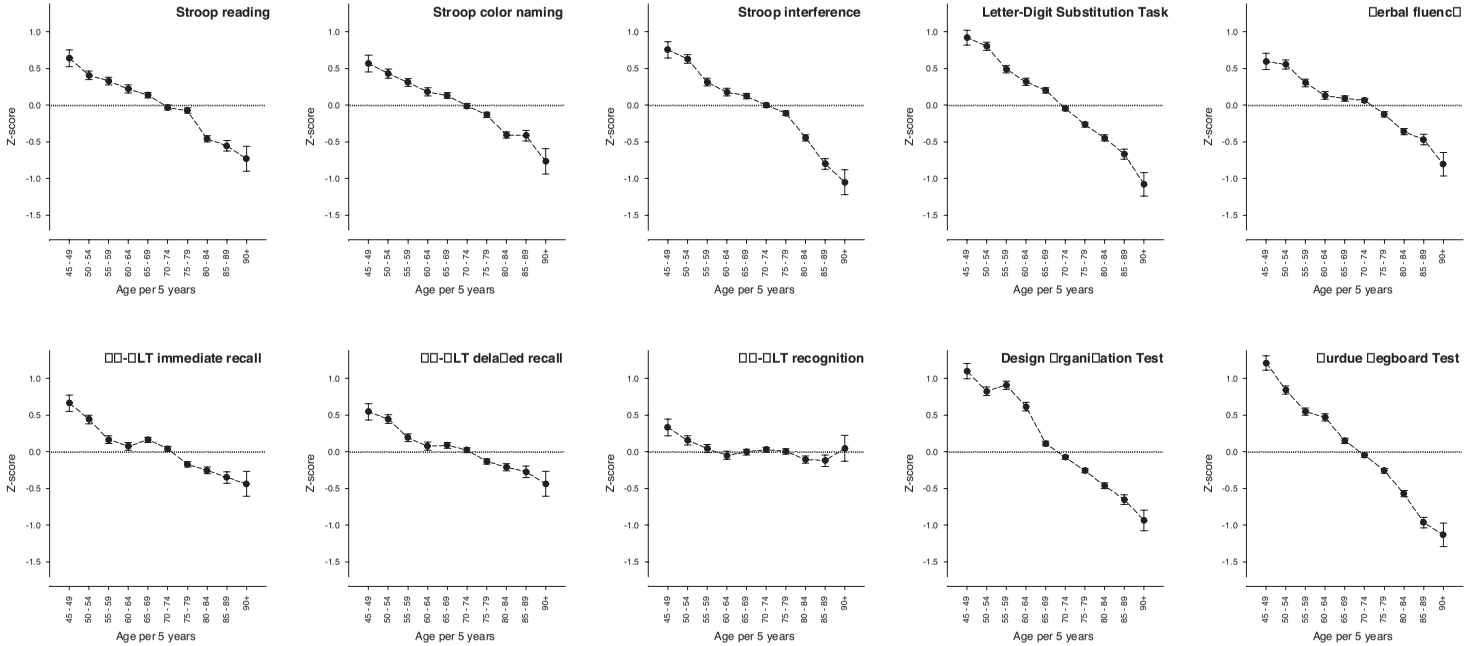

Figure 2. Cognitive function in 5-year bins. The x-axis represents age per 5 years and the y-axis represents the z-score on the test. Error bars represent 95% confidence intervals. All estimates are adjusted for level of education. 15-WLT = 15-Word learning test

mediate recall ($p < 0.001$). Still, the strongest effects of age were on the g-factor, rather than any individual cognitive test.

Table 5. Association of age with cognitive test scores

	Total	Men	Women	$P_{interaction}$ *	$P_{quadratic}$ **
Stroop reading, n = 4042	-0.32 (-0.35; -0.29)	-0.31 (-0.35; -0.26)	-0.31 (-0.35; -0.27)	0.43	< 0.01
Stroop naming, n = 4041	-0.32 (-0.35; -0.29)	-0.34 (0.39; -0.29)	-0.30 (-0.33; -0.26)	0.10	< 0.01
Stroop interference, n = 4030	-0.41 (-0.44; -0.38)	-0.43 (-0.47; -0.38)	-0.40 (-0.44; -0.36)	0.12	< 0.01
Letter-digit substitution task, n = 4074	-0.49 (-0.51; -0.46)	-0.42 (-0.46; -0.38)	-0.53 (-0.56; -0.49)	0.01	< 0.01
Verbal fluency test , n = 4176	-0.32 (-0.35; -0.29)	-0.29 (-0.33; -0.24)	-0.34 (-0.38; -0.30)	0.19	< 0.01
15-Word learning test immediate recall, n = 3826	-0.25 (-0.28; -0.22)	-0.25 (-0.30; -0.21)	-0.25 (-0.29; -0.21)	0.77	0.25
15-Word learning test delayed recall, n = 3825	-0.23 (-0.26; -0.20)	-0.23 (-0.28; -0.18)	-0.23 (-0.28; -0.19)	0.75	0.71
15-Word learning test recognition, n = 3902	-0.09 (-0.12; -0.05)	-0.09 (-0.15; -0.04)	-0.08 (-0.13; -0.04)	0.75	0.39
Design Organization Test, n = 3706	-0.48 (-0.51; -0.45)	-0.50 (-0.55; -0.46)	-0.46 (-0.50; -0.42)	0.21	0.12
Purdue Pegboard Test, n = 3801	-0.53 (-0.56; -0.50)	-0.48 (-0.53; -0.44)	-0.56 (-0.60; -0.53)	0.02	< 0.01

Values represent differences in cognitive test scores per 10-year increase, adjusted for level of education. All cognitive scores are expressed as z-scores. *P-value for interaction between age and sex. **P-value for quadratic effect of age on cognition for total sample.

Finally, we found that for the Purdue Pegboard test and LDST, age effects were stronger in women than men. Also, quadratic effects of age on cognition were found for the Stroop tasks, the LDST, verbal fluency, and the Purdue Pegboard test. Adding subcohort as an extra covariate to the model did not reduce the effects of age on cognitive scores.

Discussion

In a large community-dwelling cohort of persons 45 years and older, we found that age strongly affects general cognitive function, measured by the g-factor. The effect of age on general cognitive function was already apparent from 45 years onwards. Investigating separate cognitive domains, we found strongest associations of age with fine motor skill, processing speed, and visuospatial ability.

Strengths of this study include the large community-dwelling study sample and availability of multiple cognitive tests. An important limitation to the interpretation of our results is the cross-

sectional design. Also, relations between age and cognition could partly be influenced by cohort effects. However, differences in age effects across cognitive tests are comparable since all analyses were performed on the same group of persons. Another problem is that not all cognitive tests were completed by all participants to our study and that participants are younger and usually in better health compared to non-participants.[24] Therefore, in our g-factor analyses, we selected a sample with fully available cognitive data. We should keep in mind that this may have introduced some selection bias and has may reduce the generalizability of the results. We also note that in order to summarize the different cognitive tests into one g-factor, we selected six cognitive test variables under the assumption that these are representatives of various cognitive domains (executive function, processing speed, verbal fluency, memory, visuospatial ability, and fine motor skill), which are frequently used in cognitive aging research. Other studies may select different tests to construct a g-factor and will possibly get a slightly different outcome. However, it was previously found that g-factors constructed from variable test batteries result in factors that are highly correlated.[13] Thus, the g-factor is likely to be a stable concept. It is comprised of shared variance between tests, and can be interpreted as a factor which is common to a variety of cognitive domains.

In this study sample, we showed that the g-factor is affected already from age 45 onwards. Also, compared to the other cognitive tests in our battery, the g-factor was most strongly related to age. The strength of relation between age and cognition was consistent with those found by others.[25, 26] MMSE score only showed a decline from age 70 onwards. The MMSE is often used to test global cognitive function in older adults, yet it has frequently been criticised for its ceiling effect.[27, 28] In agreement with a large study of healthy elderly, we did not find strong effects of age on MMSE score.[29]

Among our other cognitive tests, we found that fine motor skill, processing speed and visuospatial ability were most affected by age. In agreement with the observed relation between age and visuospatial ability, WAIS-III Block Design performance starts to decline from the mid-forties onward [12]. Other studies have also suggested a more prominent role for decline in visuospatial ability in aging research.[30, 31] One study reported a composite score of visuospatial ability to be a significant predictor of developing cognitive decline.[2] However, another large cohort study reported relatively small effects of age on visuospatial ability.[4] Already in the youngest age groups we found an effect of age on performance on the Purdue Pegboard Test. Population studies in the healthy elderly that looked into age effects on fine motor skills are scarce. The relatively large age effects on the LDST are in line with previous studies showing strong age effects on processing speed.[9, 32] Interestingly, these findings are supported by indirect evidence from neuroimaging studies which found that white matter declined faster than grey matter and white matter deterioration was associated with decline in motor skill and tasks of processing speed.[33-35] However, others concluded there is a relative stability of white matter volume in aging.[36, 37] The effect size we found relating age to memory was small compared to age effects on other cognitive scores. Again, this is in line with evidence showing that memory function is more dependent on grey matter which decreases gradually with aging.[38, 39] Furthermore, we found that women scored better on memory tests than men, which is in accordance with previous findings that women have better verbal memory than men.[40, 41] No dif-

ference in age effects on memory was found between men and women. It is expected that memory would be more strongly affected in dementia rather than normal aging. The exclusion of prevalent dementia cases from our study possibly contributed to the small negative effects of age on memory. However, there is a continuum between normal cognitive aging and dementia, and persons in the preclinical stages of dementia were not excluded from the study population. Normal cognitive aging research has often found that the more frontal brain functions such as attention and executive function are affected earlier than memory.[42-44] The relatively smaller effect on the Verbal fluency test may reflect the fact that we used a category fluency test rather than a phonemic fluency test. Category fluency places a larger demand on memory performance rather than frontal lobe function.[45, 46] Furthermore, we found a stronger effect on the color-word interference subtask of the Stroop, compared to the reading and naming subtasks. The Stroop color-word interference task requires more cognitive control than the first two subtasks and is more dependent on executive function, specifically on attention and inhibition.[19]

In conclusion, in persons of 45 years and older, age is most strongly related general cognitive function. Our findings also suggest that not memory, but fine motor skill, processing speed, and visuospatial ability are affected most by advancing age.

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Chapter 3.2

The role of cerebellar volume in cognition in the general elderly population

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Abstract

Background It is unknown whether the cerebellum affects cognitive function in an aging community-dwelling population. In a population-based study of 3745 non-demented persons of 45 years and older we investigated the relationship between cerebellar volume and cognitive function.

Methods Brain volumes were obtained using automatic tissue segmentation of magnetic resonance imaging (MRI) scans. Cognitive functioning was assessed using MMSE and cognitive compound scores of global cognition, executive function, information processing speed, memory and motor speed. Linear regression modeling was used to study the associations between cerebellar volumes and cognitive measures, independent of cerebral volumes.

Results We found a relationship between larger cerebellar volume and better global cognition, executive function, information processing speed and motor speed. After adjustment for cerebral volume, only cerebellar grey matter volume remained borderline significantly associated with global cognition and information processing speed. After Bonferroni correction, the few associations found between cerebellar volume and cognition disappeared.

Conclusions We only found a minor relation between larger cerebellar volume and better cognition in healthy older adults, which further attenuated after correcting for cerebral volume. Our findings support the notion that cerebellar volume has an influence on cognition in aging, but that is not the major leading structure.

Introduction

Cognitive impairment and dementia pose an ever-increasing burden on aging societies.[1, 2] Much research focuses on detection of the earliest brain changes that may be harbingers of incipient cognitive impairment and dementia. To this aim, magnetic resonance imaging (MRI) is a cornerstone in research on the preclinical phase of dementia. There is abundant evidence showing that hippocampus atrophy, cerebral atrophy and small vessel disease visualized on MRI are strong markers of cognitive decline and incident dementia.[3, 4] Most previous neuroimaging studies have almost exclusively focused on cerebral brain changes.[5-7] There is, however, emerging evidence that the cerebellum may also play a role in many different cognitive domains, e.g. executive function, visuospatial skills, working memory, linguistic processes and sequencing.[8-11] Physiological work in trained primates showed that cerebellar output is involved in both motor and cognitive functions.[12, 13] Furthermore, in patients with lesions in the cerebellum, intellectual function was reduced.[14] Voxel based morphometry studies found regional differences in cerebellar volume when comparing older to younger persons, and a relation between specific cerebellar regions and cognition was previously described.[15, 16] However, imaging studies investigating the role of the cerebellum in cognition often include a relatively small sample size or are conducted in a pre-selected or patient-based sample.[10, 17-19] It remains unknown whether the cerebellum also affects cognitive function in a non-demented community-dwelling population. To our knowledge, no population-based imaging studies have been performed describing the contribution of cerebellar properties, such as volume, to cognitive function in the elderly. Moreover, as the cerebellum is connected to the cerebrum and both have been described to be dependent on the other,[20-22] the question remains whether the cerebellum exerts an effect on cognition independent from the cerebrum.

The aim of this study therefore was to investigate the relationship between cerebellar volume and cognition in a large sample of community-dwelling persons of 45 years and older. Furthermore, we sought to investigate the relation of cerebellar volume and cognition independent of the association between cerebral volume and cognitive function.

Methods

Participants

The study is based on the Rotterdam Study,[23] a population-based study in middle-aged and elderly participants that started in 1990, investigating causes and consequences of age-related disease. The cohort was expanded in 2000 and 2006. From 2005 onwards, standardized brain MRI scanning was implemented in the core protocol of the study.[24] The present study included all persons that participated between August 2005 and September 2009. From a total of 4898 persons, 30 persons with a diagnosis of prevalent dementia were excluded from the study and 389 persons were considered non-eligible 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.

backpain), imaging was not performed or completed in 44 individuals. In total, 4038 complete MRI examinations were acquired. The institutional review board of Erasmus MC approved the study and participants gave written informed consent.

MRI acquisition & image analysis

MRI 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 three-dimensional fast radio frequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse (FASTSPGR-IR) sequence (TR = 13.8 ms, TE = 2.8 ms, TI = 400 ms, FOV= 25 cm^2, matrix = 416x256, flip angle = 20°, NEX= 1, BW= 12.50 kHz, 96 slices with slice thickness 1.6mm zero-padded to 0.8 mm). All slices were contiguous. According to our standard acquisition protocol images were resampled to 512x512x192 voxels (voxel size: 0.5x0.5x0.8 mm^3).[24]

Non-uniformity correction was performed,[25] prior to segmentation and labeling of brain structures by FreeSurfer.[26] FreeSurfer is a publicly available, validated software package. For segmentation, FreeSurfer automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information obtained from a manually labeled training set, and resulted in intracranial volume (ICV) and grey and white matter volumes for cerebellum and cerebrum. A trained observer inspected a sample of segmented scans from random individuals (n = 192) and all outliers (n = 170). Outliers were defined as segmentations 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 one scan a large meningioma was present, both interfering with tissue segmentation results. Seventy-three scans of the outlier sample were excluded, owing to insufficient segmentation quality. Problems in the segmentation were due to either technical problems (n = 62; e.g. motion artefacts, susceptibility artefacts due to dental implants) or pathology (n = 11; e.g. large arachnoid cysts, meningioma's) that could influence the volume estimates. Finally, 3962 scans were included in our analyses. The total of 76 persons that were excluded, were on average older (68.4 ± 12.73 versus 60.2 ± 8.58) than those included in the analysis.[22]

Cognitive function

Participants underwent a battery of neuropsychological tests, including the Mini-Mental State Examination (MMSE) [27] the Stroop test,[28] the Letter-Digit Substitution Task,[29] a verbal fluency task [30] and a 15-word verbal learning test.[31] The Purdue Pegboard Test was used as a measure of fine manual dexterity. It consists of a pegboard with two parallel rows of 25 holes and a number of pins.[32] Participants were asked to place as many pins as possible into the holes on the board, within 30 seconds. Higher scores indicate a better performance on all cognitive tests, except for the Stroop

task in which a higher score indicates a worse performance. For better comparison to other tests, scores of the Stroop task were inverted by multiplying scores with -1. We calculated *z*-scores for each test separately, except for the MMSE because of its skewed nature. Compound scores were constructed in order to obtain more robust outcome measures for cognition. The compound score for global cognitive function was the average of the *z*-scores for the Stroop test, the Letter-Digit Substitution Task, the verbal fluency test, and the immediate and delayed recall of the 15-word verbal learning test. The score for 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 information processing speed was computed as the average of the *z*-scores for the first and second subtask of the Stroop test and the Letter-Digit Substitution 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. Motor speed was defined by the *z*-score of the Purdue Pegboard test (both hands).[5, 33] In case of technical problems, refusal of participation, physical limitations, or deviation from instructions, the test results were excluded, which left us with 3745 persons in our analyses. Level of education was obtained and categorized into seven levels, ranging from primary to university education. MMSE is significantly related to all cognitive domains, also after adjustment for age, sex, and level of education ($p < 0.001$). The strongest correlation is found with global cognitive function ($r = 0.37$).

Statistical analysis

To enable comparison across analyses we first calculated Z-scores for all volumetric measures. Next, we used linear regression models to investigate associations of cerebellar and cerebral volumes with MMSE score and cognitive compound scores. All analyses were adjusted for intracranial volume to correct for head size differences, and for age, sex and level of education where appropriate. Pearson's correlation coefficient between total cerebellar and total cerebral volume was 0.68 ($p < 0.001$). Since we were interested in the independent relation of cerebellar volume and cognition, we used cerebral volume as a covariate in our analyses thereby estimating the effect of cerebellar volume on cognition, independent of cerebral volume. Conversely, we used cerebellar volume as a covariate in our analyses to estimate the independent effect of cerebral volume on cognition. In Supplementary table 1 we show partial correlations of brain volumes with cognition, while controlling for age, sex, level of education and intracranial volume. Similar to our regression analyses, we adjusted for cerebral volume to estimate the independent association of cerebellar volume on cognition. To study whether inclusion of outliers changed our results we reanalyzed the effect of cerebellar and cerebral volume on cognition, with inclusion of persons with brain volumes that were an outlier outside a range of +/- 2.58 SD from the mean. Bonferroni correction was done for 72 tests. All analyses were performed using the statistical software package SPSS (Chicago, IL, USA), version 20.0 for Windows. Results are presented with 95% confidence intervals (CI).

Supplementary table 1. Partial correlations of cerebellar and cerebral volumes with cognition

		MMSE	Global cognition	Executive function	Information processing speed	Memory	Motor speed
				Cerebellum			
Model 1	Total cerebellum	0.014	**0.047**	**0.040**	**0.057**	0.033	0.019
	Cerebellar grey matter	0.023	**0.049**	**0.045**	**0.058**	0.031	0.013
	Cerebellar white matter	-0.016	0.025	0.011	0.036	0.028	0.030
Model 2	Total cerebellum	0.007	**0.034**	0.018	**0.038**	**0.035**	-0.002
	Cerebellar grey matter	0.018	**0.039**	0.029	**0.043**	0.032	-0.002
	Cerebellar white matter	-0.027	0.006	-0.022	0.007	0.032	0.000
				Cerebrum			
Model 1	Total cerebrum	**0.047**	**0.090** *	**0.151** *	**0.132** *	-0.013	**0.138** *
	Cerebral grey matter	**0.089** *	**0.074** *	**0.116** *	**0.077** *	0.005	**0.110** *
	Cerebral white matter	0.001	**0.071** *	**0.124** *	**0.125** *	-0.021	**0.110** *
Model 2	Total cerebrum	**0.045**	**0.084** *	**0.147** *	**0.125** *	-0.018	**0.137** *
	Cerebral grey matter	**0.089** *	**0.071** *	**0.114** *	**0.073** *	0.003	**0.109** *
	Cerebral white matter	-0.001	**0.064** *	**0.119** *	**0.117** *	-0.026	**0.109** *

Values in bold indicate significance at level $p < 0.05$. * Significance after Bonferroni correction.
Model 1: adjusted for age, sex, education, intracranial volume
Model 2: adjusted for age, sex, education, intracranial volume, cerebral volume (for analyses with cerebellar volume in upper panel) or cerebellar volume (for analyses with cerebral volume in lower panel).

Results

Characteristics of the study population (N = 3745) are shown in Table 1. The population contained 54.5% women. The average age was 60.0 years, within an age range of 45.7 to 96.7 years.

Table 1. Characteristics of the study population

	N = 3,745
Age (years)	60.0 ± 8.4
Females, N (%)	2042 (54.5)
Primary education only, N (%)	339 (9.1)
Cognitive test results	
MMSE test score	28.1 ± 1.9
15-WLT immediate recall (average of 3 trials)	7.9 ± 2.1
15-WLT delayed recall	7.9 ± 2.9
Stroop reading subtask, s	16.6 ± 3.5
Stroop color naming subtask, s	22.6 ± 4.5
Stroop interference subtask, s	44.7 ± 14.2
Letter Digit Substitution Task, number of correct digits	31.6 ± 6.6
Word Fluency Test, number of animals	23.4 ± 5.9
Purdue Pegboard test, number of pins placed	10.8 ± 1.8
Intra-cranial volume, mL	1491.4 ± 156.5
Cerebellar grey matter volume, mL	102.9 ± 10.7
Cerebellar white matter volume, mL	25.1 ± 3.3
Cerebral grey matter volume, mL	437.6 ± 42.5
Cerebral white matter volume, mL	456.2 ± 58.7

Values are means ± standard deviation or numbers (%). MMSE = Mini-Mental State Examination; 15-WLT = 15 Word learning test; s = seconds; mL = millilitres.

Table 2 shows the association of brain volumes with cognition. Larger total cerebellar volume was related to higher scores on global cognition (0.037 (0.009; 0.065), but not to MMSE score. This relationship disappeared after adjustment for total cerebral volume. Larger cerebellar grey matter volume showed a relationship with better global cognition, both before (0.037 (0.010; 0.064)) and after additional adjustment (0.029 (0.002; 0.056)) for total cerebral volume. Cerebellar white matter volume was neither related to MMSE nor to global cognition. Regarding cerebral volume, both larger total volume and cerebral grey matter volume were related to higher MMSE score (0.218 (0.069; 0.366)) and better global cognition (0.139 (0.088; 0.190)), also after adjustment for total cerebellar volume. Larger cerebral white matter volume was only related to better global cognition and not to MMSE score. This effect remained after additional adjustment for total cerebellar volume.

Table 2. Brain volumes related to global cognitive scores

		MMSE	Global cognition
		Cerebellum	
Model 1	Total cerebellum	0.032 (-0.051;0.115)	**0.037 (0.009; 0.065)**
	Cerebellar grey matter	0.057 (-0.024;0.138)	**0.037 (0.010; 0.064)**
	Cerebellar white matter	-0.056 (-0.133; 0.022)	0.018 (-0.008; 0.044)
Model 2	Total cerebellum	0.013 (-0.071; 0.097)	0.026 (-0.002; 0.054)
	Cerebellar grey matter	0.044 (-0.038; 0.125)	**0.029 (0.002; 0.056)**
	Cerebellar white matter	**-0.086 (-0.165; -0.006)**	0.002 (-0.024; 0.029)
		Cerebrum	
Model 1	Total cerebrum	**0.218 (0.069; 0.366)**	**0.139 (0.088; 0.190)** *
	Cerebral grey matter	**0.367 (0.240; 0.495)** *	**0.096 (0.052; 0.140)** *
	Cerebral white matter	0.002 (-0.119; 0.123)	**0.090 (0.048; 0.132)***
Model 2	Total cerebrum	**0.214 (0.064; 0.364)**	**0.132 (0.080; 0.183)** *
	Cerebral grey matter	**0.366 (0.238; 0.494)** *	**0.092 (0.048; 0.136)** *
	Cerebral white matter	-0.005 (-0.128; 0.117)	**0.084 (0.041; 0.126)** *

Values represent standardized differences in global cognitive score, per standard deviation increase in brain volume (95% confidence interval).
MMSE score was not standardized because of its skewed distribution. Values in bold indicate significance at level $p < 0.05$. * Significance after Bonferroni correction.
Model 1: adjusted for age, sex, education, intracranial volume.
Model 2: adjusted for age, sex, education, intracranial volume, cerebral volume (for analyses with cerebellar volume in upper panel) or cerebellar volume (for analyses with cerebral volume in lower panel).

Table 3 shows the relation between cerebellar volumes and the various cognitive domains. We found that larger total cerebellar volume was related to better performance on executive function and information processing speed. Cerebellar grey matter volume was also positively related to these domains. Larger cerebellar white matter volume was related to a higher score on motor speed. However, after additional adjustment for total cerebral volume, only the relationship between cerebellar grey matter volume and information processing speed remained significant (0.016 (0.001; 0.031) at $p < 0.05$). In comparison, larger cerebral volume was related to better performance in all cognitive domains, except for memory. Moreover, these associations remained significant after additional adjustment for total cerebellar volume. Partial correlations (Supplementary table 1) showed similar associations between brain volumes and cognition. Note that including persons with brain volumes that were an outlier outside a range of +/- 2.58 SD from the mean did not result in major changes in estimates or conclusions. For example, the most notable change when including outliers was found between total cerebellar volume and MMSE score. The association changed from 0.032 (-0.051; 0.115) excluding outliers to 0.024 (-0.058; 0.105) with inclusion of outliers. Also note that after Bonferroni correction, all associations between cerebellar volume and cognition disappeared.

Table 3. Brain volumes related to cognitive compound scores

		Executive function	Information processing speed	Memory	Motor speed
			Cerebellum		
Model 1	Total cerebellum	**0.025 (0.000; 0.051)**	**0.022 (0.007; 0.038)**	0.034 (-0.004; 0.073)	0.032 (-0.008; 0.071)
	Cerebellar grey matter	**0.028 (0.004; 0.053)**	**0.022 (0.007; 0.037)**	0.032 (-0.006; 0.070)	0.025 (-0.014; 0.063)
	Cerebellar white matter	0.005 (-0.019; 0.028)	0.011 (-0.003; 0.025)	0.025 (-0.011; 0.061)	**0.037 (0.000; 0.074)**
Model 2	Total cerebellum	0.009 (-0.016; 0.035)	0.013 (-0.002; 0.029)	0.037 (-0.002; 0.077)	0.004 (-0.036; 0.043)
	Cerebellar grey matter	0.017 (-0.008; 0.041)	**0.016 (0.001; 0.031)**	0.034 (-0.004; 0.072)	0.004 (-0.034; 0.042)
	Cerebellar white matter	-0.018 (-0.042; 0.006)	-0.002 (-0.016; 0.013)	0.029 (-0.008; 0.066)	0.001 (-0.037; 0.038)
			Cerebrum		
Model 1	Total cerebrum	**0.250 (0.196; 0.304)** *	**0.236 (0.178; 0.294)** *	-0.027 (-0.099; 0.045)	**0.316 (0.246; 0.387)** *
	Cerebral grey matter	**0.162 (0.116; 0.209)** *	**0.121 (0.070; 0.171)** *	0.018 (-0.044; 0.081)	**0.223 (0.162; 0.284)** *
	Cerebral white matter	**0.169 (0.125; 0.212)** *	**0.180 (0.133; 0.227)** *	-0.042 (-0.100; 0.017)	**0.201 (0.143; 0.259)** *
Model 2	Total cerebrum	**0.247 (0.193; 0.301)** *	**0.227 (0.169; 0.286)** *	-0.038 (-0.111; 0.035)	**0.315 (0.244; 0.387)** *
	Cerebral grey matter	**0.160 (0.113; 0.206)** *	**0.115 (0.065; 0.166)** *	0.014 (-0.048; 0.077)	**0.221 (0.160; 0.282)** *
	Cerebral white matter	**0.165 (0.121; 0.210)** *	**0.173 (0.125; 0.220)** *	-0.051 (-0.110; 0.009)	**0.199 (0.140; 0.257)** *

Values represent standardized differences in cognitive score, per standard deviation increase in volume (95% confidence interval).
Values in bold indicate significance at level $p < 0.05$. * Significance after Bonferroni correction.
Model 1: adjusted for age, sex, education, intracranial volume
Model 2: adjusted for age, sex, education, intracranial volume, cerebral volume (for analyses with cerebellar volume in upper panel) or cerebellar volume (for analyses with cerebral volume in lower panel).

Discussion

In a large (n = 3745) community-dwelling sample of persons aged 45 and older, we found an association between larger cerebellar volume and better performance in several cognitive domains. However, these associations were weak, and further attenuated when cerebral volume was taken into account.

A major strength of this study is the large sample size of elderly persons in a population-based study setting. Moreover, we were able to investigate the influence of cerebellar and cerebral tissue volumes on cognition in one single study. Therefore we were able to compare the independent influence each structure has on cognition. A limitation of this study is that our cognitive testing battery does not include all possible areas of cognition. Therefore, it could be that we missed cognitive domains that might specifically relate to the cerebellum. Another important issue is that we only divided the cerebellum into grey and white matter volumes and our current segmentation tool did not allow us to investigate separate regions of the cerebellum in relation to cognition. We assessed the quality of segmentations of the MRI scans by visually inspecting all outliers and a random sample. Thus, we are unable to fully rule out possible segmentation errors in the uninspected scans.

We found that larger cerebellar volume was related to better global cognition. Regarding cerebellar grey matter, this effect was independent of the relationship between cerebral volume and global cognition. However, there was no relation between cerebellar white matter and global cognition, with or without adjustment for cerebral volume. Thus, cerebellar grey matter volume seems to be more important for global cognitive functioning than cerebellar white matter volume. Still, more studies are needed to confirm this finding. It is noteworthy that we did not find an association with MMSE, which is also considered a test for global cognition.[27, 29] Possible explanations are the ceiling effect in MMSE-score precluding associations in this non-demented population, or the non-specificity of the MMSE for subtle cognitive deficits as the MMSE is only a screening tool.

Considering specific cognitive domains, we found that larger cerebellar volume was related to better executive function, information processing speed and motor speed, although again this finding was not independent of cerebral volume. We consistently found a lack of association between cerebellar volume and memory. This fits the description of the cognitive affective syndrome,[14] where patients with lesions confined to the cerebellum were found to have disturbances in executive, spatial, linguistic and affective functions, but not so much in (verbal) memory tests. Surprisingly, we did not find any relation between cerebral volume and memory either, which might indicate that the memory compound score used possibly lacks the sensitivity needed to detect a relation with general measures of brain volumes.

Furthermore, we found no convincing association between cerebellar volume and motor speed measured by the Purdue Pegboard test. Since the cerebellum is well known to be involved in motor performance, this test is apparently not reflective of cerebellar motor function, or at least not sensitive to differences in cerebellar volumes in a community-dwelling population.

The general trend in contemporary literature is that the cerebellum is not only important in motor function, but also in cognition.[9, 10, 34] There are, however, few studies investigating the relation between cerebellar volume and cognition in a healthy aging population. One study found a correlation between cerebellar volume and cognition, but similar to our analyses the effect disappeared after adjusting for prefrontal volume.[35] Also, a study in healthy elderly men found a correlation between size of the neocerebellar vermis and cognition, but they used no correction for cerebral volume and vermian size was assessed as a two-dimensional area instead of a three-dimensional volume.[36] Only one other study so far did find a relation between cerebellar grey matter volume and general cognitive ability, even after adjustment for frontal lobe volume.[15] Inconsistencies between these studies might be explained by the fact that cognition was measured differently across studies. It also has to be noted that the aforementioned volumetric studies accounted for (pre)frontal lobe volumes and not total cerebral volume,[15, 35] as was done in our study. Another explanation for the remaining ambiguities of the role of cerebellar tissue volumes in cognition might be found in one of the theories describing only subtle effects of the cerebellar output on cognitive processing.[14, 34, 37, 38] In line with this theory, we showed only marginal associations between cerebellar tissue volumes and cognition.

We also showed that the association between cerebellum and cognition attenuated after adjusting for cerebral volume. There are several explanations for this finding. First, cognition is a cortical brain function, which receives input from various other brain regions, including basal ganglia, limbic system, and cerebellum. It is therefore conceivable that the cerebrum is an intermediate factor in the association between cerebellum and cognition. Consequently, adjustment for cerebral volume would actually be an overadjustment. Still, we note that even in unadjusted models, effects of cerebellar volume on cognitive function were small compared to effects of cerebral volume. Also, after Bonferroni correction, the associations between cerebellar volume and cognition disappeared, while most associations between cerebral volume and cognition remained. Second, the test battery used in the Rotterdam Study was specifically designed to examine cognitive function in the context of dementia, in particular Alzheimer disease. Possibly, the effects of cerebellar volume on cognitive function can only be detected by using a more sensitive cognitive test battery that is tailor-made to cerebellar function. For example, our test battery did not include tests of visuospatial ability, whereas previous studies have shown that the cerebellum is particularly involved in spatial cognition.[11, 14, 39] Finally, in our study we only looked at cerebellar grey and white matter volumes in a healthy aging population. It is possible that other structural or functional measures are required to investigate the relation between cerebellum and cognition. Also, it is important to realize that not all functional changes in the brain result in structural brain changes. Indeed, a recent meta-analysis summarized the role of PET and fMRI in cognition and described consistent associations between the cerebellum and cognition.[19, 40]

In a general population of persons 45 years and older, we found that cerebellar volume was only weakly related to global cognition, executive function and motor speed, especially compared to the relation between cerebral volume and these cognitive areas. The findings of the current study support the notion that cerebellar volume has an influence on cognition in aging, but that it is not

the major leading structure and has a more modulating role in cognitive functioning.[14, 34] Future studies in healthy elderly should investigate whether the cerebellum plays a role in other aspects of cognition.

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Chapter 3.3

Visuospatial ability in relation to dementia and MRI correlates

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Abstract

In the setting of a large population-based study (N = 4,106) we investigated the association between visuospatial ability and presence of dementia. Furthermore, in a sample of non-demented persons (N = 2,963), we studied the relation between brain pathology and visuospatial ability. To measure visuospatial ability we used a paper and pencil task based on the WAIS-III Block Design Test. Magnetic resonance imaging was performed to obtain cerebral, cerebellar and white matter lesion volumes. We showed that persons with worse visuospatial ability were more likely to have dementia. In a sample of non-demented persons, larger cerebral grey matter volume, rather than white matter volume, was related to better visuospatial ability. Predominantly, effects were found for temporal, and frontal lobe volumes. Also, white matter lesion volumes were related to visuospatial ability.

Introduction

Dementia is a preceded by a long preclinical phase, during which brain changes occur that affect cognition.[1] Already early on, memory impairments were identified as a hallmark of dementia.[2, 3] However, memory problems are usually accompanied by deficits in other cognitive domains which can each be differentially affected by aging and pathology that accumulates in the brain.[4, 5] The relation between diminished visuospatial ability in the early stages of dementia has also been recognized.[6-8] For example, it was recently found that decline in visuospatial ability is one of the earliest signs in the preclinical phase of Alzheimer disease.[9] Still, especially compared to the amount of studies focusing on memory impairments, deficits of spatial ability have received much less attention. Also, most studies have used small selected groups of patients and healthy elderly to study the relation between visuospatial ability and dementia. Moreover, studies of visuospatial ability often failed to integrate findings into a broader context of decline in other cognitive domains. And while we know that brain pathology characteristic of dementia is also prevalent in a pre-clinical phase of dementia and cognitively healthy elderly, not many studies investigated the relation between brain characteristics linked to dementia and visuospatial ability in a healthy elderly population.[10, 11]

In the current study using data from the large population-based Rotterdam Study, we investigated the association between visuospatial ability and dementia, while comparing it to the relation of dementia and other cognitive domains. Furthermore, in a subsample free of persons with dementia we studied how brain pathology, measured by brain volume and white matter lesions, was associated to visuospatial ability.

Methods

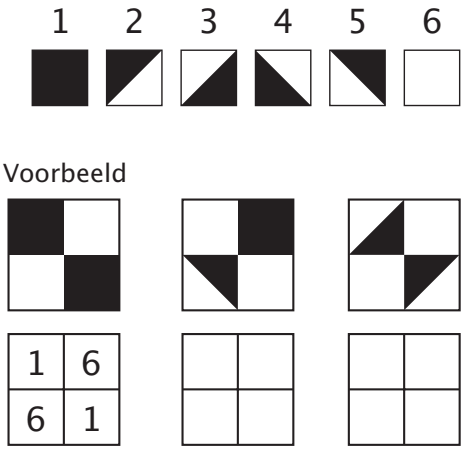
Participants

The study is based on the Rotterdam Study, a population-based study in middle-aged and elderly participants that started in 1990, investigating causes and consequences of age-related disease.[12] The present study included 4,106 persons that participated between February 2006 and September 2012 and from whom we obtained test scores of visuospatial ability. For analysis in non-demented persons, brain volumes were available in 2,963 persons who also had visuospatial ability data. The institutional review board of Erasmus MC approved the study and participants gave written informed consent.

Visuospatial ability

The Block Design test is widely recognized as a good measure of visuospatial organization and motor skills.[13] However, examination of the Block Design test takes more than ten minutes. The Design Organization Test (DOT) is a test which is based on and highly correlated to WAIS-III Block de-

sign, but is administered in two rather than ten minutes and is less dependent on motor skills than the Block Design test.[14] The DOT consists of black-and white square designs comprised of smaller black and white triangles. After two practice items (Supplementary Figure 1) subjects are required to reproduce as many designs as possible in 2 minutes using a numerical code key. The test form consists of nine designs (five 2x2 grids; four 3x3 grids), yielding in total 56 blank response squares. Test score on the DOT has a range from 0 to 56 points for each subject.



Supplementary figure 1. Code key and practice items of the Design Organization Test

Other cognitive tests

Cognitive function was assessed by using a battery of neuropsychological tests, including Mini-Mental State Examination (MMSE),[15] Stroop test,[16] Letter-Digit Substitution Task (LDST),[13] verbal fluency test,[17] 15-word verbal learning test (15-WLT),[18] and Purdue pegboard test.[19] Higher scores indicate a better performance on all cognitive tests, except for the Stroop task in which a higher score indicates a worse performance. Thus, for better comparison to other tests, scores of the Stroop task were inverted. In case of technical problems, refusal of participation, physical limitations, or deviation from instructions, test results were excluded. Level of education was obtained and categorized into seven levels, ranging from primary to university education.

Dementia assessment

Dementia was diagnosed using a three-step protocol. All participants were screened by administering the Mini- and Geriatric Mental State schedule. Participants with a Mini-Mental State Examination score < 26 or Geriatric Mental State organic level > 0 underwent the Cambridge Examination for Mental Disorders of the Elderly. If necessary, subjects suspected of having dementia were given neurological, neuropsychological and neuroimaging examinations. Additionally, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and medical records obtained from general practitioners and the regional institute for outpatient mental health. Final diagnoses were made by a consensus panel which was led by a neurologist, according to the internationally accepted criteria for dementia (DSM-III-R), and Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association). Dementia patients in the current study population include prevalent cases (n = 23) at date of cognitive testing and incident cases (n = 36) until January 1, 2011.

MRI acquisition & 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 three-dimensional fast radio frequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse (FASTSPGR-IR) sequence (TR = 13.8 ms, TE = 2.8 ms, TI = 400 ms, FOV= 25 cm^2, matrix = 416x256, flip angle = 20°, NEX= 1, BW= 12.50 kHz, 96 slices with slice thickness 1.6mm). All slices were contiguous. According to our standard acquisition protocol images were resampled to 512x512x192 voxels using zero-padding (voxel size: 0.5x0.5x0.8 mm^3).[20]

We used Freesurfer to obtain grey and white matter brain volumes.[21] As Freesurfer does not provide a lobar subdivision of the cerebral WM we combined it with our standard protocol for lobar segmentation.[20] This resulted in a grey and white matter volumes, for the cerebral lobes and cerebellum. White matter lesions (WMLs), were obtained using a k-nearest-neighbor classifier, according to a protocol previously described elsewhere.[22] According to a method previously described, outliers were defined as segmentations with an intracranial, cerebral or cerebellar volume outside a range of +/- 2.58 SD from the mean, stratified by sex.[23] A trained observer inspected all outliers (n = 214) and a random sample of 500 scans. From the random sample 9 scans were excluded due to poor segmentation quality, due to pathology (e.g. large arachnoid cysts, meningiomas) or technical problems (e.g. motion artefacts, susceptibility artefacts). From the outliers 31 scans were excluded. The total of 40 persons that were excluded were on average younger (M = 66.0, SD = 13.6) than the persons who were included (M = 69.0; SD = 10.1); t = -1.43, p = 0.16. In addition, in analyses using WML volumes, 7 outliers were excluded.

Statistical analysis

We calculated odds ratios (OR) using logistic regression analyses to investigate a cross-sectional association between cognitive test scores and presence of dementia. Cognitive test scores were standardized to enable comparison between different tests. To study the association of brain volumes and DOT score, we used linear regression models, and we corrected the associations for age, sex and intracranial volume. To aid comparison across brain regions we first calculated Z-scores for volumetric measures. White matter lesions were natural log transformed because of skewness of the untransformed measure. All analyses were performed using the statistical software package SPSS version 20.0 for Windows. Results are presented with 95% confidence intervals (CI).

Results

The mean age of the study sample was 70.9 years (SD = 9.9), with 57.2 % women (Table 1). The DOT was normally distributed. On average men had higher scores (mean (M) = 26.1, standard deviation (SD) = 10.0) on the DOT than women (M = 23.5, SD = 10.4); $p < 0.001$. However, men (M = 1.8, SD

Table 1. Characteristics of the study population

Overall population	**N = 4,106**
Age, years	70.9 ± 9.9
Female, (%)	57.2%
Primary education only, (%)	12.8%
Cognitive tests	
Design Organization Test, number of corrects	24.6 ± 10.3
Design Organization Test, percentage of corrects*	91.2 ± 11.3
Mini Mental State Examination, test score	27.7 ± 2.2
Stroop reading subtask, seconds	17.8 ± 3.8
Stroop color naming subtask, seconds	24.2 ± 5.2
Stroop interference subtask, seconds	53.1 ± 19.5
Letter-digit substitution task, number of correct digits	28.1 ± 7.2
Verbal fluency test, number of animals	21.6 ± 5.8
15-word learning test immediate recall, number of words	22.2 ± 6.3
15-word learning test delayed recall, number of words	7.1 ± 2.9
15-word learning test recognition, number of words	13.3 ± 1.9
Purdue Pegboard test both hands, number of pins placed	9.7 ± 1.9

Values are means ± standard deviation. *Percentage of corrects = (total number of corrects/ total number of completed squares)*100.

Table 2. Population characteristics to study MRI measures and visuospatial ability

MRI population	**N = 2,963**
Intracranial volume	1481.2 ± 162.8
Cerebral grey matter	470.2 ± 46.4
Cerebral white matter	412.4 ± 57.3
Cerebral volume	882.7 ± 99.1
Frontal lobe volume	302.0 ± 37.4
Parietal lobe volume	185.6 ± 20.5
Temporal lobe volume	183.2 ± 23.3
Occipital lobe volume	108.7 ± 14.1
Cerebral deep region	103.1 ± 10.7
Cerebellar volume	123.4 ± 13.2
White matter lesions	7.6 ± 10.5

Values are mean volumes in millilitres ± standard deviation. MRI; Magnetic resonance imaging.

= 1.9) did not make less errors than women (M = 1.9, SD = 2.2); p = 0.15. All neuropsychological tests were related to number of corrects on the DOT, also when adjusted for age, sex and level of education. The strongest correlation of DOT number of corrects was found with the LDST (r = 0.63, p < 0.001).

Table 3. The relation between cognition and dementia; non-demented persons n = 4047, persons with dementia n = 59

	OR dementia	P-value
Design Organization Test, number of corrects	0.37 (0.21; 0.64)	< 0.001
Design Organization Test, percentage of corrects	0.96 (0.75; 1.24)	0.77
Stroop interference subtask	1.07 (0.85; 1.35)	0.55
Letter-digit substitution task	0.51 (0.33; 0.80)	< 0.05
Verbal fluency test	0.42 (0.26; 0.67)	< 0.001
15-Word learning test, immediate recall	0.27 (0.14; 0.52)	< 0.001
15-Word learning test, delayed recall	0.20 (0.10; 0.41)	< 0.001
15-Word learning test, recognition	0.81 (0.63; 1.03)	0.81
Purdue Pegboard test	0.74 (0.51; 1.07)	0.11

All cognitive scores are standardized scores. Odds ratios (95% confidence intervals) are adjusted for age, sex and Mini-Mental State Examination. Dementia patients include prevalent cases at date of neuropsychological testing and incident cases until January 1, 2011.

The strongest association between cognitive test and dementia was found for the 15-WLT delayed recall (odds ratio (OR) per SD increase 0.20, 95% CI 0.10; 0.41) and 15-WLT immediate recall (0.27, 95% CI 0.14; 0.52) (Table 3). Furthermore, persons with a worse score on the DOT were more likely to have dementia (0.37, 95% CI 0.21; 0.64). Lower scores on the verbal fluency test and LDST also were related a larger likelihood of dementia.

Table 4. Brain volumes related to visuospatial ability in non-demented persons

N = 2,963	DOT number of corrects
Intracranial volume	1.52 (1.11; 1.93)
Cerebral volume	2.08 (1.68; 2.49)
Cerebral grey matter	3.00 (2.31; 3.68)
Cerebral white matter	0.93 (0.30; 1.57)
Frontal lobe volume	1.66 (1.00; 2.33)
Parietal lobe volume	1.39 (0.80; 1.99)
Temporal lobe volume	2.31 (1.65; 2.98)
Occipital lobe volume	1.21 (0.68; 1.75)
Cerebral deep region	0.82 (0.16; 1.47)
Cerebellar volume	0.30 (- 0.15; 0.76)
White matter lesions	-1.05 (-1.47; -0.63)

Values represent increase in Design Organization Test scores per standardized increase in brain volume or intracranial volume (95% confidence interval) and are adjusted for age, sex and all brain and lesion volumes are additionally adjusted for intracranial volume. White matter lesion volumes are natural log transformed and additionally adjusted for regional brain volumes.

Table 4 shows brain volumes, intracranial volume and WML volumes in relation to the number of correct scores on the DOT. In this sample free of dementia, larger cerebral volume, and especially larger temporal lobe and frontal lobe volume were associated with a higher number of corrects on the DOT. Moreover, cerebral grey matter showed a stronger positive association (3.00, 95% CI 2.31; 3.68) to the number of corrects on the DOT than cerebral white matter (0.93, 95% CI 0.30; 1.57). Cerebellar volume was the only volume which was not related to the number of corrects on the DOT. Larger WML volume was related to a higher number of corrects on the DOT. WMLs in different brain regions did not have differential effects on DOT score.

Discussion

In a large cohort study in a population of 45 years and older, we found that worse memory performance was related to a greater likelihood of having dementia. Also, we found a strong relation between visuospatial ability and presence of dementia. Furthermore, in persons free of dementia we found that larger cerebral lobe volume, and especially temporal lobe volume were related to better visuospatial ability. Larger WML volume in each of the cerebral lobes was related to worse visuospatial ability.

A limitation of this study is that we used a test of visuospatial ability, which is not commonly used. Also, while the DOT is a two-dimensional paper and pencil test, a three-dimensional test might more closely reflect visuospatial skills needed for interaction with the environment. However, the DOT was based on and strongly correlated to the Block Design Test, which is a three-dimensional test and is frequently used to measure visuospatial ability.[14] Still, future studies should investigate how well the DOT relates to other tests of visuospatial ability. Also, since in this study we were only able to establish a relation between worse visuospatial ability and presence of dementia, for future investigations, it would be of interest to find out what the value of the DOT is in predicting dementia. A second limitation is that we found a moderate correlation between scores on the DOT and LDST. Like the DOT the LDST uses a code key. In the DOT numbers are coupled to squares with a certain pattern, and in the LDST numbers are coupled to letters. The apparent similarity between these tests may play a role in their correlation. Although we chose the DOT as a representative of visuospatial ability, like most other cognitive tests it is probably reflective of more than one cognitive domain. For example, the relation to the LDST and the nature of the DOT, suggest that this test is related to executive function and processing speed. Still, we did not find a perfect correlation between the LDST and the DOT and we also found different associative estimates for these two tests in relation to presence of dementia. A more general problem with tests of visuospatial ability is that this cognitive domain comprises a wide variety of components and we cannot say how well one specific aspect of can be generalized to the greater domain of visuospatial ability.[24] There are also some advantages to our study. For example, the large sample size from large community-dwelling population gives precise estimates of visuospatial ability in the elderly. Also, in this study setting, a variety of other cognitive tests was available to which we could compare the performance

of visuospatial ability with regard to the relation with dementia. The availability of brain volumes in this study population gave us the opportunity to investigate the relationship of several brain volumes and brain pathology with visuospatial ability. For future investigations, it should be interesting to study the relation between other brain imaging measures, e.g. hippocampal volume, and visuospatial ability.

The strongest relation with presence of dementia was found for memory performance on both delayed and immediate recall tests. The relation between memory and dementia, was followed by a rather strong relation between visuospatial ability and dementia. This is in agreement with findings that Block Design scores are especially low in Alzheimer patients.[13] Even though our analysis only included a relatively small number of dementia cases we still established an association between presence of the disease and a worse score. Also, we found associations of verbal fluency and LDST with dementia. In a sample excluding persons with dementia, we found that intracranial volume and supratentorial brain volumes were related to DOT score. While some researchers have described involvement of cerebellar volume in visuospatial processing, our findings do not support this.[25, 26] All cerebral lobes were related to visuospatial ability. This is in agreement with the widespread neural substrates that have been linked to visuospatial ability.[24, 27] The strong association we found between temporal lobe volume, and visuospatial ability, is consistent with studies describing deficits of visuospatial ability after temporal lobe damage or lobectomy.[28] Structural and functional imaging studies have also related the temporal lobe to visuospatial ability.[29-32] Since the parietal lobe is consistently found to be involved in a variety of visuospatial tasks, we expected to find a stronger relation of visuospatial ability to parietal lobe volume.[33] Compared to cerebral white matter volume, we found a larger effect of grey matter volume on visuospatial ability. Furthermore, we found that larger WML volume was related to worse visuospatial ability. We did not find large regional differences in effects of WML volume on visuospatial ability. The finding of a relatively stronger relation between cerebral grey matter rather than white matter, with visuospatial ability, could imply that intactness of the temporal lobe itself, and not its connections to other brain regions is of greatest importance in the functioning of visuospatial ability. Moreover, the absence of differential effects of WMLs per region is supportive of this idea. The strong association between temporal lobe volume and visuospatial ability, combined with the relation of dementia and visuospatial ability, is congruent with the findings that the temporal lobe is affected in cognitively healthy persons and that visuospatial ability is already strongly affected in preclinical phases of dementia and healthy aging.[11, 34] However, another study found no differences in visuospatial ability when comparing persons with or without Alzheimer pathology.[10]

In conclusion, we have shown in persons of 45 years and older, visuospatial ability is inversely related to presence of dementia. Furthermore, in elderly without dementia better visuospatial ability is related most strongly to larger temporal lobe volume. Higher WML volume in each of the cerebral lobes is related to worse visuospatial ability.

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Chapter 4

Brain aging and motor function

Chapter 4.1

Gait patterns in a community-dwelling population aged 50 years and older

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Abstract

Poor gait is an important risk factor for falls and associated with higher morbidity and mortality. It is well established that older age is associated with worse gait, but it remains unclear at what age this association is first seen. Moreover, previous studies focused mainly on normal walking, but gait also encompasses turning and tandem walking. In a large study of community-dwelling middle-aged and elderly persons we investigated the association of age with gait, focusing on normal walking, turning and tandem walking. In 1500 persons aged 50 years and over, we measured gait using an electronic walkway. Participants performed normal walks, turning and a tandem walk. With principal components analysis of 30 variables we summarized gait into five known gait factors: *Rhythm*, *Variability*, *Phases*, *Pace* and *Base of Support*; and uncovered two novel gait factors: *Tandem* and *Turning*. The strongest associations with age were found for *Variability* (difference in Z-score -0.29 per 10 years increase (95% confidence interval: -0.34; -0.24)), *Phases* (-0.31 per 10 years (-0.36; -0.27)) and *Tandem* (-0.25 per 10 years (-0.30; -0.20)). Additionally, these factors already showed association with the youngest age groups, from 55-60 years of age and older. Our study shows that *Variability*, *Phases* and *Tandem* have the strongest association with age and are the earliest to demonstrate a poorer gait pattern with higher age. Future research should further investigate how these gait factors relate with gait-related diseases in their earliest stages.

Introduction

Proper gait is very important to function independently in a community. Not only is gait an important indicator of general health, but poor gait is also a predictor of adverse events, such as falls and mortality.[1-6] Various studies have shown that higher age is associated with worse gait.[2, 7-12] With increasing life-expectancy, gait disturbances are therefore expected to become even more frequent.[2]

Gait is a highly complex concept and can be studied using many different variables. These variables include simple measurements such as velocity, step length and step width, but also more complex measurements such as the variability within variables.[7-8, 13] Consequently, the overlap across studies in variables used to study gait is limited. Ideally, gait is studied using as many variables as possible, but this would result in multiple testing as well as collinearity across variables.

In recent years, various studies have sought to solve this issue by principal components analysis (PCA). Using PCA on 7 and 8 variables, two studies summarized gait into three independent factors, referred to as *Pace*, *Rhythm* and *Variability*.[3-4] These factors were found to be associated with cognitive decline and risk of falls.[3-4] Another study expanded on this finding by including 15 additional gait variables in the PCA and uncovered two additional gait factors, which were named *Phases* and *Base of Support*.[9] Consecutively, the factors were found to be associated with age and sex.[9]

The five gait factors described so far are all based on normal walking.[3-4, 9] However, gait is a broader concept encompassing not only normal walking, but also turning and tandem (heel-to-toe) walking among others. Little is known about the effect of age on these aspects of gait. Furthermore, it is unknown whether these other aspects constitute additional gait factors or whether these can be captured by the previously described gait factors of normal walking.

Another consideration is that previous studies on aging and gait focused on elderly populations (60 years and over). The question remains whether the association between age and gait already starts at an earlier age. Investigating the earliest age-related changes in gait would provide novel insights into the normal aging progress and can serve as a basis to study pathologic gait disturbances.

The aim of our study was to investigate the association between age and gait in a population-based cohort study of middle-aged and elderly persons. We not only investigated normal walking, but also focused on turning and tandem walking. Similar to previous studies, we used PCA to summarize gait into a few independent factors.

Methods

Setting

The study was embedded in the Rotterdam Study, a prospective, population-based cohort study, originally started in 1990.[14] The initial cohort was expanded in 2000 and 2005 and currently totals 14,926 persons. At study entry and during follow-up every three to four years, each participant undergoes a home interview and extensive physical examination at the research center. At these assessments height and weight are measured, and self-reported chronic diseases are recorded. From March 2009 onwards, gait assessment has been implemented in the core protocol. The current study comprises all participants that completed gait assessment until March 2011. All participants gave written informed consent. The study has been approved by the institutional Medical Ethics Committee.

Gait assessment

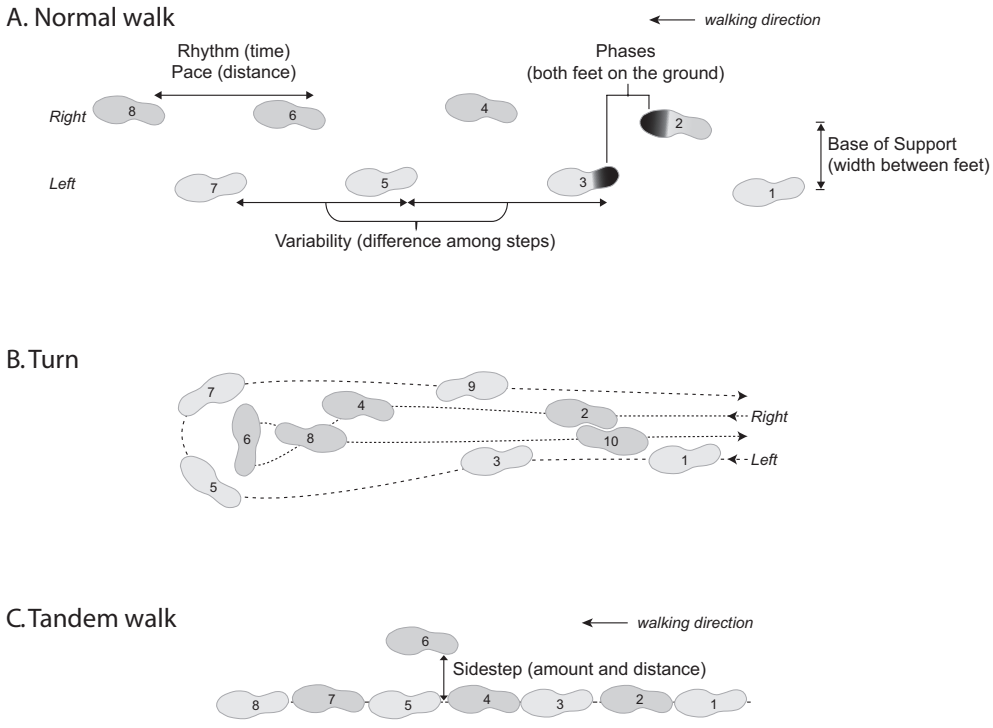
Gait was assessed with a 5.79 meter long walkway (GAITRite Platinum; CIR systems, USA: 4.88 meter active area; 120 Hertz sampling rate) with pressure sensors, activated by the pressure of footfalls. This device is an accurate system to determine gait parameters.[15-18]

Participants were asked to perform a standardized protocol consisting of three different types of walking: normal walk, turning and tandem walk. In the normal walk, participants walked over the walkway at their own pace. This walk was performed four times in both directions (8 recordings). In turning, participants walked over the walkway, turned halfway and returned to the starting position (1 recording). In the tandem walk, participants walked tandem (heel-to-toe) over a line visible on the walkway (1 recording). Examples of the three walks can be found in supplement 1.

In recordings of the normal and tandem walks, footsteps that did not fall entirely on the walkway at the start and the end were deleted. The first recording of the normal walk was treated as a practice walk and not included in the analyses. Recordings of individual walks were removed if instructions were not followed correctly or when fewer than four footprints were available for analyses. Spatio-temporal variables were calculated by the walkway software.

Study Population

Between March 2009 and March 2011, we invited 1905 participants for gait assessment. Of these, 405 were excluded for various reasons: 196 participants were removed for technical reasons; 21 participants were excluded for use of walking aids, self-reported prosthesis or Parkinson's disease; 113 participants were excluded because of a too poor physical ability to walk; 41 participants were removed because they had fewer than 16 steps available for analyses, which lowers the validity of their gait parameters[19]; 14 participants refused to participate; 9 participants refused to perform all



Supplement 1: Examples of the three walks performed
a: the normal walk includes measures of Rhythm, Pace, Variability, Phases, and Base of Support; b: turning; c: the tandem walk. For turning only the part of the walk used in the analyses is shown.

walks; 9 participants were removed because they did not follow instructions; and 2 participants did not perform the walks for other reasons.

After exclusion, 1500 participants were included in the analyses.

Statistical Analysis

PCA with varimax rotation was performed on thirty variables to derive independent summarizing factors. A description of these thirty gait variables can be found in supplement 2. These were all variables that could be reliably measured using the GAITRite. Preliminary analysis did not suggest differences between legs; hence the mean of both legs was taken.

Factors were selected from the PCA if their eigenvalue was 1 or higher, signifying that each factor explains at least as much variance as a single variable. Communalities were calculated, reflecting the amount of variance in the variable explained by all factors. Variables were appointed to a certain factor if their correlation with the factor was ≥0.5. If necessary, factors were inverted so that

Supplement 2: Variable definitions

Variable/Factor	Definition	Indication of a poorer gait pattern[a]
Rhythm		**lower**
Single Support Time	The time elapsed between the last contact of the opposite foot and the first contact of the next footfall of the opposite foot when a foot touches the ground	higher
Swing Time	The time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot in seconds	higher
Step Time	The time elapsed between the first contact of one foot and the first contact of the opposite foot	higher
Stride Time	The elapsed time between the first contacts of two consecutive footfalls of the same foot in seconds	higher
Cadence	The number of steps/minute	lower
Stance Time	The time elapsed between the first contact and the last contact of two consecutive footfalls on the same foot in seconds. It is initiated by heel contact and ends with the toe off of the same foot	higher
Variability		**lower**
Stride Length SD	The standard deviation in the Stride Length in centimeters	higher
Step Length SD	The standard deviation in the Step Length in centimeters	higher
Stride Velocity SD	The standard deviation in the Stride Velocity (Stride Length/Stride Time) in centimeters/second	higher
Stride Time SD	The standard deviation in the Stride Time in seconds	higher
Step Time SD	The standard deviation in the Step Time in seconds	higher
Stance Time SD	The standard deviation in the Stance Time in seconds	higher
Swing Time SD	The standard deviation in the Swing Time in seconds	higher
Single Support Time SD	The standard deviation in the Single Support Time in seconds	higher
Double Support Time SD	The standard deviation in the Double Support Time in seconds	higher
Phases		**lower**
Single Support (%GC)	The Single Support Time as a percentage of the Stride Time	lower
Swing (%GC)	The Swing Time as a percentage of the Stride Time	lower
Stance (%GC)	The Stance Time as a percentage of the Stride Time	higher
Double Support (%GC)	The Double Support Time as a percentage of the Stride Time	higher
Double Support Time	The amount of time that two feet are on the ground at the same time within one footfall in seconds	higher

Pace		**lower**
Stride Length	The distance between the heel points of two consecutive footprints of the same foot on the line of progression in centimeters	lower
Step Length	The distance between the heel points of two consecutive opposite footprints on the line of progression in centimeters	lower
Velocity	The velocity in centimeters/second	lower
Tandem		**lower**
Sum of Feet Surface	The sum of the surfaces of the side steps[b] as a percentage of the surface of a normal step	higher
Sum of Step Distance	The sum of the distances of the side steps[b] from the line on the walkway in centimeters	higher
Double Step	A double-step was a step with one foot, followed by a step with the same foot, where both feet were on the line of the walkway	higher
Turning		**lower**
Turning Step Count	The number of steps used within the Turning Time	higher
Turning Time	The turning time was defined as the time between the last contact of the second foot before the first turn foot and the first contact of the second foot with a normal angle coming out of the turn. In which the first turn foot is defined as the first foot deviating from the normal angle of the feet (subject dependent)	higher
Base of Support		**lower**
Stride Width SD	The standard deviation in the Stride Width in centimeters	higher
Stride Width	The distance from heel center of one footprint to the line of progression formed by two footprints of the opposite foot in centimeters	lower

Abbreviations: SD = standard deviation, %GC = as a percentage of the gait cycle time, the cycle time equals the stride time.

[a] = "lower" indicates that lower values are considered a poorer the gait pattern, "higher" indicates that higher values are considered a poorer gait pattern.

[b] = A sidestep was defined as a step next to the line on the walkway, which was followed by a step with the same foot or a step with the other foot.

lower values represent "worse" gait. The PCA yielded standardized factors (Z-scores) that were uncorrelated to each other.

Multiple linear regression analyses were used to determine the independent associations between demographics (age, sex, height and weight) and gait factors. Analyses involving tandem walk related variables were adjusted for the step length and step count in the tandem walk. We applied Bon-

ferroni correction for 28 tests to correct for multiple testing. Additional adjustments were made for self-reported osteoarthritis and rheumatoid arthritis. We also calculated mean Z-scores of gait factors per 5-year age strata and per sex using ANOVA, adjusted for height and weight. Differences between sexes in the effects of age were tested using interaction terms (age x sex). All statistical analyses were performed using SPSS PASW version 17.0.2 for Windows.

Results

Characteristics of the study population are summarized in Table 1. Mean age was 68.8 years, and 817 (54.5%) were women. After summing all normal walks, an average of 41.75 (standard deviation (SD) 8.92) steps was available per participant. For turning an average of 4.88 (SD 0.87) steps was available, and for the tandem walk an average of 12.99 (SD 2.76) steps was available.

Table 1. Population characteristics

Characteristic	**Total (n = 1500)**	**Men (n = 683)**	**Women (n = 817)**
Age [yrs]	68.8 (10.1)	69.2 (10.3)	68.4 (9.9)
Height [cm]	168.5 (9.4)	175.7 (7.1)	162.6 (6.6)
Weight [kg]	78.0 (14.7)	85.1 (13.7)	72.1 (12.7)
Self-reported locomotor disorders			
Osteoarthritis [n]	343 (22.9 %)	118 (17.3 %)	225 (27.5 %)
Rheumatoid Arthritis [n]	46 (3.1 %)	14 (2.0 %)	32 (3.9 %)

Values are mean (standard deviation) or numbers (%).
Abbreviations: yrs = years, cm = centimeters, kg = kilograms, n = number

The mean and SD of the variables used in the PCA are shown in Table 2. The PCA summarized these 30 variables into seven factors, explaining 87.3% of the total variance in gait (Table 2). In line with previous studies and based on the variables constituting these factors, we labeled these: *Rhythm*, *Variability*, *Phases*, *Pace*, *Tandem*, *Turning* and *Base of Support*.[3-4, 9] High communalities (>=0.60) were found for all original gait variables, except double step. All variables contributed to a factor with a correlation higher than 0.5 (Table 2). The correlations between each gait variable and each gait factor can be found in supplement 3.

Table 3 shows the multivariable adjusted associations of age, sex, height and weight with the gait factors. Higher age was significantly associated with a lower Z-score on all factors but *Rhythm*, which showed a higher Z-score with age. Strongest associations with age were found for *Phases*: difference in Z-score per 10 years increase in age -0.31 (95% confidence interval: -0.36; -0.27), *Variability*: -0.29 per 10 years (-0.34; -0.24) and *Tandem*: -0.25 per 10 years (-0.30; -0.20).

Table 2. Summarization of gait variables within independent gait factors

Variable/Factor	Percentage explained [a]	Mean (SD)	Communality [b]	Correlation with factor [c]
Rhythm	21.5 %			
Single Support Time [s]		0.42 (0.03)	0.99	-0.96
Swing Time [s]		0.42 (0.03)	0.99	-0.96
Step Time [s]		0.55 (0.05)	0.99	-0.94
Stride Time [s]		1.11 (0.10)	0.99	-0.94
Cadence [steps/min]		109.0 (9.3)	0.98	0.94
Stance Time [s]		0.68 (0.07)	0.99	-0.84
Variability	20.0 %			
Stride Length SD [cm]		4.71 (1.68)	0.83	-0.89
Step Length SD [cm]		2.92 (0.96)	0.82	-0.87
Stride Velocity SD [cm/s]		6.04 (1.92)	0.78	-0.86
Stride Time SD [s]		0.03 (0.02)	0.86	-0.80
Step Time SD [s]		0.02 (0.01)	0.88	-0.79
Stance Time SD [s]		0.03 (0.01)	0.88	-0.79
Swing Time SD [s]		0.02 (0.01)	0.82	-0.71
Single Support Time SD [s]		0.02 (0.01)	0.82	-0.71
Double Support Time SD [s]		0.02 (0.01)	0.60	-0.57
Phases	19.0 %			
Single Support (%GC)		38.3 (1.6)	0.99	0.97
Swing (%GC)		38.3 (1.6)	0.99	0.97
Stance (%GC)		61.7 (1.6)	0.99	-0.97
Double Support (%GC)		23.5 (3.2)	0.99	-0.96
Double Support Time [s]		0.26 (0.05)	0.99	-0.83
Pace	9.8 %			
Stride Length [cm]		129.8 (17.0)	0.92	0.82
Step Length [cm]		64.7 (8.5)	0.92	0.82
Velocity [cm/s]		118.0 (18.5)	0.92	0.69
Tandem	7.2 %			
Sum of Feet Surface [fraction]		0.34 (0.71)	0.87	-0.92
Sum of Step Distance [cm]		9.1 (17.0)	0.84	-0.90
Double Step [n]		0.08 (0.32)	0.41	-0.63
Turning	6.1 %			
Turning Step Count [n]		4.88 (0.87)	0.87	-0.91
Turning Time [s]		2.81 (0.62)	0.85	-0.85
Base of Support	3.7 %			
Stride Width SD [cm]		2.34 (0.76)	0.73	-0.79
Stride Width [cm]		10.1 (4.0)	0.69	0.63
Total	87.3 %			

Abbreviations: SD = standard deviation, s = seconds, min = minutes, cm = centimeters, %GC = percent of the gait cycle time, n = number

[a], The percentage explained is the amount of total variance in all gait variables explained by this factor.

[b], The communality is the amount of variance of the variable explained by all gait factors.

[c], Factors were inverted so that lower values represent "worse" gait. The numbers shown represent correlations after the inversion.

Supplement 3: Correlations between the gait variables and the factors

Gait variable	Rhythm	Variability	Phases	Pace	Tandem	Turning	Base of Support
Single Support Time	-0.96	-0.09	0.22	0.04	0.06	-0.03	0.00
Swing Time	-0.96	-0.09	0.22	0.04	0.06	-0.03	0.00
Step Time	-0.94	-0.16	-0.27	-0.04	0.02	-0.05	0.01
Stride Time	-0.94	-0.16	-0.27	-0.04	0.02	-0.05	0.01
Cadence	0.94	0.14	0.27	0.02	-0.03	0.04	-0.01
Stance Time	-0.84	-0.18	-0.49	-0.08	0.00	-0.05	0.02
Stride Length SD	0.01	-0.89	-0.12	0.13	-0.07	-0.08	-0.03
Step Length SD	-0.00	-0.87	-0.15	0.11	-0.09	-0.11	-0.01
Stride Velocity SD	0.18	-0.86	0.05	0.07	0.01	0.06	-0.07
Stride Time SD	-0.29	-0.80	-0.14	-0.34	-0.01	-0.00	-0.00
Step Time SD	-0.32	-0.79	-0.15	-0.35	-0.04	-0.05	0.04
Stance Time SD	-0.32	-0.79	-0.19	-0.33	-0.02	-0.05	0.03
Swing Time SD	-0.37	-0.71	-0.11	-0.37	-0.05	-0.12	0.10
Single Support Time SD	-0.37	-0.71	-0.11	-0.37	-0.05	-0.12	0.10
Double Support Time SD	-0.32	-0.57	-0.22	-0.33	-0.01	-0.07	-0.08
Single Support (%GC)	0.07	0.13	0.97	0.16	0.06	0.05	-0.02
Swing (%GC)	0.07	0.13	0.97	0.16	0.06	0.05	-0.02
Stance (%GC)	-0.07	-0.13	-0.97	-0.16	-0.06	-0.05	0.02
Double Support (%GC)	-0.07	-0.13	-0.96	-0.18	-0.07	-0.04	0.01
Double Support Time	-0.49	-0.17	-0.83	-0.16	-0.04	-0.05	0.01
Stride Length	-0.13	0.22	0.35	0.82	0.15	0.19	-0.05
Step Length	-0.13	0.22	0.35	0.82	0.15	0.19	-0.05
Velocity	0.39	0.25	0.43	0.69	0.11	0.18	-0.05
Sum of Feet Surface	0.05	-0.09	-0.08	-0.10	-0.92	-0.01	-0.09
Sum of Step Distance	0.04	-0.06	-0.06	-0.05	-0.90	-0.03	-0.10
Double Step	0.02	-0.01	-0.05	-0.06	-0.63	0.03	0.11
Turning Step Count	0.07	-0.09	-0.07	-0.13	-0.03	-0.91	0.01
Turning Time	-0.25	-0.10	-0.07	-0.20	0.05	-0.85	0.04
Stride Width SD	-0.04	-0.17	-0.08	0.23	-0.09	-0.09	-0.79
Stride Width	-0.11	-0.27	-0.24	0.26	-0.08	-0.27	0.63

Factors were inverted so that lower values represent "worse" gait. The numbers shown represent correlations after the inversion.

The figure shows the mean Z-scores across factors in 5-year age strata per sex. For both men and women, the earliest decrease in Z-score was seen for *Variability*, followed by *Tandem* and *Phases*: these three factors already showed a decrease in the earliest age-categories (55-60 years and older).

Women had a significantly lower Z-score on *Phases*, *Pace* and *Base of Support*, while men had a significantly lower Z-score on *Rhythm*. No significant interaction between age and sex was found for any of the gait factors ($p > 0.05$).

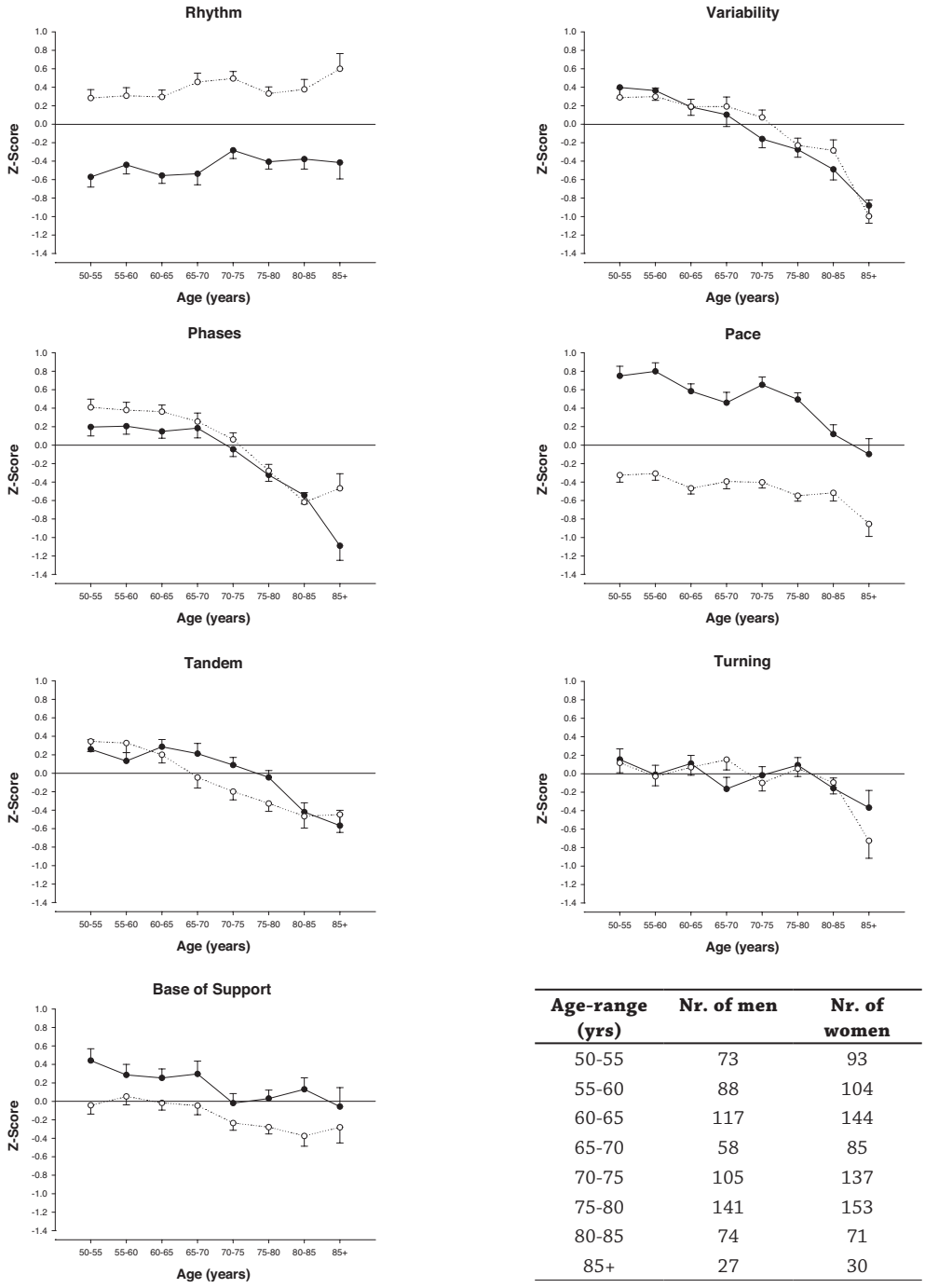
Table 3. Independent associations between the demographics and the gait factors

Factor	Rhythm	Variability	Phases	Pace	Tandem [a]	Turning	Base of Support
Age (/10 yrs increase)	0.06	-0.29	-0.31	-0.14	-0.25	-0.08	-0.14
	(0.01; 0.10)	(-0.34; -0.24)	(-0.36; -0.27)	(-0.18; -0.10)	(-0.30; -0.20)	(-0.13; -0.03)	(-0.19; -0.08)
Female vs. Male	**0.52**	-0.08	**-0.15**	**-0.42**	-0.12	-0.10	**-0.43**
	(0.39; 0.65)	(-0.22; 0.06)	**(-0.28; -0.03)**	**(-0.54; -0.30)**	(-0.26; 0.03)	(-0.25; 0.04)	**(-0.57; -0.28)**
Height (/10 cm increase)	**-0.27**	**-0.14**	**0.19**	**0.42**	-0.03	0.01	**-0.17**
	(-0.35; -0.20)	**(-0.23; -0.06)**	**(0.12; 0.26)**	**(0.35; 0.49)**	(-0.12; 0.05)	(-0.08; 0.10)	**(-0.26; -0.09)**
Weight (/10 kg increase)	0.05	**0.04**	**-0.42**	0.01	0.00	**-0.08**	**0.09**
	(0.01; 0.08)	**(0.00; 0.09)**	**(-0.45; -0.38)**	(-0.02; 0.05)	(-0.04; 0.04)	**(-0.12; -0.03)**	**(0.05; 0.13)**

Numbers represent changes in Z-score of the gait factors with their 95% confidence interval. A lower Z-score represents "worse" gait. Results in bold represent significant findings ($p<0.05$)

Abbreviations: yrs = years, cm = centimeter, kg = kilogram

[a], additionally adjusted for step length and step count of the tandem walk



Age-range (yrs)	Nr. of men	Nr. of women
50-55	73	93
55-60	88	104
60-65	117	144
65-70	58	85
70-75	105	137
75-80	141	153
80-85	74	71
85+	27	30

Figure: The association between age and gait factors, in 5-year strata and by sex. A lower Z-score on a gait factor corresponds with worse gait. Black dots represent men and white dots represent women. Dots are height and weight adjusted means. Error bars represent the standard errors of the mean.

Larger height was associated with lower *Rhythm*, *Variability* and *Base of Support* and higher *Phases* and *Pace*. Higher weight was associated with lower *Phases* and *Turning*, and higher *Rhythm*, *Variability* and *Base of Support*.

After Bonferroni correction the associations of age with *Rhythm* and *Turning* were no longer significant. The associations of sex with *Phases* and weight with *Rhythm* and *Variability* did not survive Bonferroni correction either.

After adjustment for self-reported osteoarthritis and rheumatoid arthritis the associations remained similar: for example the association between age and *Variability* became -0.30 per 10 years (-0.35; -0.25), between sex and *Phases* became -0.14 (-0.27; -0.02) and between weight and *Turning* became -0.07 (-0.12; -0.03). For the other factors, too, the associations remained unchanged.

Discussion

Our study showed that gait assessed by normal walking, turning and tandem walking can be summarized in 7 factors, which are *Rhythm*, *Variability*, *Phases*, *Pace*, *Tandem*, *Turning*, and *Base of Support*. We found that higher age was associated with worse gait as reflected in *Variability*, *Phases*, *Pace*, *Tandem* and *Base of Support*. The factor to show an association with the youngest age group was *Variability*, followed by *Tandem* and *Phases*. Between the sexes, women had poorer *Pace* and *Base of Support*, but better *Rhythm* than men.

The strengths of our study include the population-based design, the large sample size, the relatively wide age-range, the many variables included and the different types of walk investigated. Our study also has some limitations. First, the cross-sectional design precludes the repeated assessment of age-related changes within participants. Second, participants only walked at their normal pace. Future studies should investigate whether results differ when walking at higher or lower velocity. Thirdly, apart from normal walking, turning, and tandem walking, gait comprises other aspects which were not investigated, such as running, backward walking, and backward tandem walking. Inclusion of other walking conditions may reveal additional gait factors. Finally, our study sample was drawn from the general population and thus relatively healthy compared to clinic-based samples, both in terms of cognitive and physical health. This precluded the investigation of the effect of clinical disease on gait.

We found that gait can be summarized in seven factors. Of these, four factors were constituted by exactly the same variables as in another study summarizing gait[9]: *Rhythm*, representing most temporal variables of the normal walk; *Phases*, representing support time variables as percentages of the gait cycle and double support time; *Pace*, representing stride- and step length and velocity; and *Base of Support*, representing stride width and its variability. For *Variability*, which represents all variability variables excluding stride width variability, the same constituting variables were

found as well, but we expanded this finding by showing that single support- and double support variability represent the same underlying factor. This supports the suggestion that all variability variables, except for stride width variability, represent the same underlying process.[9] The high correspondence of the gait factors we found for normal walking with those found in other studies demonstrates their robustness, and suggests that adding more gait variables to the component analysis would not substantially change the composure of the already identified gait factors for normal walking.[3-4, 9] Extending these findings, we identified two new factors representing additional walking conditions: *Tandem*, representing errors in the tandem walk and *Turning*, representing the number of turning steps and turning time. This result shows that investigating turning and tandem walking besides normal walking indeed yields additional information. Given that other studies have shown variables constituting *Turning* and *Tandem* to be associated with falls,[20-21] this suggests that measuring *Turning* and *Tandem* may provide incremental value in assessing fall risk.

We found that higher age was associated with worse values on *Variability*, *Phases*, *Pace*, *Tandem* and *Base of Support*. This is in line with previous studies that found similar associations with individual variables constituting these factors.[7-8, 10-11] A previous study using summarizing factors only found an association with age for *Phases* and *Pace*, but not for *Rhythm*, *Variability* and *Base of Support*.[9] This discrepancy could be due to less power, or the narrower age-range in that study. While other studies have found gait velocity to influence associations between age and gait[8, 22], in our study gait velocity is part of a separate factor, *Pace*. This ensures that associations found for all other factors are largely independent from gait velocity.

We found *Variability*, *Phases* and *Tandem* to associate strongest with age and to be associated already with the youngest age groups. Interestingly, variables that constitute these factors have also been associated with falls.[4-6, 20] This suggests that assessing gait may aid in identifying those at the highest risk of falls. Furthermore, the difficulty in the visual assessment of especially *Variability* and *Phases* indicates that electronic walkways for measuring gait may have a role in clinical practice to assess gait disturbances in their earliest stages.

Although higher age was also associated with worse *Pace* and *Base of Support*, these associations demonstrated smaller effect sizes and only showed differences at a higher age. The associations with age for *Rhythm* and *Turning* did not survive Bonferroni correction and should therefore be confirmed by future studies.

In our study, women had better *Rhythm*, but worse *Pace* and *Base of Support* compared to men. This suggests that women walk with quicker, but smaller steps, and have a narrower but more variable stride width. These findings are in line with other studies, which found similar associations for these factors or constituting variables.[7, 9-10] We did not find differences between men and women in the association between age and gait.

The various factors together explain a high proportion of the total variance in gait. Each gait factor represents a different group of highly correlated variables. The use of gait factors has several

advantages over the use of conventional gait variables. Previous studies have already demonstrated the use of gait factors in the assessment of various clinical outcomes, such as risk of falls and cognitive impairment.[3-4] One study found that worse *Phases* and, independently, *Variability* are associated with a higher risk of falls.[4] However, they did not recommend specific cut-off values to be used clinically. Furthermore, another study demonstrated that worse *Rhythm* and *Pace* may indicate a decline in global cognition, memory or executive functioning. Furthermore, they found that worse *Rhythm* and *Variability* are associated with an increased risk of dementia.[3] Additionally, many other morbidities appear to be associated with gait, such as sensory impairment, mobility disability and arterial stiffness.[13, 23-24] Unraveling the associations between gait and these morbidities will aid in further understanding the aging process. Furthermore, assessment of gait may aid in the early detection or prediction of these morbidities. However, more research is needed before this can be materialized.

In conclusion, our study shows that gait can be summarized in seven factors: *Rhythm*, *Variability*, *Phases*, *Pace* and *Base of Support* representing normal walking, and *Turning* and *Tandem* originating from turning and tandem walking. This suggests that turning and tandem walking provide additional information on gait beyond normal walking. We found that higher age is associated with worse gait, with the strongest associations for *Variability*, *Phases* and *Tandem*. These were also the gait factors to show an association with the youngest age groups. Future studies should investigate the processes underlying this association between age and gait and investigate its association with the development of gait disorders and other morbidities.

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Chapter 4.2

Older age relates to worsening of fine motor skills: a population-based study of middle-aged and elderly persons

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Abstract

Introduction In a population-based study of 1,912 community-dwelling persons of 45 years and older we investigated the relation between age and fine motor skills using the Archimedes spiral-drawing test. Also, we studied the effect of brain volume on fine motor skills.

Methods Participants were required to trace a template of a spiral on an electronic drawing board. Clinical scores from this test were obtained by visual assessment of the drawings. Quantitative measures were objectively determined from the recorded data of the drawings. As tremor is known to occur increasingly with advancing age, we also rated drawings to assess presence of tremor.

Results We found presence of a tremor in 1.3% of the drawings. In the group without tremor we found that older age was related to worse fine motor skills. Additionally, participants over the age of 75 showed increasing deviations from the template when drawing the spiral. Larger cerebral volume and smaller white matter lesion volume were related to better spiral drawing performance, whereas cerebellar volume was not related to spiral drawing performance.

Conclusions Older age is related to worse fine motor skills, which can be captured by clinical scoring or quantitative measures of the Archimedes spiral-drawing test. Persons with a tremor performed worse on almost all measures of the spiral-drawing test. Furthermore, larger cerebral volume is related to worse fine motor skills.

Introduction

Fine motor skills of the hand are important in many daily activities, such as buttoning a shirt, unlocking doors, or selecting coins from a wallet. If these skills deteriorate, this may give rise to a large variety of minor to major obstacles in daily life. Effects of aging have received much attention for their impact on cognition, either in the context of normal aging or dementia. In particular, aging of the brain quantified by reduced brain volumes or accumulating pathology, has been of great interest in explaining cognitive decline.[1-3] Even though fine motor skills have also been found to decline with aging, population-based studies have been relatively less concerned with describing age effects on fine motor skills in the general population.[4-6]

Movements are initiated by cerebral structures, but the cerebellum also plays an important role in fine motor skills.[7, 8] Patients with selective cerebellar damage present with balance problems and uncoordinated movements, but also with tremor.[9-11] Thus, both cerebral as well as cerebellar volumes have an influence on the production of coordinated and smooth movements.

To test fine motor skills the Archimedes spiral-drawing test can be used.[12, 13] Conventional assessment of fine motor skills is done using a clinical score, which is based on a visual inspection of the drawing. However, with use of an electronic drawing tablet, automatic quantification of this test can be performed.[14-16] The spiral-drawing test has been found useful in characterizing movement abnormalities, for example by quantifying tremor intensity,[17] or assessing advanced Parkinson disease,[18] multiple sclerosis [19] or Niemann-Pick disease.[20]

In the current study, we aimed to describe effects of age on fine motor skills in a general population of middle-aged and elderly persons. For the purpose of this study, we measured fine motor skills using both a qualitative clinical score as well as quantitative measures obtained from the Archimedes spiral-drawing test. We also wanted to characterize differences of fine motor skills between persons with and without tremor. Furthermore, we aimed to relate cerebellar and cerebral volume to fine motor skills.

Materials and methods

Population

The study was embedded in the Rotterdam Study, a prospective, population-based cohort study (n = 14,926) that started in 1990 and investigates causes and consequences of age-related disease.[21] The institutional review board of Erasmus MC approved the study and participants gave written informed consent. Between January 2009 and December 2010 a random sample of 1,922 persons came to the research center for assessment of fine motor skills using a spiral drawing test.

Population for analysis

Of 1,922 persons, we excluded 8 persons based on self-reported Parkinson disease. Self-reported problems of joints in the dominant hand due to osteoarthritis or rheumatoid arthritis were present in 25 persons. Furthermore, in 2 persons (of which one person is familiar with autosomal dominant cerebellar ataxia) drawings were not suited for our post-processing analyses. Therefore, we chose to exclude these results and 1,912 persons were left for further analyses.

Fine motor skill assessment

Fine motor skill was assessed by requiring participants to trace a picture of a spiral template that was printed on a piece of paper attached to an electronic drawing board (WACOM Graphire Wireless Pen Tablet, model CTE-630BT). Participants were instructed to place the pen in the middle of the spiral before the tracing started (Figure 1A). They were not allowed to lean on the drawing board with their hand or arm. Participants were asked to trace the spiral as accurately and as fast as possible using their dominant hand.

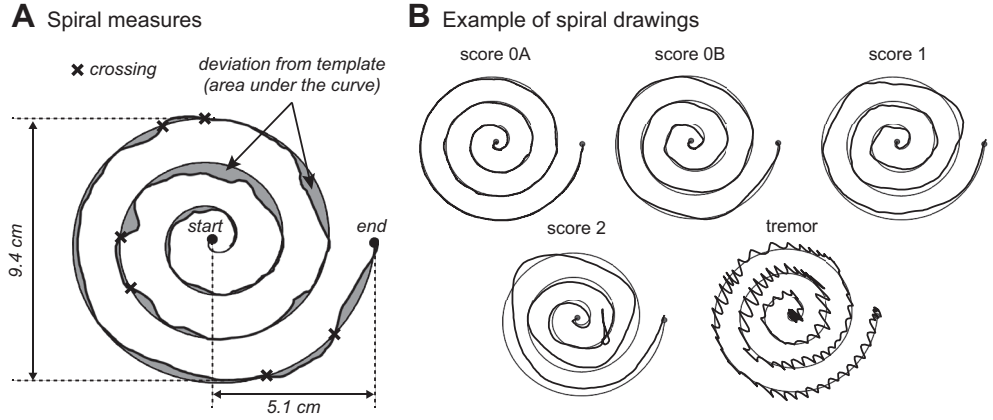

Figure 1. Examples of spiral drawing quantification and clinical scores. Figure 1A shows an example of the calculation of quantitative measures of fine motor skills. The start and endpoint are indicated by a dot. The figure explains how deviation from template and crossings are defined. Figure 1B shows examples of clinical scores of the spiral drawings with score 0A, 0B, 1, 2 and a tremor.

Clinical scoring of spiral drawing

Pen position was recorded at a rate of 60 Hz and stored for offline quantitative analysis. Drawings of participants were evaluated visually to ensure proper data collection. Incomplete drawings were removed from further data processing. Drawings were analysed visually by a trained observer for qualitative analyses. First, suspected tremors were noted; these drawings were later re-evaluated by an experienced neurologist. Persons with a tremor were included in Table 1 and not included in any further analyses, due to the fact that these persons show very different scores on the spiral draw-

ing variables. Second, each drawing was rated with a clinical score ranging from 0 to 4, according to the Archimedes spiral-drawing test of the International Cooperative Ataxia Rating Scale (ICARS).[12] As this rating scale is intended for patients with movement difficulties, we subdivided score 0: score 0A was given to drawings without any disturbances; score 0B was given to drawings with minor disturbances. Adhering to the ICARS, score 1 is reserved for drawings with impairment and decomposition, score 2 was given to drawings with a line completely drawn outside of the pattern and/or hypermetric swerves. Two persons with a score over 2 were excluded, because quantitative measures could not be reliably obtained from these drawings. Example spiral drawings and associated ratings are shown in Figure 1.

Quantitative analysis of spiral drawing

Automatic quantitative analyses were performed using custom-made software written in MatLab (version 8.1; The Mathworks, Natick, MA). This yielded the following outcome measures: movement time (seconds), defined by the time it took the participant to trace the spiral; length of drawing (cm), defined as the length of the drawn spiral; *average speed,* defined by the ratio of length of drawing and movement time; speed variability (cm/s), defined as the standard deviation (SD) of the instantaneous velocity; deviation from template (cm^2), defined as the area between the template and the drawn spiral; and number of crossings, defined as the number of times the drawn spiral crossed the template (Figure 1A). A smoothly drawn spiral with a clinical score of 0A would have a length of drawing about 56 cm (the length of the template) with little deviation from the template, a low variability in speed and no crossings (Figure 1B).

MRI acquisition & 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 T1-weighted sequence, and a fluid-attenuated inversion recovery (FLAIR) sequence.[22] We used Freesurfer to obtain grey and white matter brain volumes.[23] White matter lesion volumes were obtained using a k-nearest-neighbor classifier, according to a protocol previously described elsewhere.[24] Quality control of the brain volumes was performed based on all persons with a completed segmentation. According to a method previously described, outliers were defined as segmentations with an intracranial, cerebral or cerebellar volume outside a range of +/- 2.58 SD from the mean, stratified by sex.[25] A trained observer inspected all outliers (n = 214) and a random sample of 500 scans. From the random sample 9 scans were excluded due to poor segmentation quality, due to pathology (e.g. large arachnoid cysts, meningiomas) or technical problems (e.g. motion artefacts, susceptibility artefacts). From the outliers 31 scans were excluded. The total of 40 persons that were excluded were on average younger (M = 66.0, SD = 13.6) than the persons who were included (M = 69.0; SD = 10.1); t = -1.43, p = 0.16. Additionally, in the white matter lesion volume quantifications, 5 outliers were excluded. Brain volumes were available in 1,126 persons who also performed a fine motor skill assessment.

Table 1. Population characteristics

	No tremor n = 1,888	**Tremor present n = 24**
Age, years	77.4 ± 6.8	78.1 ± 4.3
Female, (%)	60.6%	33.3% *
Primary education only, (%)	20.7%	29.2%
Spiral drawing: clinical score		
0A	54.7%	N/A
0B	31.8%	N/A
1	13.0%	N/A
2	0.5%	N/A
Spiral drawing: quantitative data		
Length of drawing (cm)	57.6 ± 3.9	73.9 ± 18.6 *
Movement time (s), median (IQR)	16.4 (11.7 – 22.4)	12.8 (9.8 – 16.4) *
Average velocity (cm/s), median (IQR)	3.5 (2.6 – 4.9)	5.8 (4.3 – 7.6) *
Speed variability, median (IQR)	1.7 (1.3 –2.3)	3.8 (3.2 – 5.2) *
Deviation from template (cm^2), median (IQR)	5.8 (4.4 – 7.8)	11.9 (8.4 – 24.7) *
Number of times crossing template	5.3 ± 2.8	8.0 ± 5.6 *
Brain volumes [a]		
Intracranial volume, mL	1462.5 ± 162.7	N/A
Cerebral volume		
Cerebral grey matter, mL	454.8 ± 41.8	N/A
Cerebral white matter, mL	392.7 ± 52.8	N/A
Cerebellar volume		
Cerebellar grey matter, mL	97.8 ± 10.6	N/A
Cerebellar white matter, mL	22.0 ± 2.9	N/A
White matter lesion volume, mL	6.9 (3.5; 14.5)	N/A

Values are means ± standard deviation or percentages. Median and inter-quartile range (IQR) are given for variables with a skewed distribution. [a] Brain volumes were available in 1,126 persons. *Different for tremor and non-tremor when adjusted for age, sex, and level of education ($p<0.01$).

Statistical analysis

To test for differences between the persons with or without tremor we used analysis of covariance with age, sex, and level of education as covariates. Quantitative spiral drawing measures were standardized using z-scores to enable comparison between different variables. Drawing measures with skewed distributions (movement time (s), speed variability of movement (cm/s), deviation from template (cm^2)) were natural log transformed variables prior to z-scoring. To calculate mean scores per five years of age when controlling for sex differences we used analysis of covariance. To establish a linear or quadratic trend we used regression analyses. We related brain volumes to spiral

drawing measures using regression analyses while adjusting for age, sex, education and intracranial volume. White matter lesion volumes were natural log transformed because of skewness of the untransformed measure. To aid comparison between volumes, we used z-scores of brain volumes. When relating cerebral volume to spiral drawing measures, we additionally adjusted for cerebellar volume. Conversely, when relating cerebellar volume to spiral drawing, we additionally adjusted for cerebral volume. Leaving out these additional adjustments did not change the associations. We performed additional analyses modelling joint problems as an extra covariate, to test whether this would alter our findings. Analyses were performed using SPSS version 20.0 for Windows. Results are presented with 95% confidence intervals (CI).

Results

Characteristics of the study population are shown in Table 1. The mean age was 77.4 years with an age range from 48.7 to 96.3 years. In the overall population (n = 1,912) 24 persons with had a tremor in the drawing (1.3%). In men (2.1%) tremor occurred more often than in women (0.7%). Furthermore, all electronically collected data of the spiral drawing was different for persons with or without tremor ($p < 0.01$; Table 1). Notably, persons with a tremor had a greater average speed of drawing (median = 5.8 cm/s) compared to persons without tremor (median =3.5 cm/s).

Supplementary table 1. Partial correlations across all spiral drawing measures

n = 1,888	Clinical score	Length of the drawing (cm)	Movement time (s)	Average velocity (cm/s)	Speed variability	Deviation from template (cm^2)	Number of times crossings template
Clinical score	1						
Length of the drawing (cm)	0.07 (0.00)	1					
Movement time (s)	-0.45 (0.00)	0.43 (0.00)	1				
Average velocity (cm/s)	0.48 (0.00)	-0.32 (0.00)	-0.99 (0.00)	1			
Speed variability	0.59 (0.00)	-0.16 (0.00)	-0.90 (0.00)	0.92 (0.00)	1		
Deviation from template (cm^2)	0.66 (0.00)	-0.06 (0.01)	-0.54 (0.00)	0.55 (0.00)	0.62 (0.00)	1	
Number of times crossing template	0.10 (0.00)	0.36 (0.00)	0.09 (0.00)	-0.04 (0.06)	-0.03 (0.13)	-0.12 (0.00)	1

Values represent Pearson r coefficients (p-value) and are adjusted for age and sex.

We correlated spiral drawing clinical scores and quantitative measures (Supplementary table 1). We found that better clinical score showed a small (r = 0.06, p = 0.02) to moderate correlation (r = 0.66, p < 0.01) to better quantitative measures of spiral drawing. Since average speed was calculated by dividing length of drawing by movement time, movement time and average speed were highly correlated, also after correcting for age and sex (r = -0.99, p < 0.001). Therefore, we did not include average speed in any further analyses.

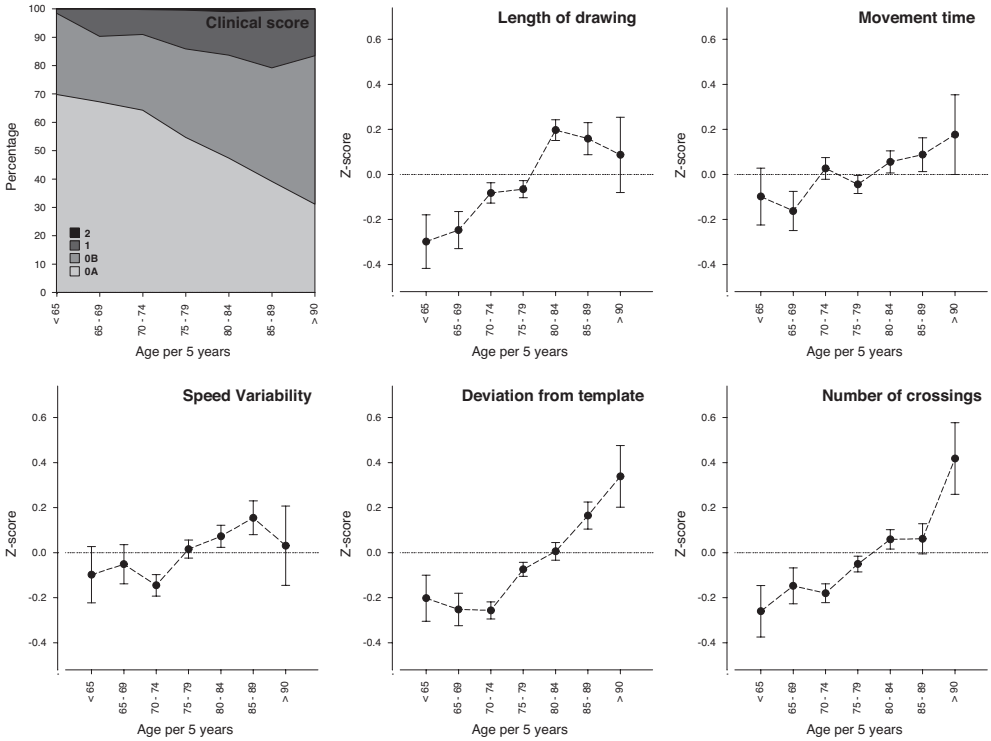

Figure 2. Age effects on fine motor skills. The x-axis represents age per 5 years and the y-axis represents the clinical score or z-score of the s spiral drawing measures. Error bars represent standard errors of the mean. Estimates are adjusted for sex. SD = standard deviation.

Figure 2 shows spiral drawing data as function of age, with participants grouped in five year intervals. Only 9 persons had a clinical score of 2 and this is therefore barely visible in the figure. Overall, with higher age the proportion of persons with a clinical score of 0B, 1 or 2 increased. Regarding the quantitative measures, older age was linearly related to worse performance on all spiral drawing measures, except for movement time. An additional quadratic effect of age was found for deviation from template. Persons in the age categories over 75 years old started to show an increasing deviation from the template. Adding persons with joint problems of the hand into these analyses, while using joint problems as a covariate, did not alter our results.

Table 2. The association of brain volumes with fine motor skills

n = 1,126	Clinical score	Length of drawing (cm)	Movement time (s)	Speed variability (cm/s)	Deviation from template (cm^2)	Number of crossings template
Cerebral grey matter [a]	**-0.06 (-0.10; -0.02)**	-0.09 (-0.20; 0.02)	0.05 (-0.07; 0.16)	**-0.13 (-0.24; -0.01)**	**-0.20 (-0.31; -0.09)**	**-0.12 (-0.24; -0.01)**
Cerebral white matter [a]	-0.03 (-0.07; 0.01)	0.05 (-0.06; 0.15)	**0.13 (0.02; 0.23)**	**-0.15 (-0.26; -0.05)**	**-0.14 (-0.25; -0.04)**	0.02 (-0.08; 0.13)
Cerebellar grey matter [b]	-0.01 (-0.04; 0.02)	0.02 (-0.04; 0.10)	-0.01 (-0.09; 0.07)	0.00 (-0.08; 0.08)	0.03 (-0.05; 0.11)	0.00 (-0.08; 0.08)
Cerebellar white matter [b]	-0.01 (-0.04; 0.01)	0.03 (-0.04; 0.10)	0.04 (-0.04; 0.11)	-0.02 (-0.09; 0.05)	0.01 (-0.06; 0.08)	0.06 (-0.02; 0.13)
White matter lesions	**0.04 (0.02; 0.07)**	0.04 (-0.02; 0.10)	0.00 (-0.07; 0.07)	0.04 (-0.03; 0.10)	0.06 (-0.01; 0.13)	0.01 (-0.05; 0.07)

Values represent standardized differences in spiral drawing characteristics per standard deviation increase in brain volume (95% confidence interval). Adjusted for age, sex, education, and intracranial volume. [a] Additionally adjusted for cerebellar volume. [b] Additionally adjusted for cerebral volume. Values in bold indicate significance at level $p < 0.05$.

In the 1,126 persons without tremor for which MRI scans were available, average intracranial volume was 1462.5 mL (SD = 162.7 mL). Table 2 shows associations between brain volumes and spiral drawing measures. Larger cerebral grey matter was related to better clinical score, less speed variability, less deviation from the template, a smaller number of crossings of the template. Larger cerebral white matter was related to a longer movement time, smaller speed variability, and smaller deviation from the template. Cerebellar grey and white matter volumes were not related to any of the spiral drawing measures. Larger white matter lesion volume was related to a worse clinical score of the spiral drawing.

Discussion

Compared to persons without a tremor, persons with a tremor (1.3% of the participants) showed worse performance on most spiral drawing measures, except that they drew faster in a shorter amount of time. We found that older age was related to a worse performance on all measures of fine motor skill. Furthermore, larger cerebral volume was both related to better clinical score and better quantitative measures of fine motor skills. Larger white matter lesion volume was related to worse clinical score, but not to the quantitative measures. Cerebellar volume was not related to any of our measures of fine motor skills.

Strengths of this study include the population-based design in a large group of middle-aged and elderly and the availability of both clinical scores and electronically obtained spiral drawing data. Therefore, we were able to give precise estimates of fine motor function in the general elderly population. Furthermore, MRI scans were available in a subsample of the study population, which enabled us to study the relation of brain volumes and fine motor skills in an elderly study sample. An important limitation of the study is the absence of objective diagnoses of Parkinson disease and other diseases of the central or peripheral nervous system that are known to affect motor skills. Unfortunately, we only had data on self-reported Parkinson disease, and one person reported to be diagnosed with autosomal dominant cerebellar ataxia. These persons were removed from the analyses. Adjusting for problems of the joints did not alter our findings. However, we only had data available of self-reported rheumatoid arthritis or osteoarthritis and no other objective measures of problems in the hand or arm that could have influenced performance on the spiral drawing test.

We found that only 1.3% of persons in a general elderly population had an action tremor. This is low in comparison to most other prevalence studies, although there is a large variation. In a meta-analysis, essential tremor prevalence was estimated to be between 0.4% and 6.3%.[26] Establishing reliable tremor prevalence is difficult due to the increasing prevalence with older age and also possible ethnic differences.[27] Recently, a community-based study in Brazil reported a prevalence of 17.4% for unspecified tremor in persons over 65 years.[28] Several factors are likely to contribute to our relatively low estimates of tremor occurrence. For instance, our study included younger persons, and participants did not receive a neurological examination. Therefore we were unable to

formally diagnose and distinguish tremor type.[29] Relatively more frequent, a tremor was found in men compared to women. In agreement, sex differences in tremor have been described in adults and children.[30, 31]

We showed age effects on fine motor skills for both clinical score and quantitative spiral drawing measures. Since we created standardized scores for the quantitative measures, we were able to compare which measures were affected more strongly by age. We saw an increase in length of drawing and number of times crossing the template. Movement time and speed variability showed a less steep increase with older age. Linear effects of age were previously found for simpler fine motor tasks such as the Purdue Pegboard and finger tapping tasks.[32-34] Deviation from the template seemed to stay stable up to age 75, and thereafter showed a more steep increase. Such non-linear effects of age were previously found to affect the amount of time needed to finish demanding fine motor tasks.[4] Clinical scores detect age effects, but quantitative measures give extra information about movement time and speed variability.

Larger cerebral grey matter was associated with a better clinical score and a lower amount of crossings of the template. Thus, persons with a larger grey matter volume drew with a more stable speed, while persons with a smaller grey matter volume drew with a more varying speed. Larger cerebral white matter volume was related to a longer movement time. Apparently, persons with more cerebral white matter volume took more time to complete the spiral drawing. Furthermore, larger white matter lesion volume was related to worse fine motor skills measured by clinical score, but not to quantitative measures. White matter integrity has been related to fine finger movement,[35] although other researchers found no relation between white matter hyperintensities and fine motor performance.[36, 37]

Although the cerebellum is known to be involved in fine motor skills, surprisingly neither cerebellar grey matter nor cerebellar white matter volume was related to the spiral-drawing test, which was developed to detect problems in cerebellar functions.[12] Since we had expected to find less variability due to the fact that we used a clinical score in a normal elderly population instead of a patient sample, we had already added an extra category to our clinical score before starting the scoring procedure. Still, this clinical score may not have been sufficiently sensitive to detect an association with cerebellar volume. We were also unable to detect associations between cerebellar volume and quantitative measures of spiral drawing. This leads us to conclude that our measure of cerebellar volume was not sensitive enough to detect any relation to fine motor skills. Particular areas of the cerebellum may show a relation with motor skill as has often been found in functional imaging or lesion studies.[38, 39] In addition, the motor task used in this study may not have been suitable to detect relationships between cerebellar volume and fine motor skills in a general elderly population, especially since it was developed to assess motor skills in patients.[12]

In conclusion, older age was related to worsening of fine motor skills, as was observed by a worsening clinical score. Also, age affected different quantitative measures of the spiral drawing test that reflect different aspects of fine motor skills. Furthermore, we found associations between larger

cerebral volume and better clinical and quantitative spiral drawing measures. The absence of association between cerebellar volume and fine motor skills is in contrast to common findings of an important cerebellar involvement in fine motor skills. Future studies would benefit from using a more extensive subdivision of cerebellar volume. Relating these subdivisions of the cerebellum to various aspects of fine motor skills, may provide relevant insights into the etiology of cerebellar malfunction.

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Chapter 4.3

Late effects of adjuvant chemotherapy for breast cancer on fine motor function

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** These authors contributed equally*

Abstract

Introduction Adjuvant chemotherapy for breast cancer has been associated with cognitive problems and simple tasks of fine motor skill. However, most motor tests used did not allow differentiating between effects on speed and accuracy. The current study aims to investigate late effects of adjuvant chemotherapy for breast cancer on fine motor function, using both speed and accuracy measures.

Method We compared fine motor function of 174 women who had received adjuvant Cyclophosphamide-Methotrexate-5-Flurouracil (CMF) chemotherapy for breast cancer on average 20 years ago, to that of a population sample of 163 women without a history of cancer. Fine motor function was measured with the Purdue pegboard test and the Archimedes spiral test.

Results The group of chemotherapy-exposed breast cancer survivors was slower but had a more constant velocity in drawing an Archimedes spiral than the reference group. Furthermore, in the chemotherapy-exposed subjects we found that older age related to more crossings of the spiral template and more return movements. Such relationships were not observed within the reference group. No between group differences were found for any of the Purdue Pegboard measures.

Discussion Compared to a population-based reference group, chemotherapy-exposed breast cancer survivors demonstrated motor slowing, steadier performance, and a marginally higher rate of errors while drawing an Archimedes spiral. This suggests that adjuvant CMF chemotherapy for breast cancer is associated with a change in strategy of motor performance and long-term worse motor functioning. Furthermore, the Archimedes spiral test is a sensitive measure to detect adjuvant chemotherapy-related changes in motor performance.

Introduction

Adjuvant chemotherapy for breast cancer has been associated with cognitive problems [1] up to decades post treatment,[2] and has been related to structural as well as functional brain changes.[3] The most prominent cognitive sequelae of adjuvant chemotherapy are observed in the domains of learning and memory, processing speed, and executive functioning.[1] We previously found that chemotherapy-exposed long-term (i.e., ~20 years post-treatment) breast cancer survivors performed worse with their non-dominant hand on the Purdue pegboard test.[4] Moreover, out of 13 [4-16] studies investigating the adverse effects of chemotherapy that included a measure of motor function in their test battery, 8 reported worse performance in the group of chemotherapy-exposed breast cancer survivors compared to either baseline (i.e., pre-chemotherapy) measurements [8, 9, 12, 14, 16] or non-cancer control subjects.[4, 10, 13] The other five studies of these 13 reported no differences in motor skills between groups, or from baseline in the chemotherapy-exposed subjects. Motor skill tests that were used in these studies were either finger tapping tests [17] or versions of the pegboard test.[18] The finger tapping test measures motor speed and is an indirect measure of the integrity of the cortical motor areas and efferent motor pathways.[17] Pegboard tests assess eye–hand coordination, dexterity, and motor speed and thus require sensorimotor integration and a high level of motor processing.[18] Nevertheless, these measures only provide insight into a small spectrum of fine motor functioning and are not able to distinguish between speed and accuracy.

A motor test that does allow separation of different aspects of motor skills is the computerized version of the Archimedes spiral-drawing test.[19] Different outcomes can be derived from this test, including movement time, speed variability, and spatial deviation from the spiral template. These outcome measures can provide insight into both speed and accuracy aspects of fine motor skills.

The number of long-term chemotherapy survivors is rapidly increasing,[20] and impairment of manual fine motor skills may reduce quality of life.[21] Therefore, it is increasingly relevant to report effects of adjuvant chemotherapy on fine motor skills. The aim of this study was to investigate effects of adjuvant chemotherapy for breast cancer on speed and accuracy measures of fine motor skills. We compared performance on the Archimedes spiral-drawing test of 174 women who had received adjuvant chemotherapy for breast cancer on average 20 years before, to that of 163 women who had never been diagnosed with cancer. In addition, we looked if results from the spiral test corroborated with those of the Purdue pegboard test and if the spiral test is a more sensitive measure of motor dysfunction.

Methods

Participants

We compared chemotherapy-exposed breast cancer survivors to a reference group of non-cancer reference subjects. The reference group was selected from the Rotterdam Study: an ongoing population study in the Netherlands.[22] The review boards of the participating institutes (the Netherlands Cancer Institute and the Erasmus University Medical Center) approved this study. All participants gave written informed consent.

Chemotherapy-exposed subjects

From the registries of the Netherlands Cancer Institute and the Erasmus University Medical Center-Daniel den Hoed Cancer Center we identified consecutive female breast cancer patients who, as part of their primary treatment had received six cycles of adjuvant CMF chemotherapy (Cyclophosphamide 100 mg/m^2, taken orally, on days 1-14, Methotrexate 40 mg/m^2, given intravenously, on days 1 and 8, 5-Fluorouracil 600 mg/m^2, given intravenously, on days 1 and 8) between 1976 and 1995. Eligibility criteria included age between 50 and 80 years at recruitment time in 2008, and sufficient command of the Dutch language. Only women who never had had a relapse, secondary primary tumor or distant metastasis were selected. Exclusion criteria were ever use of adjuvant endocrine therapy and contra-indications for MRI (MRI results have been presented elsewhere [23]). Subjects completed all examinations during one test session, which took place between October 2008 and October 2009. Of 196 subjects that participated in our previously published cognitive study,[2] 174 completed the Archimedes spiral test; none of these subjects had a tremor. Data on the Purdue Pegboard test was available in 165 persons (Table 1).

Reference group

The study was embedded in the Rotterdam Study, a prospective, population-based cohort study that started in 1990 and investigates causes and consequences of age-related disease.[22] The initial cohort was expanded in 2000 and 2005 and currently totals 14,926 persons. The reference group included all women who were invited to the research center in the same time period (October 2008 – October 2009) as the breast cancer survivors. Of the 171 women who were invited, 165 completed the spiral drawing test. Two subjects were excluded, due to a tremor observed in the drawing that would interfere with the quantitative measures of the test. Therefore, 163 women were left for further analyses. In the reference group data was available on the Purdue Pegboard test for 158 persons.

Fine motor skill assessment

Fine motor skill was assessed using a) the Purdue pegboard test, and b) a computerized version of the Archimedes spiral drawing test. a) The Purdue pegboard test [24] is a test of dexterity and fine motor skill. Participants are asked to use their dominant hand, non-dominant hand and both hands to place as many metal pins as possible within 30 seconds in vertical rows of holes on a wooden board. In case of physical limitations, e.g. being unable to hold the pegs, or deviation from instruction, data were excluded from analysis. b) The computerized version of the Archimedes spiral test measures speed and accuracy functions of fine motor skills (see below) consists of a spiral template that was printed on a piece of paper attached to an electronic drawing board (WACOM Graphire Wireless Pen Tablet, model CTE-630BT). Participants were instructed to place the pen in the middle of the spiral before the tracing started (Figure 1A). They were not allowed to lean on the drawing board with their hand or arm. Participants were asked to trace the spiral as accurately and as fast as possible using their dominant hand.

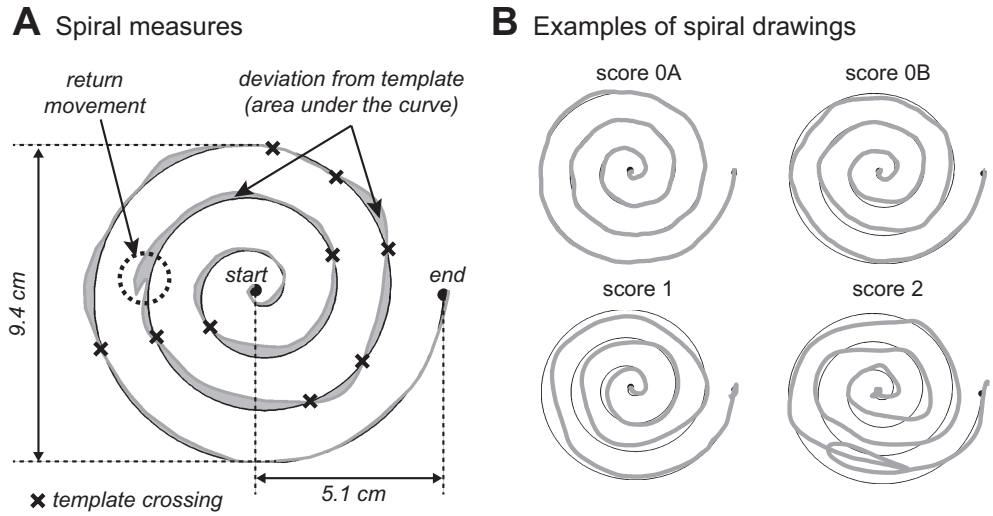

Figure 1. Examples of spiral drawing quantification and clinical scores. Figure 1A shows an example of the calculation of quantitative measures of fine motor skills. The start and endpoint are indicated by a dot, and the green line represents the drawing made by the participant. The figure explains how deviation from template, crossings and return movements are defined. Figure 1B shows examples of clinical scores of the spiral drawings with score 0A, 0B, 1, and 2.

Clinical scoring of spiral drawing

Pen position was recorded at a rate of 60 Hz and stored for offline quantitative analysis. Drawings of participants were evaluated visually to ensure proper data collection. Drawings were visually rated by a trained observer (YYH) for qualitative analyses. First, suspected tremors were noted; these drawings were later re-evaluated by an experienced neurologist (PJK, see acknowledgements). Two persons from the reference group with a tremor were excluded from any further analyses, due to the fact that these persons show very different scores on the spiral drawing variables. No tremors were observed in the chemotherapy-exposed subjects. Second, each drawing was rated with a clini-

cal score ranging from 0 to 4, according to the Archimedes spiral-drawing test of the International Cooperative Ataxia Rating Scale (ICARS).[25] This rating scale is intended for patients with movement difficulties, and thereby not very sensitive to detect minor deviations from normal motor performance. Therefore, we subdivided the original score 0 into two sub scores: score 0A was given to drawings without any disturbances; score 0B was given to drawings with minor disturbances. ICARS score 1 is reserved for drawings with impairment and decomposition, score 2 was given to drawings with a line completely drawn outside of the pattern and/or hypermetric swerves. Two persons with a score over 2 were excluded, because quantitative measures could not be reliably obtained from these drawings. Example spiral drawings and associated ratings are shown in Figure 1B.

Quantitative analysis of spiral drawing

Automatic quantitative analyses were performed using custom-made software written in MatLab (version 8.1; The Mathworks, Natick, MA). This yielded the following outcome measures: *movement time* (seconds), defined by the time it took the participant to trace the spiral; *length of drawing* (cm), defined as the length of the drawn spiral; *average speed,* defined by the ratio of length of drawing and movement time; *speed variability* (cm/s), defined as the standard deviation (SD) of the instantaneous velocity; *deviation from template* (cm^2), defined as the area between the template and the drawn spiral; *number of crossings*, defined as the number of times the drawn spiral crossed the template and *return movements*, defined as the absence or presence of one or more return movements (i.e. brief movements in the opposite direction, see Figure 1A). A smoothly drawn spiral with a clinical score of 0A would have a length of drawing of about 56 cm (the length of the template) with little deviation from the template, a low variability in speed and no crossings or return movements (Figure 1B).

Statistical analysis

To test for group differences between chemotherapy-exposed breast cancer survivors and the reference group, we used analysis of covariance (ANCOVA) with age as a covariate. Additionally, we studied group differences with exclusion of outliers +/- 2.58SD from the mean. For all variables, the number of outliers never exceeded 6 (i.e., 1.78%) observations of the total sample. Median and interquartile range are presented for skewed variables (movement time, average velocity, speed variability, and deviation from template). These variables were natural log transformed prior to use in further analyses. To explore the possibility that level of education would confound the relation between differences in motor functions between groups, we studied the relation between level of education and our outcome variables (Purdue Pegboard scores, and Spiral test measures). Within the chemotherapy-exposed breast cancer survivors, we found that higher level of education related to a better clinical score. In the reference group we found that higher level of education related to a fewer number of crossings. No relationships were found between level of education and any of the

other 9 outcome measures. Since a variable can only be considered a confounder if it relates to both exposure and outcome,[26] we added level of education as a covariate in analyses regarding clinical score and number of crossings.

In order to test whether movement time influenced the quality of the drawn spiral in the Archimedes spiral-drawing test, we added movement time as a covariate to test for group differences on the other outcome parameters including deviation from template, number of crossings and return movements. However, this adjustment did not change the results and is therefore not reported. Finally, we related age and fine motor skills using regression analyses. First, all variables, except clinical score and return movements (due to their categorical nature), were standardized using z-scores to enable comparison between different variables. To test for group differences, we added an age-group interaction term. Using level of education as a covariate in our regression model, studying age effects on motor performance did not change the results in Table 2, and are therefore not discussed any further. All analyses were performed using the statistical software package SPSS version 20.0 for Windows. Results are presented with 95% confidence intervals (CI).

Results

Table 1 shows characteristics of the chemotherapy-exposed breast cancer survivors and the reference subjects. No significant differences in age or handedness were found between groups. Performance on the Purdue Pegboard task was not different between the two groups. In the Archimedes Spiral drawing test, breast cancer survivors on average had a better clinical score on the spiral-drawing test than the reference group. However, after adjusting for age, we found that their median movement time was 2.7 seconds longer ($p = 0.03$), their average velocity was lower ($p = 0.04$), and their speed was less variable ($p = 0.048$) compared to the reference group. Adding level of education as a covariate made the difference in clinical score between groups disappear ($p < 0.09$), but this did not change the results of the analysis on number of crossings of the spiral-drawing test. The proportion of chemotherapy-exposed breast cancer survivors that made return movements was larger than the proportion of subjects from the reference group who made return movements, but this did not reach statistical significance at the 5% level (10.4% more; $p= 0.06$).

Table 2 shows effects of age on fine motor skills for chemotherapy-exposed breast cancer survivors and the reference group. Older age was related to a worse clinical score for both groups. Older age was also related to a longer length of drawing for the chemotherapy-exposed breast cancer survivor group (0.039; 95%CI 0.020 to 0.057). No age effects were found for either group for movement time and speed variability. For both groups, similar effects of age were found for deviation from the template, and Purdue pegboard test using both hands and dominant hand only. Interaction effects of age and group were found for the number of crossings ($p = 0.009$) and return movements ($p = 0.002$). In the chemotherapy-exposed breast cancer survivor group, older age was related to a larger amount of crossings of the template (0.037; 95%CI 0.014 to 0.060) and a greater occurrence

of return movements (0.022; 95%CI 0.011 to 0.032). In the reference group, age was not related to these variables.

Table 1. Sample characteristics

	Chemotherapy-exposed breast cancer survivors	Reference group	Significance of group difference adjusted for age [a]
Age (years)	63.9 ± 6.3	62.8 ± 6.1	0.13
Left-handed, %	4.6%	4.9%	0.88
Primary education only, %	8.6%	12.3%	0.29
Spiral drawing, number of participants	n = 174	n = 163	
Spiral drawing: clinical score, %			
0A	70.7%	58.9%	0.09*
0B	20.7%	30.7%	
1	8.0%	9.8%	
2	0.6%	0.6%	
Spiral drawing: quantitative data			
Length of drawing (cm)	57.4 ± 2.9	57.1 ± 4.2	0.11
Movement time (s), median (IQR)	18.0 (11.5 – 24.8)	15.3 (11.6 – 20.8)	**0.03**
Average velocity (cm/s), median (IQR)	3.2 (2.3 – 4.9)	3.7 (2.7 – 4.8)	**0.04**
Speed variability, median (IQR)	1.5 (1.1 – 2.3)	1.7 (1.3 – 2.3)	**0.048**
Deviation from template (cm^2), median (IQR)	5.0 (3.9 – 6.9)	5.1 (4.2 – 7.1)	0.26
Number of times crossing template	5.1 ± 2.3	4.9 ± 2.4	0.09*
Presence of return movements, %	31.9%	21.5%	0.06
Purdue Pegboard, number of participants	n = 165	n = 158	
Purdue Pegboard both hands, number of pins	10.8 ± 1.6	11.0 ± 1.6	0.28
Purdue Pegboard dominant hand, number of pins	13.5 ± 2.0	13.6 ± 1.8	0.85
Purdue Pegboard non-dominant hand, number of pins	12.8 ± 1.8	13.2 ± 1.8	0.13

Values are means ± standard deviations (SD) or percentages. Median and inter-quartile range (IQR) are given for variables with a skewed distribution. P-values are given for age-adjusted group differences. [a] Outliers over 2.58 SD from the mean are excluded. * After additional adjustment for level of education.

Table 2. Effects of age for chemotherapy-exposed breast cancer survivors and reference subjects

	N = 174	N = 163	
	Chemotherapy-exposed breast cancer survivors	Reference group	P-value interaction*
Clinical score, per point	**0.017 (0.009; 0.025)**	**0.013 (0.004; 0.022)**	0.453
Length of the drawing, per SD increase	**0.039 (0.020; 0.057)**	0.029 (-0.001; 0.058)	0.563
Movement time, per SD increase	0.013 (-0.014; 0.040)	0.001 (-0.020; 0.022)	0.499
Speed variability, per SD increase	0.011 (-0.015; 0.037)	0.009 (-0.013; 0.031)	0.908
Deviation from template, per SD increase	**0.032 (0.010; 0.055)**	**0.033 (0.007; 0.058)**	0.981
Number of crossings, per SD increase	**0.037 (0.014; 0.060)**	-0.008 (-0.034; 0.018)	0.009
Return movements, yes/no	**0.022 (0.011; 0.032)**	-0.001 (-0.012; 0.009)	0.002
Purdue pegboard both hands, per SD increase	**-0.047(-0.068; -0.026)**	**-0.059 (-0.083; -0.035)**	0.457
Purdue pegboard dominant hand, per SD increase	**-0.058 (-0.079; -0.037)**	**-0.045 (-0.069; -0.022)**	0.432
Purdue pegboard non-dominant hand, per SD increase	**-0.054 (-0.075; -0.033)**	-0.024 (-0.050; 0.001)	0.078

Values represent differences in z-scores per year increase (95% confidence interval). * P-value of interaction between group and age.

Discussion

Our aim was to investigate long-term effects of adjuvant chemotherapy for breast cancer on fine motor skills. We compared women who received adjuvant CMF chemotherapy for breast cancer on average more than 20 year before, to a group of age-matched women from the general population who had never been diagnosed with cancer. We found that the group of chemotherapy-exposed breast cancer survivors was slower but had a more constant velocity in drawing an Archimedes spiral than the population-based reference group. No significant differences in other measures of the Archimedes spiral test, such as length of drawing, deviation from the template, and number of crossings were observed. The proportion of chemotherapy-exposed breast cancer survivors who made one or more return movements was marginally significantly larger than the proportion of those subjects from the reference group. These findings could indicate that the chemotherapy-exposed survivors adopted a different strategy in completing the Archimedes spiral test. An increased prevalence of return movements in combination with increased movement time could indicate a more conscious approach, or 'top-down' processing of drawing the Archimedes spiral. This would correspond well with changes in strategy selection that have been observed in normal aging, such as being more conservative in speed-accuracy tasks.[27, 28] Results from the current study show a differential effect of age on motor performance (see Table 2); with increasing age the chemotherapy-exposed subjects more often crossed the spiral template and made more return movements. Such relationships were not observed within the reference group. An increase in return movements in the chemotherapy-exposed group could indicate strategy changes and hence accelerated aging.

This is in line with a previous report which concluded that accelerated neurocognitive decline and physiological degeneration that result from chemotherapy indicate early onset frailty.[29] However, age-related changes in cognitive strategy have been mainly reported in the domains of memory, reasoning, problem solving, decision-making, and language and not much is known about strategic changes in psychomotor speed or neuro-motor behavior. Additional correction for movement speed in the analysis of error measures (i.e., deviation from the template, return movements, and number of times crossing the template) did not change the outcomes of these analysis, indicating that the group differences we observed can not simply be explained by as a speed-accuracy trade-off. The effect of age-related strategy changes on motor performance needs to be elucidated in future studies.

It has been postulated that voluntary speed smooth (non-ballistic) hand movement is a function of the basal ganglia,[30] and age-related slowing of movement was previously associated with basal ganglia dysfunction.[31] The cerebellum is also known to have an important role in eye-hand coordination and the production of smooth and coordinated movements.[32, 33] More specifically, Ebner et al. proposed a role for the cerebellum in the control of arm movement velocity.[34, 35] Several neuroimaging studies have reported adverse effects of adjuvant chemotherapy on the structure and function of motor brain regions. Structural MRI studies revealed long lasting decreases in cerebellar gray matter volume,[36, 37] and posterior parts of the brain up to 10 years post-treatment.[36] A resting state fMRI study showed that chemotherapy-exposed cancer survivors had long lasting changes in functional network organization of several brain regions including the striatum.[38] Hypometabolism of among others the cerebellum and putamen was observed using positron emission tomography (PET) imaging in lymphoma patients treated with adjuvant chemotherapy.[39] Chemotherapy-related changes in brain motor areas may explain the poorer motor performance of the chemotherapy-exposed breast cancer survivors compared to that of the population-based control group that we observed. Although the effects of chemotherapy on motor function may be the result of effects of chemotherapy on motor brain regions as described above, it is likely that the underlying mechanisms are not specific to these regions, but are more diffuse in nature and also are accountable for the well-described chemotherapy-induced cognitive dysfunction.[1] It is therefore important to investigate multiple functional outcomes (i.e., cognition, motor function, mood) simultaneously instead of treating them as separate entities. The small to moderate effects of chemotherapy on various individual functional outcomes could together significantly affect quality of life.

In one of our previous studies in a largely overlapping group of chemotherapy-exposed breast cancer survivors and a partially overlapping group of population-based control subjects we did observe that the breast cancer survivor group had smaller total gray matter volume than the reference group, but we were unable to attribute this volume difference to a particular brain region.[23] Note that subjects in this study were not entirely overlapping with subjects in the current study due to the fact that the Archimedes spiral-drawing test was not available in exactly the same subjects. Previously, we reported that chemotherapy-exposed breast cancer survivors had significantly worse scores than population-based reference subjects on the Purdue pegboard test performed with their non-dominant hand, but not with their dominant hand or both hands.[4] Despite the largely overlapping sample, results from the current study do not show significant performance differences on the

Purdue pegboard between the chemotherapy-exposed breast cancer survivors and the reference group. However, the group mean scores are almost identical to the ones we reported previously.[4] Our previous study had a much larger reference group (i.e., 1509 subjects) than the current study, and thus it had more power to detect differences between groups. We therefore conclude that there is a very small difference in psychomotor speed for the non-dominant hand, but that this difference is not reliably detectable with our current sample. In this light, it is of interest to see that that the Archimedes spiral-drawing test was able to detect significant differences between the groups, despite the relatively small number of participants. This suggests that the computerized Archimedes spiral test is a sensitive measure to detect adjuvant chemotherapy-related changes in motor performance. Although CMF chemotherapy is no longer the main adjuvant treatment of choice for breast cancer, we think our results may still apply to contemporary regiments considering that these regimens still incorporate Cyclophosphamide and 5-Flurouracil. In addition, cisplatin-based chemotherapy has also been associated with worse fine motor skills.[40]

Two drawbacks of the present study need to be addressed. First, its cross-sectional design prevents us to make causal inferences about the relationship between adjuvant chemotherapy for breast cancer and motor performance. Prospective longitudinal studies that include motor assessment could give more insight in the nature of the observed association. Second, we compared chemotherapy-exposed breast cancer survivors to subjects who were never diagnosed with cancer. Therefore, we cannot separate the effects of cancer and cancer treatment. Strengths of our study include the large number of chemotherapy-exposed breast cancer survivors and the large number of control subjects. In addition, we looked at the effects of chemotherapy on motor performance on average more than two decades post-treatment, and therefore we are able to report on the very late, potentially lasting effects of adjuvant chemotherapy. This is the first study that specifically investigates the effects of adjuvant chemotherapy on motor performance, and the first study that combines different measures of motor behavior to parcel out the different aspects of fine motor functioning.

Conclusions

Compared to a population-based reference group, and on average more than 20 years post treatment, chemotherapy-exposed breast cancer survivors demonstrated motor slowing, steadier performance, and a marginally higher rate of errors while drawing an Archimedes spiral. This indicates that adjuvant CMF chemotherapy for breast cancer is associated with long-term worse motor functioning.

Up until now, most behavioral studies on the effects of adjuvant chemotherapy have focused on the adverse cognitive effects of this treatment. Future studies should include motor performance tests to further investigate the adverse effect of chemotherapy on motor functioning, shortly and at longer times post treatment. To gain more insight in the neural mechanisms of chemotherapy-induced motor dysfunction, studies in chemotherapy-exposed cancer patients that combine neuroimaging and motor behavioral outcome measures are warranted.

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Chapter 5

General discussion

The aim of the research reported in this thesis was to describe age effects on multiple aspects of cognition and motor function and to further explore the relation between cerebral and cerebellar volumes with cognition and motor function in a population of middle-aged and elderly persons. To study brain volumes, we used automated segmentations of the brain acquired by structural magnetic resonance imaging. The brain can be divided in a multitude of smaller areas, however for the purpose of this thesis we focused only on grey and white matter tissue of cerebrum and cerebellum. Additionally, we looked at effects of white matter lesions and brain infarcts. Furthermore, we studied cognition using multiple cognitive tests. Motor function was assessed by an electronic walkway to study gait patterns and fine motor skills were tested using an electronic spiral drawing test. All research reported in this thesis is based on data of participants in the Rotterdam Study of 45 years and older. In chapter 4.3, results of participants of the Rotterdam Study were used as reference values, against which results of chemotherapy-exposed breast cancer survivors were tested. The current chapter presents a summary and review of the main findings and discusses the various considerations to the conducted research described in this thesis. Furthermore, directions for future research and clinical implications are explored.

Main findings

The main findings of this thesis are discussed. First, brain changes in a general population of middle-aged and elderly persons will be evaluated. Second, the relation between age and cognition and motor function will be considered. Third, the relation between brain volumes and cognition and motor function will be discussed.

Brain changes

Cerebellar volumes are sometimes reported to remain stable in aging,[1-3] whereas strong rates of atrophy have also been described.[4-9] Previous estimates of cerebellar volume are mostly obtained from smaller studies or in a selected sample. MR imaging in a large sample of 3,962 persons allowed us to measure cerebellar and cerebral volume, and to investigate risk factors for both cerebellar and cerebral volumes. Cardiovascular risk factors and cerebrovascular disease have extensively shown to be related to cerebral atrophy.[10-12] In chapter 2 we described structural characteristics of the cerebellum with aging, and assessed the contribution of cardiovascular risk factors and cerebrovascular disease on cerebellar volume. We also compared determinants of cerebellar and cerebral volumes. We found only a moderate correlation between cerebellar and cerebral volume. Furthermore, the cerebellum contains relatively less white matter than the cerebrum. Smaller cerebellar volumes with advancing age were mostly driven by loss of white matter tissue. This finding is in disagreement with several previous imaging studies.[5, 8, 13, 14] However, a histological study of the cerebellum also demonstrated that the loss of cerebellar volume was mainly due to white matter loss.[15] Diabetes, glucose and cholesterol level were found to be cardiovascular determinants for cerebellar vol-

ume. The strong relationship between diabetes and cerebellar volume was not reported elsewhere. Interestingly, a link between diabetes and clinical cerebellar symptoms was previously described.[16] Furthermore, our findings contrasted a previous study that suggested that the cerebellum is better protected from high glucose levels than the cerebrum. Higher fasting glucose and lower HDL cholesterol levels related to cerebellar volume, and did not relate to cerebral volume. Moreover, while smoking and lower diastolic blood pressure were related to smaller cerebral volume, no effects of smoking and blood pressure were found on cerebellar volume. The absence of association between ApoE e4-carriership and cerebellar or cerebral volume is in agreement with other investigations studying non-demented participants.[9, 17, 18] The presence of isolated supratentorial cortical infarcts was unrelated to cerebellar volume. However, the presence of isolated supratentorial lacunar infarcts did relate to smaller cerebellar volumes. Lacunar infarcts are considered an important hallmark of cerebral small vessel disease.[19] Therefore, the relation between cerebral lacunar infarcts and smaller cerebellar volume indicated that the cerebellum is also affected by small vessel disease. This study showed that we cannot assume that determinants of cerebellar volume are identical to those established for cerebral volume. However, as we showed that supratentorial lacunar infarcts and white matter lesions are related to smaller cerebellar volume, this study also demonstrates the interconnectivity between cerebrum and cerebellum.

Cognition and motor function

Chapter 3.1 gives an overview of age-related changes in various cognitive tests. The effects of age were studied in a population of non-demented community-dwelling middle-aged and elderly persons. The strongest association with age was found for general cognitive function or g-factor, which we quantified using principal component analysis. The g-factor is a stable concept, comprising the shared variance between cognitive tests, and can be interpreted as a common underlying factor to multiple cognitive domains.[20-22] This was followed by fine motor skill, processing speed, and visuospatial ability. Fine motor skill was measured by performance on the Purdue Pegboard test, for which participants were required to place as many pins in parallel rows of holes in 30 seconds, using left and right hand simultaneously. Processing speed was measured using the Letter-Digit substitution task, in which persons have to write down numbers underneath corresponding letters. Furthermore, visuospatial ability was measured by the Design Organization Test, a paper and pencil test that was based on and strongly correlates to the Block Design Test.[23] In comparison, immediate recall showed less decline over age, as was confirmed by formal testing. For most cognitive test results, decline was already visible from age 45 years. The smallest age effect was found on a memory subtest, in which participants are asked whether or not they recognize words shown 10 minutes before.

In a separate study, we also explored the association of visuospatial ability and other cognitive domains with dementia (chapter 3.3). We found that persons with worse visuospatial ability were more likely to have dementia. This is in agreement with previous findings that Block Design scores are especially low in Alzheimer patients.[24] We point out that our analysis included data of only

a small number of persons with dementia. However, we still established an association between presence of dementia and a worse visuospatial ability. As expected the strongest association with presence of dementia was found for tasks of immediate and delayed recall. Recognition performance was unrelated to presence of dementia. Thus, we found that in a non-demented population, older age relates most strongly to global cognitive function, fine motor skill, processing speed, and visuospatial ability, and not memory. When studying cognition in relation to dementia, memory is most strongly associated to dementia, and visuospatial ability also shows a strong relation with dementia.

Getting older is not only accompanied by decline in cognitive function. Motor functions are also likely to deteriorate. We studied both motor functioning of the arm and leg. In chapter 4.1 effects of age on changes in gait are explored. Poor gait is a risk factor for falls and associated with higher morbidity and mortality.[25-28] Using an electronic walkway, we studied thirty variables of not only normal walking, but also tandem walking and turning. Using PCA we found five components of gait representative of a normal walking pattern. These five components showed a high correspondence to those found in other studies summarizing gait factors in older adults.[25, 29, 30] *Rhythm* represents most temporal variables of a normal walk; *Phases* represents support time variables as percentages of gait cycle and double support time; *Pace* represents stride- and step length and velocity; and *Base of support* represents stride width and its variability, and *Variability* represents all variables concerning variability except for stride width variability. Additionally, we identified two new factors representing additional walking conditions. *Tandem* represents errors in the tandem-walk, and *Turning* represents the number of turning steps and turning time. We showed that Variability, Phases and Tandem, have the strongest association with age. Interestingly, variables that contribute to these components have also been associated with falls.[25-27, 31] Older age also related to worse *Pace* and *Base of Support*. However, these associations were not strong, and only showed decline at a higher age.

In chapter 4.2 we examined effects of age on fine motor skills of the hand. Participants of the study were asked to trace a template of the Archimedes spiral-drawing test with their dominant hand on an electronic drawing board. All drawings were visually inspected and a rated with a clinical score. Tremor was found in only 1.3% of the drawings, which were removed from further analyses, because these drawings interfered with the automatic quantitative analysis. Our tremor prevalence was low compared to other studies, which might be explained by the fact that our study population was relatively young. Furthermore, participants did not receive a full neurological exam and we were unable to formally diagnose tremor. We found that in persons without tremor, older age was related to a worse performance of fine motor function. This was reflected by the increased proportion of a worse clinical score in older age. Older age also related to a longer drawing, more variability in drawing speed, a larger deviation from the spiral template, and a larger number of crossings with the spiral template. Notably, a quadratic effect of age was found for the amount of deviation from the template made by participants, which confirmed the steeper increase in deviation from the template after age 75. Overall, our findings indicate that older age relates to worse fine motor function, which can be captured by clinical scoring. However, quantitative measures of the Archi-

medes spiral-drawing test can give more precise information about movement quality in aging due to the fact that certain aspects of fine motor skills affected earlier by age than others.

We also used the Archimedes spiral-drawing test to evaluate fine motor skills in breast cancer survivors and compared the results to a reference sample of the Rotterdam Study. Studies of long-term effects of chemotherapy have suggested that exposure to chemotherapy is related to early onset frailty.[32] Previous studies have mainly focused on late effects on cognitive function, while not much is known about changes in fine motor skills. In chapter 4.3 we studied long-term effects of adjuvant chemotherapy used in breast cancer treatment. We found that chemotherapy-exposed breast cancer survivors performed slower, steadier, and had a marginally higher error rate compared to the population-based reference group. This suggests that adjuvant chemotherapy for breast cancer is associated with long-term worsening of motor function. Furthermore, in the same study we looked at performance on the Purdue Pegboard test. We did not find clear differences between breast cancer survivors and our reference group. Therefore, we conclude that the electronic version of the Archimedes spiral-drawing test is a more sensitive measure to detect adjuvant chemotherapy-related changes in motor performance.

The investigations in this thesis show that effects of age on both cognitive and motor function can already be found in middle-aged persons of 45 years and older. Furthermore, the finding that various aspects of cognition and motor function are differentially affected by age, stress the importance of studying multiple cognitive domains, and multiple aspects of motor function at the same time. This will contribute to the unraveling of which skills we lose first when our brain functions begin to deteriorate.

Brain changes in relation to cognitive and motor function

The research in this thesis focuses on brain changes in aging that relate to both cognitive and motor function. In chapter 3.2 we investigated the contribution of cerebellar and cerebral volumes to various cognitive domains. We found associations between larger cerebellar volume and better cognitive performance in several domains. Cerebellar volume related to global cognition, executive function, information processing speed and fine motor skill. However, these associations were weak, and further attenuated when cerebral volume was taken into account. The lack of association between cerebellar volume and cognition, after adjustment for cerebral volume is remarkable, since many studies confirm a role for the cerebellum in cognitive function.[33-39] Possibly, the cerebrum is an intermediate factor in the association between cerebellum and cognition, which would mean that adjusting for cerebral volume is actually an overadjustment. Still, even in unadjusted models, effects of cerebellar volume on cognition were small compared to effects of cerebral volume.

Another methodological consideration pertains to the battery of cognitive tests used in the Rotterdam Study. This battery was specifically designed to examine cognitive function in the context of dementia. Perhaps the effects of cerebellar volume on cognition could be detected using a more

sensitive cognitive test battery that is tailor-made to cerebellar function. For example, previous studies have shown cerebellar involvement in spatial cognition. Although originally the neuropsychological test battery of the Rotterdam Study had not included any test of spatial cognition, we introduced the DOT as an extension of the test battery in 2008. In chapter 3.3 we related the cerebral lobes, cerebellum and supratentorial white matter lesions to DOT performance. In 2,963 persons free of dementia, we studied the association between brain volumes and performance on the DOT. We found that the cerebral lobes were all related to visuospatial ability, but no relation was found between cerebellar volume and visuospatial ability. The strong association we found between temporal lobe volume and visuospatial ability is consistent with previous findings that of deficits in visuospatial ability after temporal lobe damage and evidence from structural and functional imaging studies.[40-44]

The parietal lobe is consistently found to be involved in various tasks of visuospatial ability.[45] Therefore we had expected to find a stronger relation between parietal lobe volume and performance on the DOT. For the cerebrum, we found effects of cerebral grey matter volume were larger than those of white matter volume on visuospatial ability. In addition, we found that larger white matter lesion volume was related to worse visuospatial ability. No differential effects of white matter lesions of brain region were found. We speculated that the relatively stronger association of grey matter, rather than white matter, with visuospatial ability, might imply that the intactness of the temporal lobe itself and not its connections to other brain regions is of greatest importance for visuospatial ability. The absence of differential effects of effects of white matter lesions per region can also be considered supportive of this idea. Furthermore, we considered that the strong association between temporal lobe volume and visuospatial ability is congruent with findings that the temporal lobe may already be affected in cognitively healthy persons, and that visuospatial ability is already strongly affected in preclinical phases of dementia and healthy aging.[46, 47]

The role of brain aging in cognitive function has received much attention, but brain changes also affect motor function in the elderly. We investigated the relation of cerebellar and cerebral volumes with fine motor skills in middle-aged and elderly persons (chapter 4.2). We found that larger cerebral grey matter volume was associated with a better clinical score, a less variable drawing speed, less deviation from the drawing template, and lower amount of template crossings. Larger cerebral white matter volume related to taking more time to complete the spiral drawing. All findings were adjusted for intracranial volume, thus the relation between larger white matter volume, and a longer time needed to finish the drawing was not explained by larger head size. We also found an association between larger white matter lesion volume and worse fine motor skill, measured by clinical score, but not quantitative measures. Surprisingly, we found no relation between cerebellar grey or white matter volume and the spiral-drawing test, which was developed to detect problems in cerebellar functions.[48]

The investigations described in this thesis looked at global measures of brain structure, specifically cerebellar and cerebral volumes, in relation to brain functions covering multiple cognitive domains and multiple aspects of motor function, namely gait parameters and fine motor skills. Remarkably,

in none of our studies we found strong relations between cerebellar volume and cognition or motor function. In our investigations we only looked at cerebellar grey and white matter volumes in a relatively healthy aging population. Although we focused on rather global measures of the brain, e.g. grey and white matter of cerebrum and cerebellum, still we did find some associations between cerebral volumes and cognition and motor function. Thus, even though we studied a wide range of cognitive and motor functions, we were unable to associate global measures of cerebellar volume to any of the functions studied. In contrast, we did find cerebral volume related to global measures of cognition, executive function, information processing speed, visuospatial ability and fine motor skills. This leads us to conclude that although this thesis focused on rather grossly measured brain volumes, apparently this did not prevent the demonstration of relationships of the cerebrum with brain functions. In contrast, to find relations of the cerebellum and the same brain functions we need more precise structural or even functional measures.

Methodological considerations

Study design

The investigations described in this thesis were embedded in the Rotterdam Study, a population-based prospective study that started in 1990. We aimed to reduce selection bias by randomly inviting all participants over 45 years living in the Ommoord area.[49] However, inevitably some bias still remains as we know that participants are younger and usually in better health than non-participants. Furthermore, our study population mainly consists of Caucasian, middle-class persons, and therefore the results of our studies may not be generalizable to other ethnicities or socioeconomic groups.[50] We further aimed to minimize bias by requesting all participants to take part in a uniform protocol. Also, data acquisition and processing occurred in a standardized blinded manner. Moreover, we carefully considered possible confounders, and adjusted for confounders statistically, in case stratification or matching was not fitting. By adjusting for confounding variables in their unreduced form, e.g. keeping continuous variables as such in the model instead of a dichotomized version, we tried to keep residual confounding to a minimum. Another important consideration is that our objective was to study the relation between advancing age and variations in brain structure, cognition and motor function. Since the studies presented in this thesis are cross-sectional by design, our findings can only be interpreted as an approximation of aging effects. Moreover, especially with respect to our results linking brain volume to behavioral outcomes such as cognition and motor function, we can never truly determine direction of causality. In case of our study on late effects of chemotherapy in breast cancer survivors, we are unable to determine whether chemotherapy treatment, breast cancer or both, are responsible for the reduced fine motor skill performance of breast cancer survivors. Future studies will likely benefit from a longitudinal approach for which the results described in this thesis will be a valuable starting point.

Measuring cognition and motor function

There are some advantages to constructing compound scores to summarize cognitive or motor domains. For example, it reduces the problem of multiple testing, and results in more robust outcomes.[51] Furthermore, compared to presenting a long list of individual test outcomes, it gives a better overview of what happens in few cognitive domains. On the other hand, in constructing these compound scores, we have to deal with the problem of how to construct these scores. Compound scores could be made based on principal component analyses, but as this is not a test statistic and highly dependent on how one interprets the data, this may not be as objective as it might seem. Another way to form cognitive compound scores using multiple test outcomes is to base it on expert opinion of which test item represents a certain cognitive domain. Of course this is also very subjective. If there the number of cognitive tests to be studied is not very large, we can also consider presenting the separate test outcomes, rather than making compound scores. If clear definitions of the tests used are provided, the reader will then be able to form his or her own conclusions to which parts of cognition are involved. In this thesis we formed a g-factor, using principal component analysis. The g-factor is a stable concept that holds in different study samples.[52] However, since it is based on a complete case analysis, we need to keep in mind that results are only applicable to those participants who finished the complete cognitive test battery, thereby introducing biased estimates that are not representative to the whole study population. At the same time, participants are usually younger and in better health compared to non-participants, still the g-factor showed a strong decline with older age.

Brain measurements

Although there are some disadvantages to using automated segmentation of brain volumes, it becomes indispensable when analyzing large datasets and full manual segmentations for all participants are no longer feasible. The studies in this thesis relied on automatic segmentations of Freesurfer. This is a method frequently used to obtain brain volumes in larger study samples, where automatic segmentation is preferred over manual segmenting many MR images of the brain. Advantages of Freesurfer are that it can be used freely, and offers segmentation of both cerebral and cerebellar white matter and intracranial volume. To classify brain tissue into white or grey matter Freesurfer only takes into account information from T1-weighted scans, but still is able to attain a good grey and white segmentation. This was beneficial to our studies using cerebellar grey and white matter volumes, because the proton density sequence that is often used in our cerebral tissue segmentation, sometimes failed to include the more caudal located parts of the cerebellum.[11, 53] Even so, we also note that the white matter in the folia of the cerebellum is tightly packed and in our study often was of sub-voxel resolution. Therefore, our cerebellar grey and white matter volumes reflected the "bulk" anatomy and were not sensitive to subtle differences in the folia structure. An important disadvantage of the use of Freesurfer is that it lacks a detailed segmentation of the cerebellar lobules. Other studies have succeeded in segmentation of the cerebellar lobules and found differential age effects on cerebellar lobules. Furthermore, regional cerebellar volumes were successfully related to sensorimotor performance.[54, 55] Unfortunately, in this thesis we did

not investigate how a more precise measurement of parts of the cerebellum would have affected our findings with regard to the relation of cerebellar volume and cognitive function. In that light it is important to realize that not all functional changes in the brain are accompanied by structural brain changes (ch3.2, p13). While many functional imaging studies find a role for the cerebellum in cognition,[34, 56] cerebellar volumes may show less convincing evidence to support a role in cognition, especially in non-clinical study samples.

Future directions and clinical implications

Many people want to grow old, but in the healthiest way possible and preferably with all of their faculties remaining intact. Important faculties that are commonly affected in aging are cognitive and motor functions.

Brain imaging

As we strive for a better understanding of the brain in order to maintain its functionality in older age, future research should focus on identifying new possible risk factors for loss of brain tissue. As discussed in this thesis we described risk factors for both cerebral as well as cerebellar volume. We were able to describe brain-behavior relations for cerebral volume, but unfortunately not for cerebellar volume. As there are many ways to study brain structure, population-based studies should aim to use more advanced imaging techniques to investigate the role of the cerebellum in cognitive decline and motor functions. Possibly, automatic segmentation of the dentate nucleus using diffusion tensor imaging (DTI) will further enhance the understanding of a cerebellar role in cognition. The dentate nucleus is one of the cerebellar deep nuclei through which most output fibers leaving the cerebellum pass. Previous small studies have used DTI sequences to successfully segment the dentate nucleus, being the larger of the deep nuclei. Furthermore, DTI enables the quantification of the cerebellar peduncles connecting the cerebellum to the rest of the brain. Using DTI of the cerebellar peduncles will allow studying the conjunction of cerebellum and cerebrum.

Multiple types of tracer uptake studies (positron emission tomography[57], single photon emission computed tomography[58]) using varying tracers[59] (e.g. estimating amyloid presence or glucose uptake) to study whether certain brain regions have a higher uptake, have commonly used the cerebellum as a reference region. Some studies have criticized the use of the cerebellum as a reference region.[60-62] Nonetheless, the cerebellum is still often used as a reference region for amyloid positron emission tomography research, as it is believed not to accumulate amyloid.[63] Our study shows that profiles of risk factors differ between cerebrum and cerebellum. We recommend that neuroimaging studies take this difference in risk profile into account when choosing the cerebellum as a reference region.

Measuring cognition and motor function

Further studies should strive to involve a broad range of cognitive and motor tests in their research protocol. As was discussed in this thesis, certain brain functions are more easily affected by aging, and different brain areas may relate to specific tests. As it is not feasible to get participants to be assessed in an endless amount of testing, future research should also consider ways to gain a higher information density in assessment rounds. For example, we introduced new computerized versions of neuropsychological and motor assessments in the Rotterdam Study with regard to testing fine motor skill and obtaining information about gait patterns by the use of an electronic walkway using many sensors. By using electronic tests, a much higher information density could easily be obtained. Although implementing new computerized tests will require some investment, e.g. processing of increased quantities of data needs to be regulated and interpreted, it has large potential to gain many new insights in human behavior. Moreover, investigators should utilize statistical approaches such as item response theory to extract as much knowledge as possible from existing datasets.[64, 65]

Further studies on aging in cognition and motor function should also explore the relation between both functions. Exercise in older age is related to cognitive function, and studies in children have also shown a relation between motor function and cognition.[66-68] Also, some neuropsychological tests are difficult to categorize as a cognitive or motor test and as most tests depend on both cognitive and motor functions. As it is difficult to estimate the separate effects of cognition and motor function, it is a challenge to pull both apart and study how these are related in aging. A related issue concerns an important theory of cerebellar cognitive function, describes the effects of cerebellar cognitive dysfunction as dysmetria of thought, analogous to the dysmetria in faltering motor function.[69, 70] In this thesis we studied cerebellar volumes and cognitive and motor function. However, as we were unable to describe cerebellar-cognitive or cerebellar-motor relationships, we were incapable of providing evidence to support or contradict this theory. Future studies should aim to elucidate how brain areas contribute in producing smooth thinking and smooth movements and how this is best maintained in aging.

Clinical implications

We found that gross and fine motor skills were already affected in middle-aged persons. For gait parameters, we found that Variability, Phases, and Tandem walk, had the strongest association with age, showing a relation already in people of 50 to 55 years old. Variables that are part of these factors have been associated to fall risk.[25-27, 31] Thereby, assessment of normal gait and tandem walking in the elderly may aid in identifying people with an increased risk of falling. Since not all variables associated to falls are easily identified using visual assessment, electronic walkways may have a role in clinical practice to assess early gait disturbances. Furthermore, older persons may improve their gait pattern in order to minimize fall risk.[71] Similarly, fine motor skills are also already affected in middle-aged persons. Medical doctors should be aware of problems of fine motor skills at an early age that may cause a reduction in quality of life, and training can improve

manual fine motor skills.[72, 73] Thus, clinicians should keep in mind that motor function can start to decline rather early in life, and that improving motor function may aid in bettering quality of life. Moreover, we found that in a community-dwelling population of middle-aged and elderly persons, free of dementia, not memory but fine motor skill, information processing speed and visuospatial ability were affected mostly by age. Consequently, in a general non-demented population, memory is not the cognitive domain we should expect a decline at the fastest rate. For the current study, we lacked a sufficient amount of incident dementia cases, still we related visuospatial ability to presence of dementia. Future studies could test whether short visuospatial tests can be used to enhance dementia prediction.

The conclusions of this thesis have not resulted directly in changes in clinical practice. However, hopefully the results of this thesis offered a small contribution to a better understanding of the role of brain aging in cognitive and motor function. Ultimately, investigations of brain-behavior relations will, in the long run, be part of a foundation onto which evidence based medicine is based.

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Chapter 6

Summary / samenvatting

English summary

Aging is accompanied by loss of brain tissue, which can be quantified using magnetic resonance imaging. Brain changes can already be visible in absence of clinical disease of the brain. Still, even when no clinical disease is apparent, decline in brain functions can cause considerable discomfort in daily activities. Cognition and motor function are important brain functions that are affected by aging. Both functions are controlled by the cerebrum and cerebellum. However, most research has concentrated on either the role of cerebrum or cerebellum, and has taken place outside the scope of population-based imaging studies in community-dwelling elderly.

The aim of this research reported in this thesis was to describe age effects on multiple aspects of cognition and motor function and to further explore the relation between cerebral and cerebellar volumes with cognition and motor function in a population of middle-aged and elderly persons. All research was embedded in the Rotterdam Study, a population-based study among persons of 45 years and older in Ommoord, a district of Rotterdam, The Netherlands.

In chapter 2 determinants of cerebellar and cerebral volume in a community-dwelling elderly population were described. Using automatic segmentations of brain volumes acquired by magnetic resonance imaging performed in 3,962 persons, we investigated the relation of age, sex, cardiovascular risk factors, and the presence of infarcts with cerebellar volume, and its interrelationship with cerebral volumes. We found that 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. We concluded that determinants of cerebellar volume do not entirely overlap with those established for cerebral volume. We also found that the presence of infarcts or white matter lesions in the cerebrum affect cerebellar volume, and also that infratentorial infarcts can affect cerebral volume.

The next chapters report on effects of brain aging and cognitive function. In chapter 3.1 we studied cross-sectional age effects on cognitive function across various cognitive domains over 3,000 non-demented persons aged 45 – 99 years. In addition, we assessed general cognitive function by constructing a g-factor, which was based on principal component analysis and captured 49.2% of all variance in cognition. We found that age was most strongly related to general cognitive function. Furthermore, our findings led us to conclude that not memory, but fine motor skill, processing speed, and visuospatial ability are affected most by age. In a separate study of non-demented middle-aged and older persons, we investigated effects of cerebellar volume on several domains of cognitive function (chapter 3.2). We observed only a minor relation between larger cerebellar volume and better cognitive function that further attenuated after correcting for cerebral volume. We concluded that cerebellar volume has an association with cognition in aging, but that it is not the most prominent structure in this regard. The cerebellum is more likely to have a modulating role in cognitive functioning. However, it should be noted that a relation between cerebellum and cognition might only be detected with use of other imaging techniques, or a more sensitive cognitive test battery tailored to measure cerebellar functions. In chapter 3.3 we studied the association between visuospatial ability and presence of dementia. In a subsample of non-demented persons for which brain imaging was available, we also studied the relation of brain volumes and white matter lesions with visuospatial

ability. We showed that persons with worse visuospatial ability were more likely to have dementia. In a subsample of non-demented persons we found that larger cerebral grey matter volume, rather than white matter volume, was related to better visuospatial ability. Predominantly, effects were found for temporal, and frontal lobe volumes. Also, we found a relation between larger white matter lesion volume in any of the cerebral lobes and worse visuospatial ability.

In chapter 4 we studied brain aging and motor function. Gross motor function was studied using an electronic walkway to measure gait patterns. Fine motor function was studied using an electronic version of the Archimedes spiral-drawing test in which participants were asked to trace a spiral pattern on an electronic drawing board. In persons of 50 years and older, we studied thirty variables of gait, encompassing normal walks, turning and tandem walk (chapter 4.1). We found that gait variables could be summarized into five components representative of a normal walking pattern, including Rhythm, Phases, Pace, Base of support, and Variability. These factors showed a high correspondence to factors described in previous studies of gait. Also, two new components were identified which represented Tandem and Turning. The strongest associations with age were found for Variability, Phases and Tandem, which were the earliest to demonstrate a poorer gait pattern in older age.

In chapter 4.2 we studied the relation between age and fine motor skills using clinical scores and quantitative measures of the Archimedes spiral-drawing test. Also, we studied effects of brain volume on fine motor skills. We found a tremor in 1.3% of the participants. In persons without tremor, we found that older age related to worse fine motor skills, as was reflected by an increased proportion of a worse clinical score and worse quantitative measures in older age. Even though clinical scores captured decline in fine motor skill, quantitative measures of the Archimedes spiral-drawing test produced more precise information about movement quality in aging. We also found an association between larger cerebral volume and better fine motor skills. We found no association between cerebellar volume and fine motor skills, which contrasts common findings of cerebellar involvement in fine motor skills.

Finally, in chapter 4.3, we used the Archimedes spiral-drawing test to study the long-term effects of adjuvant chemotherapy for breast cancer treatment. We found that chemotherapy-exposed breast cancer survivors performed slower, steadier, and had a marginally higher error rate compared to a population-based reference group that was sampled from the Rotterdam Study. Our findings suggest that adjuvant chemotherapy for breast cancer is related to long-term worsening of fine motor skills. We also studied performance on the Purdue Pegboard test, in which participants are asked to place as many pins in parallel rows of small holes in 30 seconds. Using this test we did not find clear differences between breast cancer survivors and our reference group. Therefore, we concluded that the electronic version of the Archimedes spiral-drawing test is a more sensitive measure to detect adjuvant chemotherapy-related changes in motor performance.

Chapter 5 discusses main findings, methodological considerations, clinical implications, and directions for future investigations.

Nederlandse samenvatting

Veroudering gaat gepaard met verlies van hersenweefsel dat kan worden gekwantificeerd met behulp van 'magnetic resonance imaging' (MRI). Veranderingen in de hersenen kunnen reeds zichtbaar zijn in afwezigheid van klinische ziekte van de hersenen. Echter, zelfs wanneer er geen klinische ziekte blijkt, kan een achteruitgang van hersenfuncties aanzienlijke ongemak in dagelijkse activiteiten veroorzaken. Cognitie en motoriek zijn belangrijke hersenfuncties die beïnvloed worden door veroudering. Beide functies worden gereguleerd door de grote hersenen (cerebrum) en kleine hersenen (cerebellum). Desondanks hebben de meeste onderzoeken zich gericht op de rol van specifiek óf de grote hersenen óf de kleine hersenen. Daarbij heeft onderzoek veelal plaatsgevonden buiten het toepassingsgebied van grootschalige onderzoeken onder de algemene oudere bevolking die gebruik maken van geavanceerde beeldvormingstechnieken zoals MRI.

Het doel van het onderzoek beschreven in dit proefschrift was om binnen een populatie van personen van middelbare leeftijd en ouderen leeftijdseffecten op meerdere aspecten van cognitie en motorische functie te beschrijven, en daarbij het verband tussen volumes van de grote en kleine hersenen met cognitie en motoriek verder te verkennen. Al het onderzoek is ingebed in de Rotterdam Study, een populatiestudie in Ommoord, een wijk in Rotterdam in Nederland. Hieraan nemen personen van 45 jaar en ouder deel.

In **hoofdstuk 2** werden determinanten van volumes van de kleine en de grote hersenen in de algemene oudere bevolking beschreven. Met behulp van MRI verkregen we automatisch gesegmenteerde hersenvolumes van 3.962 personen. Hiermee onderzochten we de relatie tussen leeftijd, geslacht, cardiovasculaire risicofactoren, de aanwezigheid van infarcten en volume van de kleine hersenen, alsook de verhouding tot het volume van de grote hersenen. We vonden dat kleinere volumes van de kleine hersenen bij toenemende leeftijd vooral werden gedreven door verlies van witte stof. Diabetes, hoger niveau van serum glucose en een lager cholesterolgehalte waren gerelateerd aan een kleiner volume van de kleine hersenen. We concludeerden dat determinanten van het volume van de kleine hersenen niet volledig overlappen met de determinanten van het volume van de grote hersenen. Verder vonden we dat de aanwezigheid van infarcten of afwijkingen van de witte stof in de grote hersenen een invloed hadden op het volume van de kleine hersenen. Tevens vonden we dat infratentoriële infarcten het volume van de grote hersenen kunnen beïnvloeden.

De volgende hoofdstukken rapporteren over effecten van veroudering van de hersenen en cognitieve functie. In **hoofdstuk 3.1** onderzochten we de effecten van leeftijd op het cognitief functioneren in verschillende cognitieve domeinen in een groep van meer dan 3.000 niet-demente personen met een leeftijd van 45 - 99 jaar. Daarnaast hebben we de algemene cognitieve functie geëvalueerd door het vormen van een g-factor, welke werd gebaseerd op een principale componenten analyse en die 49,2 % van de variantie in cognitie verklaarde. We vonden dat leeftijd het sterkst gerelateerd was aan de algemene cognitieve functie. Bovendien leidden onze bevindingen tot de conclusie dat niet het geheugen, maar vooral fijne motoriek, verwerkingssnelheid en visueel-ruimtelijk inzicht het meest worden beïnvloed door leeftijd. In een afzonderlijke studie onder niet-demente personen van middelbare leeftijd en ouderen, onderzochten we effecten van het volume van de kleine hersenen op diverse domeinen van cognitieve functies (**hoofdstuk 3.2**). Wij observeerden slechts

een zwakke associatie tussen een groter volume van de kleine hersenen en een betere cognitieve functie. Deze relatie werd nog zwakker na een correctie voor het volume van de grote hersenen. Wij concludeerden dat het volume van de kleine hersenen geassocieerd is met cognitie tijdens veroudering, maar ook dat dit niet de meest belangrijke structuur is die samenhangt met cognitieve achteruitgang. De kleine hersenen hebben waarschijnlijk een modulerende rol in cognitief functioneren. Er moet echter worden opgemerkt dat een relatie tussen de kleine hersenen en cognitie waarschijnlijk alleen kan worden gedetecteerd door gebruik te maken van andere, meer gevoelige beeldvormingstechnieken dan die wij gebruikten, of door gebruik te maken van een gevoeligere cognitieve testbatterij die specifiek ontworpen is om het functioneren van de kleine hersenen te meten. In **hoofdstuk 3.3** hebben we de associatie tussen visueel-ruimtelijk inzicht en de aanwezigheid van dementie onderzocht. In een subgroep van niet-demente personen waarvoor MRI van het brein beschikbaar was, bestudeerden we ook de relatie tussen hersenvolumes en afwijkingen van de witte stof met visueel-ruimtelijk inzicht. We toonden aan dat personen met een slechter visueel-ruimtelijk inzicht vaker dement waren. In een subgroep van niet-demente personen vonden we dat groter volume van grijze stof sterker was gerelateerd aan een beter visueel-ruimtelijk vermogen dan het volume van de witte stof. We vonden voornamelijk effecten op de volumes van de temporaal- en frontaalkwab. Ook vonden we een relatie tussen een groter volume van laesies in de witte stof in elk van de kwabben van de grote hersenen enerzijds en een slechter visueel-ruimtelijk inzicht anderzijds.

In **hoofdstuk 4** bestudeerden we veroudering van de hersenen en motoriek. Grove motoriek werd onderzocht met behulp van een elektronische loopmat waarmee we looppatronen (of gangspoor) hebben gemeten. Fijne motoriek werd onderzocht met behulp van een elektronische versie van de Archimedes-spiraal test waarbij deelnemers werd gevraagd om een spiraalvormig patroon op een elektronisch tekenbord over te trekken. Onder personen van 50 jaar en ouder bestudeerden we dertig variabelen gerelateerd aan lopen. Deze omvatten normaal lopen, omkeren en koorddansersgang (**hoofdstuk 4.1**). Wij vonden dat de variabelen kunnen worden samengevat in vijf componenten representatief voor een normaal looppatroon, zoals Ritme, Fase, Tempo, Stapbreedte, en Variabiliteit. Er bleken veel overeenkomsten te zijn tussen deze factoren en factoren die in eerdere studies werden beschreven. Ook werden twee nieuwe componenten geïdentificeerd die Koorddansersgang en Omkeren vertegenwoordigen. De sterkste associaties met leeftijd werden gevonden voor Variabiliteit, Fase en Koorddansersgang. Deze componenten toonden vanaf de jongste leeftijdscategorie een verband aan met een slechter looppatroon.

In **hoofdstuk 4.2** bestudeerden we, met behulp van klinische scores en kwantitatieve maten voor de Archimedes spiraal test, de relatie tussen leeftijd en fijne motoriek. Ook hebben we gekeken naar effecten van hersenvolume op fijne motoriek. We vonden een tremor bij 1,3% van de deelnemers. Bij personen zonder tremor vonden we dat oudere leeftijd was gerelateerd aan slechtere fijne motoriek, wat tot uiting kwam doordat met het vorderen van de leeftijd meer mensen een slechte klinische score hadden. Voorts hing oudere leeftijd samen met slechtere kwantitatieve motorische maten. Hoewel door middel van klinische scores een achteruitgang in fijne motoriek kon worden aangetoond, gaven de kwantitatieve maten van de Archimedes spiraal test meer precieze infor-

matie over de kwaliteit van beweging bij veroudering. We vonden ook een verband tussen groter volume van de grote hersenen en een betere fijne motoriek. In tegenstelling tot vaak beschreven bevindingen over de betrokkenheid van de kleine hersenen bij fijne motoriek, vonden wij geen verband tussen het volume van de kleine hersenen en de prestatie op de Archimedes spiraal test.

Tenslotte hebben we in **hoofdstuk 4.3** gebruik gemaakt van de Archimedes spiraal test om de langetermijneffecten van adjuvante chemotherapie voor de behandeling van borstkanker te bestuderen. Wij vonden dat overlevenden van borstkanker die zijn blootgesteld aan chemotherapie langzamer en stabieler tekenden, en een marginaal hoger foutenpercentage hadden ten opzichte van de referentiegroep die werd gebaseerd op de Rotterdam Study. Onze bevindingen suggereren dat adjuvante chemotherapie voor borstkanker is gerelateerd aan een verslechtering van fijne motoriek op de lange termijn. We bestudeerden ook de prestaties op de Purdue Pegboard test. Hierbij wordt deelnemers gevraagd om binnen 30 seconden zoveel mogelijk pinnetjes te plaatsen in parallelle rijen van kleine gaten. Met behulp van deze test vonden we geen duidelijke verschillen tussen overlevenden van borstkanker en onze referentiegroep. We concludeerden dat de elektronische versie van de Archimedes-spiraal test een gevoeligere maat is om adjuvante chemotherapie-gerelateerde veranderingen in motorische prestaties te detecteren.

In **hoofdstuk 5** worden de belangrijkste bevindingen, methodologische overwegingen, klinische implicaties, en aanwijzingen voor toekomstige onderzoeken besproken.

Chapter 7

Dankwoord
List of publications
PhD Portfolio
About the author

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List of publications

Manuscripts based on the studies described in this thesis

Chapter 2
Hoogendam YY, van der Geest JN, van der Lijn F, van der Lugt A, Niessen WJ, Krestin GP, Hofman A, Vernooij MW, Breteler MMB, Ikram MA. Determinants of cerebellar and cerebral volume in the general elderly population. *Neurobiology of Aging* 2012;33(12):2774-81.

Chapter 3.1
Hoogendam YY, Hofman A, van der Geest JN, van der Lugt A, Ikram MA. Patterns of cognitive function in aging: The Rotterdam Study. *European Journal of Epidemiology* 2014;29(2):133-40.

Chapter 3.2
Hoogendam YY, van der Geest JN, Niessen WJ, van der Lugt A, Hofman A, Vernooij MW, Ikram MA. The role of cerebellar volume in cognition in the general elderly population. *Alzheimers Disease & Associated Disorders* 2014 Epub ahead of print.

Chapter 3.3
Hoogendam YY, Vernooij MW, van der Lijn F, Hofman A, Niessen WJ, van der Lugt A, Ikram MA, van der Geest JN. Visuospatial ability in relation to dementia and MRI correlates. *Submitted*.

Chapter 4.1
Verlinden VJ*, van der Geest JN*, **Hoogendam YY**, Hofman A, Breteler MM, Ikram MA. Gait patterns in a community-dwelling population aged 50 years and older. *Gait Posture* 2013;37(4):500-5. (*equal contribution)

Chapter 4.2
Hoogendam, Y.Y., Van der Lijn, F., Vernooij, M.W., Hofman, A., Niessen, W.J., van der Lugt, A., Ikram, M.A., van der Geest, J.N. Older age relates to worsening of fine motor skills: a population-based study of middle-aged and elderly persons. *Submitted*.

Chapter 4.3
Hoogendam YY, Koppelmans V, Ikram MA, Boogerd W, Seynaeve C, Seidler RD, Breteler MMB, van der Geest JN, Schagen SB. Late effects of adjuvant chemotherapy for breast cancer on fine motor function. *Submitted*.

Other Publications

Rijken BFM, Lequin MH, van der Lijn F, van Veelen-Vincent M, **Hoogendam YY**, Niessen WJ, Mathijssen IMJ. Syndromic craniosynostosis and Chiari I malformation: A volumetric study of the posterior fossa. *Submitted*.

Poels M*, Verhaaren B*, **Hoogendam YY***, Bos D*, Ikram MA*, Vernooij MW. De Rotterdam Scan Study: een grootschalig MRI-onderzoek naar hersenziekten. *Neuropraxis*, 1:14-23, 2012.

van der Lijn F, de Bruijne M, Klein S, den Heijer T, **Hoogendam YY**, van der Lugt A, Breteler MMB, Niessen WJ. Automated Brain Structure Segmentation Based on Atlas Registration and Appearance Models. *IEEE Transactions on Medical Imaging* 2012;31(2):276-86.

van der Lijn F, de Bruijne M, **Hoogendam YY**, Klein S, Hameeteman K, Breteler MMB, Niessen WJ. Cerebellum Segmentation in MRI Using Atlas Registration and Local Multi-Scale Image Descriptors. *Proceedings of IEEE International Symposium on Biomedical Imaging: Macro to Nano* 2009; 221 – 224.

PhD portfolio

Name:	Yoo Young (Jory) Hoogendam
Erasmus MC Department:	Epidemiology
Research School:	Nihes
Promotors:	Prof.dr. A. Hofman, Prof.dr. A. van der Lugt

Research skills

2008-2011 MSc in Health Sciences, specialization Genetic Epidemiology, Netherlands Institute for Health Sciences (Nihes), Rotterdam, the Netherlands (30 ECTS)

Oral Presentations

2010 Determinants of cerebellar and cerebral volume in the general elderly population', PhD seminar, Department of Epidemiology, Rotterdam, the Netherlands (1 ECTS)

2013 Aging of the cerebellum in the general elderly population: The Rotterdam Study', Neurophysiology seminar, Department of Neuroscience, Rotterdam, the Netherlands (1 ECTS)

Poster Presentations

2011 'Cerebellar and cerebral grey and white matter volumes: The Rotterdam Study', Alzheimer's Imaging Consortium (AIC), July 16, 2011 in Paris, France (1 ECTS)

2011 Cerebellar and cerebral grey and white matter volumes: The Rotterdam Study', Alzheimer's Association International Conference on Alzheimer's Disease, Paris, France (1 ECTS)

2011 'Gait patterns in the elderly and their association with cognition', Vas-Cog Society, Lille, France, September 11 -14, 2011 (1 ECTS)

International Conferences

2011 Alzheimer's Imaging Consortium (AIC), July 16, 2011 in Paris, France (0.5 ECTS)

2011 Alzheimer's Association International Conference on Alzheimer's Disease, July 16th - 21st, 2011, Paris, France (1 ECTS)

Seminars / Workshops / Courses

2007 SNPs and human disease, Molecular Medicine, Rotterdam, the Netherlands (1 ECTS)

2008-2013 Research Seminars, department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands (2 ECTS)

2008-2010 Research Seminars, department of Neuroscience, Erasmus MC University Medical Center, Rotterdam, The Netherlands (2 ECTS)

2011 Personal effectiveness training, Erasmus MC University Medical Center, Rotterdam, The Netherlands (2 ECTS)

2014 Career orientation training, Erasmus MC University Medical Center, Rotterdam, The Netherlands (1 ECTS)

Teaching

2008-2010 Teaching practicals in statistics to 4th year medical students, Rotterdam, The Netherlands (1 ECTS)

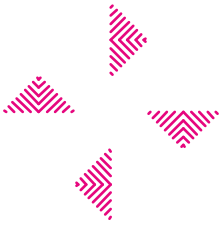
Other

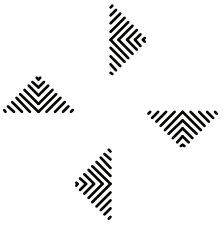
2009 Work visit with Research Institute for Diseases in the Elderly (RIDE scholarship to Kennedy Krieger Institute of Johns Hopkins University, Baltimore, United States (2 ECTS)

2014 Work visit to Prof.dr. R.D. Seidler, Neuromotor Behavior Laboratory, University of Michigan, Ann Arbor, United States (8 ECTS)

About the author

Yoo Young Hoogendam was born on September 11th, 1983 in Seoul, South Korea. After graduating in 2001 at the 'Northgo scholengemeenschap' in Noordwijk, she started to study psychology at Leiden University. She was selected for an honours research project and studied cognitive control functions in healthy elderly (supervisor: Prof.dr. K.R. Ridderinkhof). In 2005 she went to Canada to do her clinical internship and masters' research with early stage dementia patients. After obtaining a degree in Clinical- and Health Psychology in 2006, she obtained a Master of Neuroscience at Erasmus University Rotterdam. In 2008 she started the work described in this thesis at the department of Epidemiology of the Erasmus MC University Medical Center (head: Prof.dr. A. Hofman) under the supervision of Prof.dr. M.M.B Breteler (department of Epidemiology), Dr. M.A. Ikram (department of Epidemiology) and Dr. J.N. van der Geest (department of Neuroscience). In 2009 she received funding for a visit to Dr. A.J. Bastian to learn more about movement analysis at Johns Hopkins University. Before obtaining her PhD degree, she received a stipend to visit Prof.dr. R.D. Seidler at the University of Michigan. While working on her PhD projects she applied to medical school and obtained a Master of Health Sciences in Genetic Epidemiology at the Netherlands Institute for Health Sciences (Nihes). After receiving her PhD, she will enter her clinical internships to become a medical doctor.





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