Age-related decline in the brain: a longitudinal study on inter-individual variability of cortical thickness, area, volume, and cognition

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Abstract: Magnetic Resonance Imaging (MRI) studies have shown that cortical volume declines with age. Although volume is a multiplicative measure consisting of thickness and area, few studies have focused on both its components. Information on decline variability and associations between person-specific changes of different brain metrics, brain regions, and cognition is sparse. In addition, the estimates have often been biased by the measurement error, because three repeated measures are minimally required to separate the measurement error from person-specific changes. With a sample size of N = 231, five repeated measures, and an observational time span of seven years, this study explores the associations between changes of different brain metrics, brain regions, and cognitive abilities in aging. Person-specific changes were obtained by latent growth curve models using Bayesian estimation. Our data indicate that both thickness and area are important contributors to volumetric changes. In most brain regions, area clearly declined on average over the years, while thickness showed only little decline. However, there was also substantial variation around the average slope in thickness and area. The correlation pattern of changes in thickness between brain regions was strong and largely homogenous. The pattern for changes in area was similar but weaker, indicating that factors affecting area may be more region-specific. Changes in thickness and volume were substantially correlated with changes in cognition. In some brain regions, changes in area were also related to changes in cognition. Overall, studying the associations between the trajectories of brain regions in different brain metrics provides insights into the regional heterogeneity of structural changes. SIGNIFICANCE STATEMENT: Many studies have described volumetric brain changes in aging. Few studies have focused on both its individual components: area and thickness. Longitudinal studies with three or more time points are highly needed, because they provide more precise average change estimates and, more importantly, allow us to quantify the associations between changes in the different brain metrics, brain regions, and other variables (e.g. cognitive abilities). Studying these associations is important because they can provide information regarding possible underlying factors of these changes. Our study, with a large sample size, five repeated measures, and an observational time span of seven years, provides new insights about the associations between person-specific changes in thickness, area, volume, and cognitive abilities.

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A R T I C L E   I N F O

A B S T R A C T

Magnetic Resonance Imaging (MRI) studies have shown that cortical volume declines with age. Although volume is a multiplicative measure consisting of thickness and area, few studies have focused on both its components. Information on decline variability and associations between person-specific changes of different brain metrics, brain regions, and cognition is sparse. In addition, the estimates have often been biased by the measurement error, because three repeated measures are minimally required to separate the measurement error from person-specific changes. With a sample size of N = 231, five repeated measures, and an observational time span of seven years, this study explores the associations between changes of different brain metrics, brain regions, and cognitive abilities in aging.

Person-specific changes were obtained by latent growth curve models using Bayesian estimation. Our data indicate that both thickness and area are important contributors to volumetric changes. In most brain regions, area clearly declined on average over the years, while thickness showed only little decline. However, there was also substantial variation around the average slope in thickness and area. The correlation pattern of changes in thickness between brain regions was strong and largely homogenous. The pattern for changes in area was similar but weaker, indicating that factors affecting area may be more region-specific. Changes in thickness and volume were substantially correlated with changes in cognition. In some brain regions, changes in area were also related to changes in cognition. Overall, studying the associations between the trajectories of brain regions in different brain metrics provides insights into the regional heterogeneity of structural changes.

Significance statement

Many studies have described volumetric brain changes in aging. Few studies have focused on both its individual components: area and thickness. Longitudinal studies with three or more time points are highly needed, because they provide more precise average change estimates and, more importantly, allow us to quantify the associations between changes in the different brain metrics, brain regions, and other variables (e.g. cognitive abilities). Studying these associations is important because they can provide information regarding possible underlying factors of these changes. Our study, with a large sample size, five repeated measures, and an observational time span of seven years, provides new insights about the associations between person-specific changes in thickness, area, volume, and cognitive abilities.

1. Introduction

The brain undergoes pronounced structural changes with aging. Based on T1-weighted MRI data, many studies have described aging-related changes in different brain regions (Coupé et al., 2017; Fjell et al., 2014a, 2014b; Fjell and Walhovd, 2010; Frangou et al., 2020; Hoagey et al., 2019; Hogstrom et al., 2013; Lemaitre et al., 2012; Narvacan et al., 2017; Oschwald et al., 2019a; Pfefferbaum et al., 2013; Rast et al., 2018; Raz et al., 2010, 2005; Shaw et al., 2016; Storsve et al., 2014; Vidal-Pineiro et al., 2020; Vinke et al., 2018; Walhovd et al., 2011; Ziegler et al., 2012). Most previous studies have investigated changes in regional cortical volume, which can be estimated by the product of *thickness* and *area*. Even though volume is a multiplicative measure, only a few studies have focused on both its individual components and the relationship between these metrics (Hogstrom et al., 2013; Storsve et al., 2014). In the past few years, an increasing number of studies have analyzed cortical thickness changes in aging, but changes in area have received far less attention. In general, information about structural change

in aging mainly comes from cross-sectional data. Because of the large between-subject differences in brain structure, these estimates can be noisy and easily biased, even when the sample size is large. Longitudinal studies provide more precise estimates and, most importantly, allow the quantification of variation and associations between person-specific changes (Raz et al., 2005). Studying the associations between different brain regions and anatomical measures can provide information regarding the regional heterogeneity of changes in the brain and if possible factors of accelerating decline have a more global or more regional influence on the brain. Although more longitudinal studies have been conducted in the last years, information about these associations still remains very sparse (Raz et al., 2010, 2005; Sele et al., 2020).

The study of Storsve et. al (2014) is one of the few focusing on changes of cortical area, thickness, and volume over the lifespan, as well as on their interrelations. Changes in area were negatively correlated with changes in thickness in a relatively large number of vertices over the cortex. Storsve et. al (2014) further observed very strong correlations of changes in volume with changes in thickness, but not of changes in volume with changes in area. The authors concluded that changes in area and thickness each contribute individually to volumetric changes across the cortex, but that thickness changes are the main driver. However, because volume is a direct multiplicative measure of area and thickness, the estimated correlations seem to be heavily biased by the measurement error of thickness and area. Because the study by Storsve et al. (2014) only included two measurements per subject, it was not possible to disentangle the within-subject error from person-specific change.

The within-subject error consists of true deviations from the expected value of a person and the measurement error from the measuring device. Although the reliability of FreeSurfer is deemed to be very high (Liem et al., 2015), this can be deceptive as between-subject variance is included in the reliability calculations. Based on reliability studies and by using the cross-sectional processing pipeline in Freesurfer, the standard deviation of the measurement error for cortical thickness was estimated to be around or slightly below 0.1 mm for the brain regions from the Desikan parcellation scheme (Han et al., 2006; Iscan et al., 2015). Although a smaller measurement error is expected with the longitudinal processing stream of FreeSurfer (Iscan et al., 2015; Liem et al., 2015), the trajectory plots of previous longitudinal studies indicate that the measurement error of cortical thickness is large compared to the reported mean annual changes (ranging between 0.3% to 0.59% (Fjell et al., 2014b; Shaw et al., 2016; Storsve et al., 2014)), while the precision of area measurements seems to be higher.

In the study by Storsve et al. (2014), the larger measurement error of thickness compared to area may have resulted in very strong correlations between person-specific changes in volume and person-specific changes in thickness in most brain regions, whereas the contribution of area changes would have been suppressed. Three measures per subject are minimally required to separate the within-subject error from linear change and therefore to provide an unbiased correlation estimate between anatomical brain changes. Further, the wide age range (23 to 87 years) may have resulted in imprecise estimates for structural brain changes in elderly people as the number of people in the later decades of life was relatively low.

The extent to which changes in brain structure are related to changes in cognition is still under research. Mostly small correlations between changes in anatomical brain structures and changes in performance in cognitive tests in non-pathological aging have been reported thus far, typically ranging between 0.2 to 0.35 (Jäncke et al., 2020; Oschwald et al., 2019a). However, the correlation estimates in the literature should be taken with caution, because they often come from studies with only two time points or from studies that did not take the multivariate aspect of the data into consideration when estimating the correlation between the person-specific changes in cognition and the person-specific changes in brain structures. This may have led to an underestimation of the true correlations because the measurement error

(of the brain structures or of both the brain structures and the cognitive tests) could not be separated from the true changes.

The current study with five repeated measures over the span of about seven years in combination with a large sample (N = 231 at baseline) is able to provide new insights into the associations between the different brain metrics in elderly people that are unbiased by the measurement error. Further, we describe the variability of decline rates and the associations between the changes in the different brain structures in detail; e.g., is a faster-than-average decline in area of region A related to a faster-than-average decline in area of region B. Associations between brain volumes have been described in a previous paper of our group (Sele et al., 2020). Here we add information about area and thickness and updated information on volumetric changes by including data from an additional measurement occasion. This time, instead of using the raw volumetric data to estimate volumetric changes, we combined the estimated person-specific area and thickness changes to estimate person-specific volumetric changes. In addition, the number of repeated measures of our data allows the calculation of correlation estimates between changes in anatomical brain structures and performance changes in cognitive tests (measuring general intelligence, processing speed, and memory performance) that are unbiased by the measurement error.

2. Methods

2.1. Sample Description

Structural MRI and cognitive test data were taken from the Longitudinal Healthy Aging Brain Database Project (LHAB; Switzerland) – an ongoing project conducted at the University of Zürich (Zöllig et al., 2011). We used data from five measurement occasions (baseline, 1-year follow-up, 2-year follow-up, 4-year follow-up, 7-year follow up). For 24 subjects, additional 3-year follow-up MRI data were collected. The LHAB dataset included 232 participants at baseline, of which 231 had MRI data (age at baseline: M = 70.8, range = 64–87; females: 113). At each measurement occasion, participants underwent brain imaging and usually in the same week completed an extensive battery of neuropsychological and psychometric cognitive tests. Participants were mainly recruited by newspaper advertisements and during public scientific lectures. Inclusion criteria for study participation at baseline were age ≥ 64, right-handedness, fluent German language proficiency, a score of ≥ 26 on the Mini Mental State Examination (MMSE; Folstein et al., 1975), no self-reported neurological disease of the central nervous system and no contraindications to MRI. Participation was voluntary and all participants gave written informed consent in accordance with the declaration of Helsinki. Self-reported physical and mental health of the sample at baseline, as measured by the 12-Item Short Form Survey (SF-12, Ware et al., 1996), were 50.9 ± 7.4 (M ± SD) and 54.8 ± 6.3, respectively, which indicates above-average health compared to a normal population. The mean IQ of the sample was 120.6 (SD = 6.7) at baseline (measured with the LPS50+ by using the normalization of the age category of 70 to 90 years for the entire sample). Participant characteristics are summarized in Supplementary Table S1. At 4-year follow-up, the structural MRI dataset comprised 72% of the baseline sample (N = 166) and at the 7-year follow-up, the dataset comprised 52% (N = 119) of the baseline sample. Acquisition and processing of MRI data are prone to unwanted influences and errors. We excluded subjects who had a large influence on parameter estimation as indicated by Cook's distance and the log-likelihood contribution of observations (Cook, 1986; Cook and Weisberg, 1982). Subjects having a Cook's distance > 0.5 and a likelihood contribution of < -4 in univariate latent growth curve models were excluded. These values were chosen based on visual inspection of the excluded subjects. Depending on the brain structure × metric combination, 0 to 8 subjects were excluded. For the cognitive tests 0 to 4 subjects were excluded. Additionally, four data points were excluded because of a drop of MMSE scores below 23. The LHAB sample has been

used in previous publications of our group (e.g., Jäncke et al., 2020; Malagurski et al., 2020a; Oschwald et al., 2019b).

2.2. Image Acquisition

Magnetic resonance imaging was carried out at the University Hospital of Zurich on a 3.0T Philips Ingenia scanner (Philips Medical Systems, Best, Netherlands). All images were acquired on the same scanner using the same scanning parameters for all subjects at all time-points. T1-weighted images were recorded with a gradient echo sequence (3D turbo field echo, 160 sagittal slices, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm, FOV = 240 × 240 mm, repetition time = 8.18 ms, echo time = 3.80 ms, flip angle = 8).

2.3. Image Processing

The longitudinal pipeline of FreeSurfer (v. 6.0, Fischl, 2012) as implemented in the FreeSurfer BIDS-App (Gorgolewski et al., 2017) was used to obtain thickness and area measurements of cortical brain regions and volumetric measurements of subcortical structures using the Desikan-Killiany parcellation scheme (Desikan et al., 2006). In the main analysis, we used the mean of the left and the right hemisphere for each brain structure. Some of the analyses (average declines, associations between thickness and area, associations between anatomical measures and cognitive tests) were additionally rerun separately for the left and the right hemisphere. As part of our data processing pipeline, the structural MR images were visually inspected for good SNR and obvious artifacts (such as motion). Only very few images (N = 24) had to be excluded from the sample due to insufficient data quality.

2.4. Cognitive tests

Psychometric intelligence, memory, and processing speed were assessed with an extensive testing battery (Jäncke et al., 2020; Malagurski et al., 2020b; Oschwald et al., 2019b). Sum scores of the domain-specific subtests were used for our analyses. If necessary (for memory and processing speed), the scores of each domain-specific subtest were scaled as described below. Sum scores of these tests instead of latent factors were used to reduce model complexity. Building latent factors out of these tests would require them to be specified in the same models through a second-order growth process. This would increase the number of parameters and may introduce more assumptions about the underlying covariance structure. Considering the sample size and the number of parameters already included, we decided to simplify this part of the model by using sum scores.

Intelligence was measured with a German intelligence test called Leistungsprüfsystem (LPS 50+, Sturm et al., 1993). The version for subjects older than 50 years was used. This test version consists of 13 subtests (of 14 from the normal version) intended to measure the primary factors of Thurstone's intelligence model (Thurstone, 1938). In all the subtests a maximum score of 40 was possible. Therefore, a simple sum score of the tests was used as a measure of psychometric intelligence.

Memory was measured with the Verbal Learning and Memory Test (VLMT) (Helmstaedter and Durwen, 1990), a German adaption of the Rey Auditory Verbal Learning Test and the DCS figural memory test (DCS) (Diagnosticum für Cerebralschädigung; Lamberti and Weidlich, 1999). The VLMT consists of five immediate recall trials (15 items) and one delayed recall trial 20 min later, measuring different phases of learning and encoding. A sum score was built weighting equally the number of correct responses on the first four trials of the VLMT, the number of correct responses on the last trial of VLMT, the correct responses in the delayed recall of the VLMT, and the number of correctly reproduced abstract designs in the five trials of the DCS. For an equal weighting, each set of scores was scaled by the maximum possible score multiplied by 100.

Processing speed was measured weighting equally the number of correct responses of the Identical Pictures Test (IPT; Ekstrom et al., 1976), the number of correct responses on the Digit Symbol Test (DIGSY; Von Aster et al., 2006), and number of correct responses on subtest 14 from the LPS. The test scores were scaled by the maximum possible score of each test multiplied by 100.

2.5. Statistical Modeling

Trajectories of brain structures and cognitive tests were fitted using multivariate growth curve models allowing for person-specific intercepts and slopes and their associations between different brain structures. A quadratic random slope was included in addition to a linear random slope to make the models more flexible. Although a quadratic random slope should represent the true trajectories more realistically, the interpretation of person-specific change is more difficult because the person-specific change now consists of a linear and a quadratic part (e.g. these two parts may cancel each other out when they are negatively correlated). However, when the focus is on the amount of change and not on the specific trajectories, the interpretation can again be simplified by calculating the change for each person based on the linear and the quadratic part. The person-specific changes over the 7 years were obtained by adding 49 (7^2) times the quadratic slope to 7 times the linear slope. The models were fitted using Bayesian estimation with the default priors in Mplus (v. 8.4, Muthén and Muthén, 2018), which results in a whole posterior distribution of person-specific linear and quadratic slopes for each subject (called plausible values in Mplus (Asparouhov and Muthén, 2010)). Population estimates (e.g. correlation between the changes of different measures) can be obtained by calculating the estimate of interest for each posterior sample and combining these with Rubin's rule (Rubin, 1996). By using this framework, between- and within-person uncertainty is properly accounted for. Population estimates of interest were the average changes, between-person variability around average changes, as well as correlations between the changes. Correlations estimates were adjusted for entry-age and sex. Note that an option for fitting quadratic models would be to subtract the mean of the observation time from each time point. The linear part then automatically consists of the amount of change over the years. Nevertheless, using the person-specific slopes can be beneficial because it is a flexible framework and it is possible to obtain person-specific annual change percentage by dividing the slopes by each person's region-specific intercept.

We did not use the raw volumetric FreeSurfer measures to quantify volumetric changes but instead used the estimated person-specific intercepts and slopes of area and thickness. Volumetric changes over seven years can thus be defined as:

$\Delta Vol = (I\_area + 7 \times S\_area + 49 \times Q\_area) \times (I\_thickness + 7 \times S\_thickness + 49 \times Q\_thickness) - I\_area \times I\_thickness$, where I = *person-specific intercept, S = person-specific linear slope, Q = person-specific quadratic slope.*

Depending on the trajectories and the measurement error of area and thickness, this might result in more precise person-specific volumetric change and correlation estimates because the measurement error in area and thickness is reduced before multiplying them. It is, however, important to note that we used the multiplication of the (latent) mean of area and thickness for each brain region for simplification. By contrast, in FreeSurfer 5.3 volume is multiplied at each vertex and then summed over the vertices for each region of interest. The actual values between using the mean of thickness and area of a brain region and summing over the vertices of a region differs, but the correlation between the two is very high. Further, in FreeSurfer 6.0, volume is estimated with a new analytic method and not by the product of area and thickness. However, when the focus is not on the actual values (e.g. for group comparisons), inference based on the product of area and thickness and the new analytic method implemented in FreeSurfer 6.0 should be highly similar (Winkler et al., 2018). Because we focused on changes in percent-
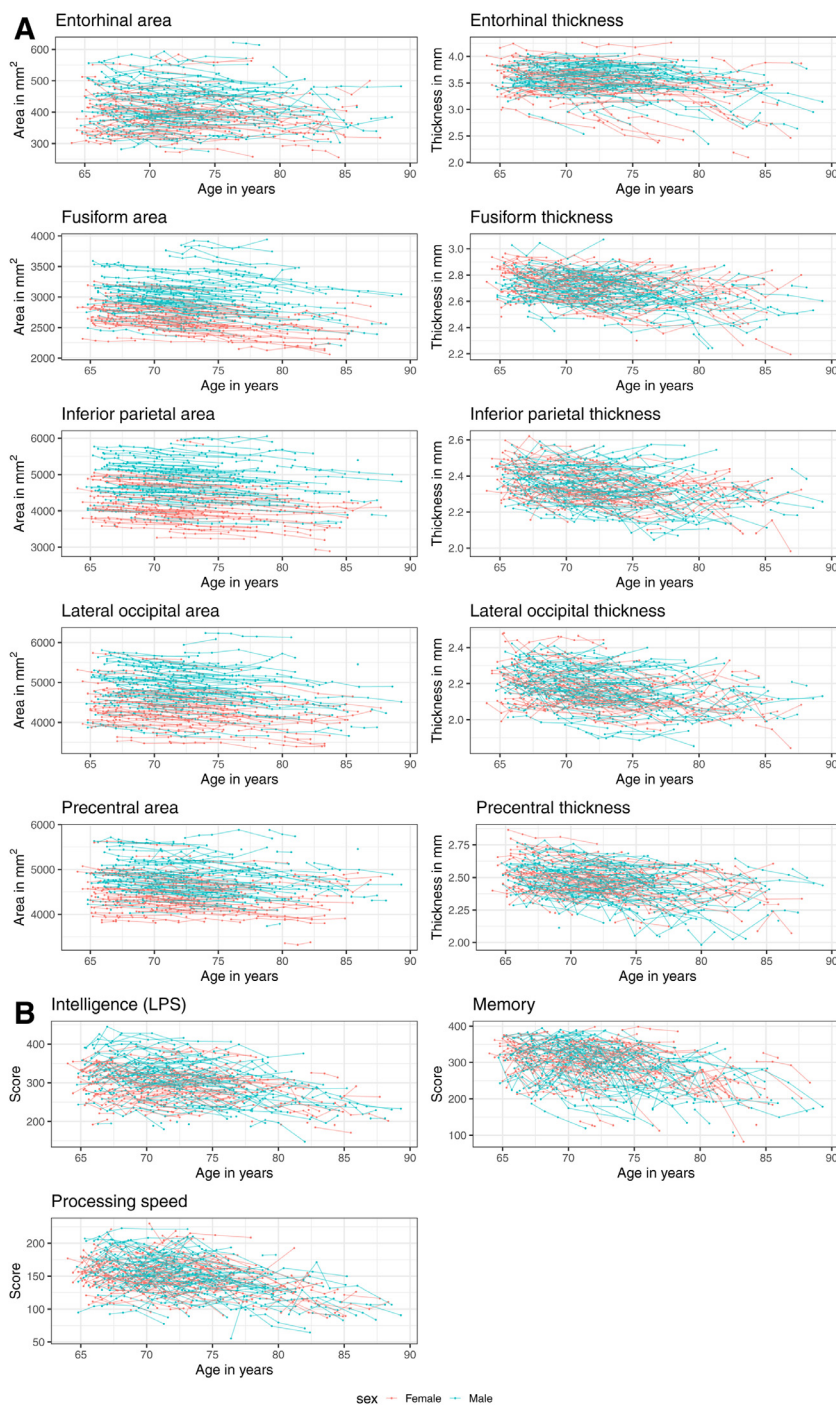
Fig. 1. A: Trajectories of area and thickness for exemplary brain regions B: Trajectories of the cognitive test scores.

age, we would expect highly similar results for the average volumetric changes using any of the three approaches but may gain slightly more precise association estimates involving volumetric changes by using the person-specific intercepts and slopes of area and thickness to quantify volumetric changes.

To obtain unbiased estimates, the growth trajectories of area and thickness of brain structure A and of brain structure B were fitted in one model, allowing for covariances between the person-specific intercepts and slopes, as well as covariances between the errors at the same time point. Because the exact time difference between measurements differed slightly between subjects, a time window approach (Grimm et al., 2016) was used to approximate the exact time difference between measurements. Ten time bins (0, 1.0, 1.1, 2.0, 2.1, 3.0, 4.1, 4.2, 6.7, 7.0 years)

were chosen based on a k-median algorithm implemented in the R package Ckmeans.1d.dp (Wang and Song, 2011).

The models were fitted in a loop using the R package MplusAutomation (Hallquist and Wiley, 2018), connecting each brain structure to each other brain structure and each cognitive measure to each brain structure. Plots were made in R using ggplot2 (Wickham, 2011) and corrplot (Wei and Simko, 2017).

3. Results

Trajectories of the cognitive test scores and area and thickness changes for exemplary brain regions are shown in Fig. 1. The trajectories of all cortical and subcortical structures are shown in Supplemen-
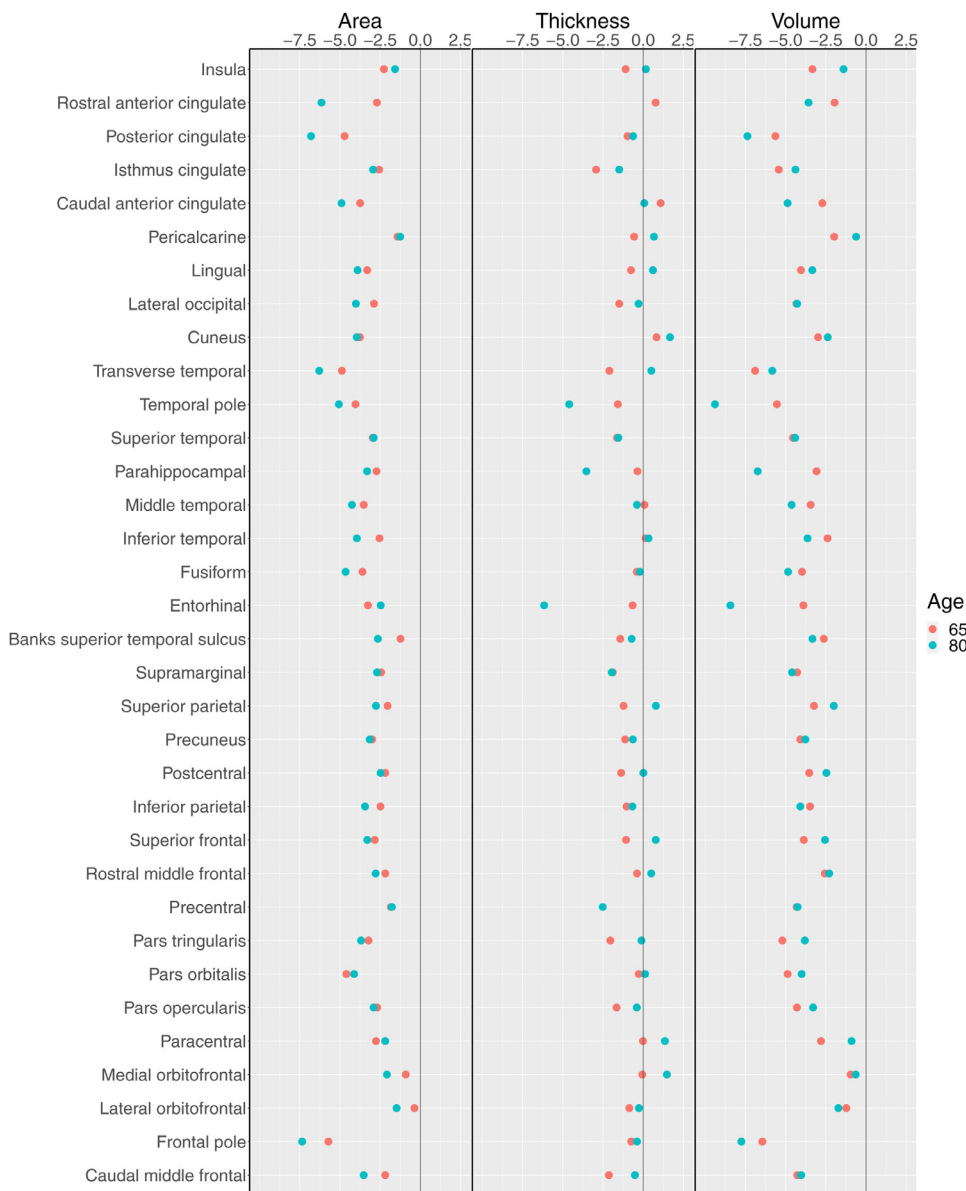
Fig. 2. Average changes (%) over seven years for a 65 and a 80 years old person.

tary Figures S1, S2, and S3. Baseline values of cortical and subcortical structures are shown in Supplementary Tables S2, S3.

3.1. Average changes in area, thickness, volume, and cognition

The estimated changes over the seven years are shown in Table 1 and Fig. 2. Area clearly declined in all brain regions. For a person aged 65, the expected changes over the seven years ranged from -1% to -5% for most brain regions. A slightly larger decline, ranging from 0.05% to 0.1% per additional entry-age year (in addition to the average slope at age 65), was estimated for persons above the age 65 in most brain regions. Some exceptions are the entorhinal cortex, the insula, and the paracentral gyrus, for which a less steep decline was observed above age 65. The variance of the person-specific changes was generally large. Based on our modeling assumptions of normally distributed deviations from the average, some individuals are expected to show almost no or only small declines, whereas others are expected to decline about twice as fast as the average slope.

In most brain regions, thickness declined on average only by a small amount. The expected changes in thickness ranged mostly from 0% to

-2% over the seven years at age 65. In general, no evidence for a larger decline with increasing age was found. Exceptions are the entorhinal cortex, the temporal pole, and the parahippocampus, for which substantially steeper declines with each additional entry-age year (0.2% to 0.37% in addition to the average slope at age 65) were estimated. Substantial variation around the average slope was found for all brain regions. Therefore, we would even expect slight increases in thickness for some subjects over the observed years, but also substantial decreases for some subjects. For most brain structures, the measurement error of thickness was larger than the measurement error of area, leading to higher uncertainty in the thickness estimates.

Volume, estimated as the product of thickness and area, showed the largest declines of the three metrics. For a person aged 65, the expected changes in volume over the seven years ranged from -3% to -6% for most brain regions. Pericalcarine, lateral and medial orbitofrontal cortex showed slightly smaller changes of about -1.5%. Steeper declines with each additional entry-age year were mainly estimated for the entorhinal cortex, the temporal pole, and the parahippocampus resulting from the accelerated decline in thickness. A large variance around the average slope was observed in all brain regions.

Table 1

Average changes (%) in cortical thickness, surface area, and cortical volume over seven years. 95% - confidence intervals in (), approximated as average ± 2 × standard error of estimate. Slope = average change for a 65 years old person. Age × slope = entry-age × slope interaction = changes of the average slope at age 65 with each additional entry-age year. Var = between-person variability around the average slope.

	Area			Thickness			Volume		
	Slope	Age × slope	Var	Slope	Age × slope	Var	Slope	Age × slope	Var
Banks superior temporal sulcus	-1.23	-0.09	1.96	-1.42	0.05	3.86	-2.62	-0.05	7.81
	(-1.66, -0.80)	(-0.16, -0.02)	(1.28, 2.65)	(-2.12, -0.72)	(-0.08, 0.17)	(2.30, 5.42)	(-3.53, -1.72)	(-0.20, 0.11)	(4.83, 10.80)
Caudal anterior cingulate	-3.75	-0.08	6.95	1.09	-0.07	5.63	-2.71	-0.14	9.40
	(-4.58, -2.92)	(-0.21, 0.06)	(4.46, 9.44)	(0.23, 1.94)	(-0.20, 0.07)	(3.01, 8.26)	(-3.72, -1.71)	(-0.30, 0.01)	(5.70, 13.11)
Caudal middle frontal	-2.19	-0.09	1.44	-2.13	0.11	3.40	-4.27	0.02	4.75
	(-2.60, -1.78)	(-0.16, -0.02)	(0.79, 2.10)	(-2.92, -1.35)	(-0.02, 0.24)	(1.08, 5.72)	(-5.10, -3.44)	(-0.12, 0.15)	(1.91, 7.59)
Cuneus	-3.76	-0.01	2.66	0.83	0.06	5.44	-2.98	0.04	4.04
	(-4.43, -3.09)	(-0.12, 0.10)	(1.27, 4.05)	(-0.05, 1.71)	(-0.08, 0.20)	(2.60, 8.29)	(-3.76, -2.19)	(-0.09, 0.17)	(1.73, 6.34)
Entorhinal	-3.26	0.05	7.30	-0.65	-0.37	19.11	-3.89	-0.30	26.55
	(-4.43, -2.09)	(-0.14, 0.24)	(2.95, 11.65)	(-1.85, 0.54)	(-0.56, -0.18)	(12.77, 25.44)	(-5.39, -2.39)	(-0.55, -0.06)	(17.20, 35.90)
Frontal pole	-5.72	-0.11	12.08	-0.74	0.02	3.59	-6.45	-0.09	9.43
	(-7.17, -4.27)	(-0.36, 0.14)	(4.84, 19.32)	(-1.64, 0.16)	(-0.11, 0.16)	(0.54, 6.65)	(-7.82, -5.07)	(-0.31, 0.14)	(2.99, 15.87)
Fusiform	-3.60	-0.07	1.74	-0.40	0.01	2.71	-3.98	-0.06	5.22
	(-4.08, -3.12)	(-0.15, 0.01)	(0.92, 2.57)	(-1.07, 0.28)	(-0.10, 0.12)	(1.22, 4.20)	(-4.77, -3.18)	(-0.18, 0.07)	(3.04, 7.41)
Inferior parietal	-2.48	-0.06	1.70	-1.03	0.02	2.20	-3.48	-0.04	4.28
	(-2.85, -2.11)	(-0.12, 0.00)	(1.09, 2.30)	(-1.65, -0.40)	(-0.07, 0.12)	(0.89, 3.51)	(-4.20, -2.76)	(-0.15, 0.07)	(2.22, 6.33)
Inferior temporal	-2.54	-0.09	2.36	0.15	0.01	2.61	-2.39	-0.08	4.49
	(-3.04, -2.04)	(-0.17, -0.01)	(1.32, 3.40)	(-0.44, 0.74)	(-0.08, 0.10)	(1.35, 3.87)	(-3.19, -1.59)	(-0.21, 0.04)	(2.00, 6.98)
Insula	-2.26	0.05	4.03	-1.09	0.08	2.71	-3.33	0.13	7.17
	(-2.91, -1.62)	(-0.05, 0.15)	(2.37, 5.70)	(-1.72, -0.46)	(-0.02, 0.19)	(1.14, 4.27)	(-4.17, -2.49)	(0.00, 0.26)	(4.17, 10.18)
Isthmus cingulate	-2.56	-0.02	3.51	-2.93	0.10	3.47	-5.42	0.07	5.42
	(-3.28, -1.85)	(-0.14, 0.09)	(1.78, 5.24)	(-3.65, -2.21)	(-0.03, 0.22)	(1.69, 5.26)	(-6.25, -4.59)	(-0.07, 0.21)	(3.33, 7.52)
Lateral occipital	-2.88	-0.08	1.00	-1.49	0.08	2.42	-4.33	0.00	3.24
	(-3.31, -2.46)	(-0.14, -0.01)	(0.42, 1.59)	(-2.11, -0.86)	(-0.02, 0.18)	(1.03, 3.82)	(-5.05, -3.60)	(-0.12, 0.12)	(1.45, 5.03)
Lateral orbitofrontal	-0.37	-0.07	2.32	-0.86	0.04	2.10	-1.22	-0.03	4.32
	(-0.97, 0.24)	(-0.17, 0.02)	(0.88, 3.75)	(-1.52, -0.20)	(-0.07, 0.15)	(0.61, 3.59)	(-2.04, -0.40)	(-0.16, 0.10)	(1.49, 7.14)
Lingual	-3.31	-0.04	2.53	-0.76	0.09	3.18	-4.04	0.05	3.60
	(-3.90, -2.71)	(-0.14, 0.06)	(1.14, 3.92)	(-1.44, -0.07)	(-0.02, 0.20)	(1.40, 4.95)	(-4.75, -3.34)	(-0.07, 0.16)	(1.69, 5.51)
Medial orbitofrontal	-0.91	-0.08	4.01	-0.05	0.10	5.25	-0.95	0.02	8.90
	(-1.72, -0.10)	(-0.21, 0.05)	(1.68, 6.34)	(-0.95, 0.84)	(-0.04, 0.25)	(2.18, 8.33)	(-2.09, 0.18)	(-0.16, 0.20)	(3.93, 13.87)
Middle temporal	-3.52	-0.05	1.28	0.08	-0.03	2.00	-3.44	-0.08	3.15
	(-3.95, -3.09)	(-0.12, 0.02)	(0.68, 1.88)	(-0.45, 0.61)	(-0.12, 0.05)	(0.96, 3.04)	(-4.11, -2.77)	(-0.19, 0.03)	(1.34, 4.95)
Paracentral	-2.76	0.04	2.42	-0.01	0.09	6.55	-2.80	0.13	3.04
	(-3.33, -2.18)	(-0.05, 0.13)	(1.28, 3.57)	(-0.98, 0.95)	(-0.06, 0.24)	(2.97, 10.12)	(-3.50, -2.10)	(0.02, 0.24)	(0.90, 5.18)
Parahippocampal	-2.73	-0.04	1.51	-0.35	-0.21	7.55	-3.07	-0.24	8.16
	(-3.20, -2.25)	(-0.12, 0.04)	(0.67, 2.36)	(-1.16, 0.45)	(-0.35, -0.08)	(4.81, 10.30)	(-3.93, -2.22)	(-0.39, -0.10)	(5.07, 11.26)
Pars opercularis	-2.69	-0.02	0.86	-1.66	0.08	2.32	-4.29	0.07	3.39
	(-3.06, -2.31)	(-0.08, 0.05)	(0.47, 1.26)	(-2.26, -1.05)	(-0.01, 0.18)	(0.91, 3.73)	(-5.01, -3.58)	(-0.05, 0.18)	(1.49, 5.30)
Pars orbitalis	-4.60	0.03	2.80	-0.27	0.03	3.69	-4.87	0.06	3.60
	(-5.25, -3.95)	(-0.07, 0.14)	(1.21, 4.39)	(-1.06, 0.52)	(-0.10, 0.15)	(1.54, 5.83)	(-5.66, -4.08)	(-0.07, 0.19)	(1.30, 5.89)
Pars tringularis	-3.22	-0.03	1.52	-2.04	0.13	2.46	-5.20	0.09	3.00
	(-3.65, -2.79)	(-0.10, 0.04)	(0.76, 2.27)	(-2.73, -1.35)	(0.03, 0.23)	(1.06, 3.87)	(-5.97, -4.42)	(-0.02, 0.21)	(1.23, 4.78)
Pericalcarine	-1.42	0.01	1.73	-0.56	0.08	6.98	-1.98	0.09	6.69
	(-1.88, -0.95)	(-0.06, 0.09)	(0.94, 2.51)	(-1.66, 0.54)	(-0.10, 0.26)	(2.88, 11.09)	(-3.06, -0.90)	(-0.08, 0.26)	(2.41, 10.97)
Postcentral	-2.19	-0.02	0.78	-1.37	0.09	2.84	-3.53	0.07	2.43
	(-2.54, -1.84)	(-0.07, 0.04)	(0.36, 1.20)	(-2.06, -0.68)	(-0.01, 0.20)	(1.17, 4.51)	(-4.14, -2.92)	(-0.03, 0.17)	(1.02, 3.83)
Posterior cingulate	-4.71	-0.14	5.70	-0.97	0.02	2.90	-5.63	-0.12	10.28
	(-5.49, -3.94)	(-0.27, -0.01)	(3.53, 7.87)	(-1.67, -0.28)	(-0.09, 0.14)	(1.43, 4.38)	(-6.67, -4.59)	(-0.29, 0.06)	(6.63, 13.93)
Precentral	-1.83	0.00	1.30	-2.52	0.00	5.83	-4.31	0.00	4.97
	(-2.27, -1.39)	(-0.06, 0.07)	(0.62, 1.98)	(-3.42, -1.62)	(-0.15, 0.15)	(2.69, 8.98)	(-5.11, -3.52)	(-0.13, 0.13)	(2.59, 7.36)
Precuneus	-3.00	-0.01	1.26	-1.12	0.03	1.77	-4.08	0.02	2.83
	(-3.34, -2.66)	(-0.06, 0.04)	(0.78, 1.73)	(-1.70, -0.53)	(-0.06, 0.13)	(0.66, 2.88)	(-4.74, -3.44)	(-0.08, 0.12)	(1.22, 4.45)
Rostral anterior cingulate	-2.70	-0.23	4.83	0.78	0.13	4.86	-1.95	-0.11	5.05
	(-3.52, -1.88)	(-0.36, -0.10)	(2.34, 7.31)	(-0.06, 1.61)	(0.00, 0.27)	(2.24, 7.48)	(-2.81, -1.10)	(-0.24, 0.03)	(2.20, 7.89)
Rostral middle frontal	-2.18	-0.04	1.51	-0.38	0.06	3.51	-2.56	0.02	3.84
	(-2.62, -1.74)	(-0.11, 0.03)	(0.76, 2.27)	(-1.12, 0.36)	(-0.06, 0.18)	(1.40, 5.62)	(-3.39, -1.73)	(-0.11, 0.15)	(1.21, 6.46)
Superior frontal	-2.84	-0.03	1.39	-1.06	0.12	2.21	-3.87	0.09	3.29
	(-3.25, -2.43)	(-0.10, 0.04)	(0.80, 1.99)	(-1.80, -0.33)	(0.01, 0.24)	(0.55, 3.88)	(-4.67, -3.07)	(-0.04, 0.21)	(1.25, 5.33)
Superior parietal	-2.04	-0.05	1.44	-1.22	0.13	3.92	-3.23	0.08	3.73
	(-2.40, -1.68)	(-0.11, 0.01)	(0.93, 1.95)	(-1.98, -0.45)	(0.01, 0.26)	(1.69, 6.16)	(-4.00, -2.46)	(-0.05, 0.21)	(1.68, 5.79)
Superior temporal	-2.96	0.00	0.64	-1.63	0.01	2.90	-4.54	0.01	4.14
	(-3.25, -2.67)	(-0.04, 0.05)	(0.39, 0.90)	(-2.27, -0.99)	(-0.10, 0.11)	(1.51, 4.29)	(-5.28, -3.80)	(-0.11, 0.13)	(2.30, 5.98)
Supramarginal	-2.44	-0.02	0.84	-1.89	0.00	2.02	-4.28	-0.02	3.15
	(-2.75, -2.13)	(-0.07, 0.03)	(0.55, 1.13)	(-2.43, -1.35)	(-0.09, 0.08)	(0.98, 3.06)	(-4.91, -3.65)	(-0.12, 0.08)	(1.58, 4.71)
Temporal pole	-4.03	-0.07	13.51	-1.57	-0.20	7.00	-5.54	-0.26	23.10
	(-5.26, -2.81)	(-0.26, 0.12)	(7.91, 19.11)	(-2.37, -0.77)	(-0.33, -0.08)	(4.09, 9.92)	(-6.89, -4.18)	(-0.46, -0.05)	(15.29, 30.91)
Transverse temporal	-4.88	-0.09	3.87	-2.10	0.17	9.77	-6.89	0.07	8.51
	(-5.71, -4.05)	(-0.23, 0.04)	(1.79, 5.95)	(-3.28, -0.92)	(-0.02, 0.36)	(4.90, 14.64)	(-7.88, -5.91)	(-0.09, 0.23)	(4.73, 12.29)

Table 2

Average changes (%) in subcortical structures and cognitive tests over seven years. 95% - confidence intervals in (), approximated as average ± 2 × standard error of estimate. Slope = average change for a 65 years old person. Age × slope = entry-age × slope interaction. Var = between-person variability around the average slope.

	Slope	Age × slope	Var
Accumbens	-11.96	-0.19	49.33
	(-14.55, -9.38)	(-0.60, 0.22)	(25.12, 73.54)
Amygdala	-3.00	-0.21	15.58
	(-4.09, -1.91)	(-0.40, -0.03)	(10.58, 20.57)
Caudate	-4.20	0.03	9.36
	(-5.10, -3.30)	(-0.11, 0.18)	(6.17, 12.56)
Cerebellum	-3.46	-0.07	1.45
	(-3.93, -2.99)	(-0.15, 0.01)	(0.70, 2.20)
Hippocampus	-6.97	-0.21	10.90
	(-7.91, -6.04)	(-0.36, -0.06)	(7.09, 14.71)
Pallidum	-0.53	0.05	2.29
	(-1.13, 0.07)	(-0.04, 0.15)	(0.93, 3.66)
Putamen	-4.11	0.12	4.60
	(-4.80, -3.42)	(0.01, 0.22)	(2.76, 6.44)
Thalamus	-5.65	-0.01	3.77
	(-6.24, -5.06)	(-0.10, 0.09)	(2.43, 5.12)
Intelligence (LPS)	-0.47	-0.83	22.90
	(-2.52, 1.58)	(-1.17, -0.49)	(7.72, 38.07)
Memory	-6.89	-1.48	106.04
	(-11.00, -2.78)	(-2.19, -0.78)	(21.23, 190.85)
Processing speed	-1.11	-1.31	82.83
	(-4.71, 2.49)	(-1.89, -0.74)	(37.94, 127.73)

Subcortical (volumetric) changes were comparably diverse (Table 2). The average decline of the nucleus accumbens was the largest of all studied brain regions. The expected decline of the hippocampus was also one of the largest and clearly got steeper with increasing age, similar to the decline of the amygdala. By contrast, the decline of the putamen and caudate decreased with increasing age. Finally, the pallidum showed almost no decline on average. As in the cortical brain regions, there was substantial person-specific variance around the average slope for all subcortical structures.

The estimated changes in cognitive tests are shown in Table 2. LPS scores showed almost no decline at age 65 over the next seven years, but a steeper decline for each additional entry-age year (0.8%) was estimated. Memory performance changed on average about -7% over seven years at age 65 with a substantially larger decline for each additional entry-age year (1.5%). Similar to the LPS scores, processing speed scores demonstrated almost no decline on average at age 65, and the decline was expected to strongly increase for each additional entry-age year (1.3%). There was substantial variation around the average slope for all cognitive tests. The measurement error of the cognitive tests was relatively large compared to the yearly changes, leading to rather imprecise estimates (especially of person-specific slopes).

3.2. Association between area, thickness, and volume

The associations between the different brain metrics are shown in Table 3. We found no evidence for an association between thickness and area in most brain regions. For a few brain regions (paracentral, frontal pole, cuneus, rostral anterior cingulate, pars orbitalis, precentral, and postcentral), substantial negative correlations were estimated. An exception is the bank of the superior temporal sulcus, for which some evidence for a positive correlation was found.

In most brain regions, volume was strongly associated with both area and thickness. In some regions, volume was more strongly correlated with thickness. This is because the variation around the average slope was usually slightly larger in thickness than in area but the association of volume with area was also large in most brain regions. Only for a few brain regions (especially those with negative correlations between area and thickness), volume was correlated with either thickness or area.

3.3. Associations between brain regions

Between-region correlation matrices of changes in area, thickness, and volume are shown in Figs. 3–5. For thickness (Fig. 3), the correlation pattern was in general homogenous, with evidence for moderate to strong correlations between most brain regions. Strong correlations were estimated between and within most regions of temporal, parietal, and frontal lobe. There were also some brain regions for which weak to moderate correlations with other brain regions were observed (e.g. frontal pole and pars orbitalis of frontal regions, occipital regions (except lateral occipital cortex), transverse temporal gyrus, medial temporal regions, and cingulate regions). For area (Fig. 4), a similar pattern but with weaker correlations was observed. There were also some exceptions. For the paracentral, precentral, and postcentral gyri, thickness was strongly correlated with other brain regions while area showed no evidence for a correlation with other brain regions. For medial temporal regions, only thickness but not area measurements were strongly correlated with one another, while both thickness and area were weakly correlated with other brain regions.

For volumetric changes (Fig. 5), the strongest correlations between brain regions were estimated. This is no surprise, given that volume was estimated as the product of area and thickness and in both measures moderate to strong correlations between brain regions were found. Strong correlations were observed between and within most regions of temporal, parietal, and frontal lobe and to a lesser extent also occipital lobe. Of interest, medial temporal regions (entorhinal cortex, temporal pole, parahippocampus) were strongly correlated with each other, but less strongly correlated to regions from other lobes.

For subcortical regions, changes in hippocampus and amygdala were strongly correlated with each other and with changes in temporal structures (especially medial temporal) and moderately correlated with other structures. The thalamus was also rather strongly correlated with temporal structures and moderately to other structures. Caudate and putamen were strongly associated with each other and rather weakly with other structures. For the Pallidum, no evidence for an association with other structures was found; a negative correlation was even estimated with the nucleus accumbens. The nucleus accumbens was weakly correlated with other brain regions.

3.4. Associations between brain regions and cognitive tests

The estimated associations between changes in the anatomical measures and changes in the cognitive tests are shown in Table 4 and Fig. 6. In general, strong evidence for associations between changes in anatomical measures and changes in LPS scores was found. Positive associations between the changes in volume and LPS scores were estimated for all brain regions, with correlation estimates up to 0.54. The strongest correlations (~0.5) were observed in the inferior parietal cortex, fusiform gyrus, caudal middle frontal gyrus, precentral gyrus, and banks of the superior temporal sulcus. In a few brain regions, evidence for an association between changes in thickness and changes in LPS scores, but not between changes in area and changes in LPS scores, were found. However, in most brain regions for which substantial correlations between volumetric changes and changes in LPS scores were estimated, area also contributes to the correlation. Of note, we did not directly compare the correlations to the LPS scores of different brain regions and brain metrics with each other and there is a large uncertainty in the region-specific estimates. Therefore, we have to be careful declaring some regions as more strongly related to LPS scores than others.

Medial temporal regions showed rather weak correlations with changes in LPS scores but, together with the hippocampus and the amygdala, were the only brain regions showing some evidence for associations with memory scores. Associations of brain regions with processing speed were similar to associations of brain regions and LPS, but not as strong. Subcortically, we only found evidence for an association between

Table 3

Correlations between surface area, cortical thickness, and cortical volume. Standard error of estimates in ().

	Area-Thickness	Volume-Area	Volume-Thickness
Banks superior temporal sulcus	0.41 (0.12)	0.78 (0.06)	0.89 (0.03)
Caudal anterior cingulate	-0.23 (0.14)	0.69 (0.08)	0.54 (0.10)
Caudal middle frontal	0.04 (0.20)	0.57 (0.13)	0.83 (0.07)
Cuneus	-0.50 (0.15)	0.25 (0.19)	0.70 (0.11)
Entorhinal	0.09 (0.16)	0.57 (0.12)	0.86 (0.04)
Frontal pole	-0.46 (0.21)	0.86 (0.08)	0.03 (0.27)
Fusiform	0.25 (0.19)	0.74 (0.09)	0.83 (0.06)
Inferior parietal	0.14 (0.17)	0.72 (0.08)	0.78 (0.07)
Inferior temporal	-0.08 (0.17)	0.67 (0.09)	0.68 (0.09)
Insula	0.10 (0.18)	0.80 (0.07)	0.67 (0.10)
Isthmus cingulate	-0.17 (0.18)	0.64 (0.10)	0.63 (0.10)
Lateral occipital	0.00 (0.22)	0.54 (0.16)	0.83 (0.07)
Lateral orbitofrontal	-0.01 (0.22)	0.72 (0.12)	0.67 (0.13)
Lingual	-0.33 (0.18)	0.52 (0.15)	0.62 (0.12)
Medial orbitofrontal	-0.03 (0.20)	0.65 (0.12)	0.73 (0.10)
Middle temporal	0.00 (0.20)	0.63 (0.12)	0.76 (0.08)
Paracentral	-0.72 (0.10)	-0.14 (0.20)	0.77 (0.09)
Parahippocampal	-0.06 (0.16)	0.36 (0.14)	0.91 (0.03)
Pars opercularis	0.13 (0.18)	0.60 (0.11)	0.86 (0.05)
Pars orbitalis	-0.42 (0.18)	0.46 (0.17)	0.59 (0.14)
Pars tringularis	-0.21 (0.19)	0.51 (0.14)	0.72 (0.10)
Pericalcarine	-0.27 (0.18)	0.23 (0.18)	0.86 (0.05)
Postcentral	-0.36 (0.16)	0.18 (0.18)	0.84 (0.06)
Posterior cingulate	0.28 (0.16)	0.88 (0.04)	0.70 (0.08)
Precentral	-0.35 (0.16)	0.12 (0.18)	0.88 (0.04)
Precuneus	-0.03 (0.19)	0.64 (0.11)	0.74 (0.08)
Rostral anterior cingulate	-0.47 (0.14)	0.55 (0.14)	0.46 (0.15)
Rostral middle frontal	-0.24 (0.20)	0.40 (0.17)	0.78 (0.08)
Superior frontal	-0.05 (0.21)	0.61 (0.13)	0.75 (0.10)
Superior parietal	-0.31 (0.15)	0.31 (0.15)	0.80 (0.06)
Superior temporal	0.30 (0.19)	0.63 (0.13)	0.93 (0.03)
Supramarginal	0.17 (0.18)	0.64 (0.10)	0.86 (0.05)
Temporal pole	0.24 (0.15)	0.86 (0.04)	0.70 (0.08)
Transverse temporal	-0.34 (0.17)	0.31 (0.16)	0.78 (0.07)

Fig. 3. Correlation pattern of changes in cortical thickness between the different brain regions. Standard error of estimates in ().
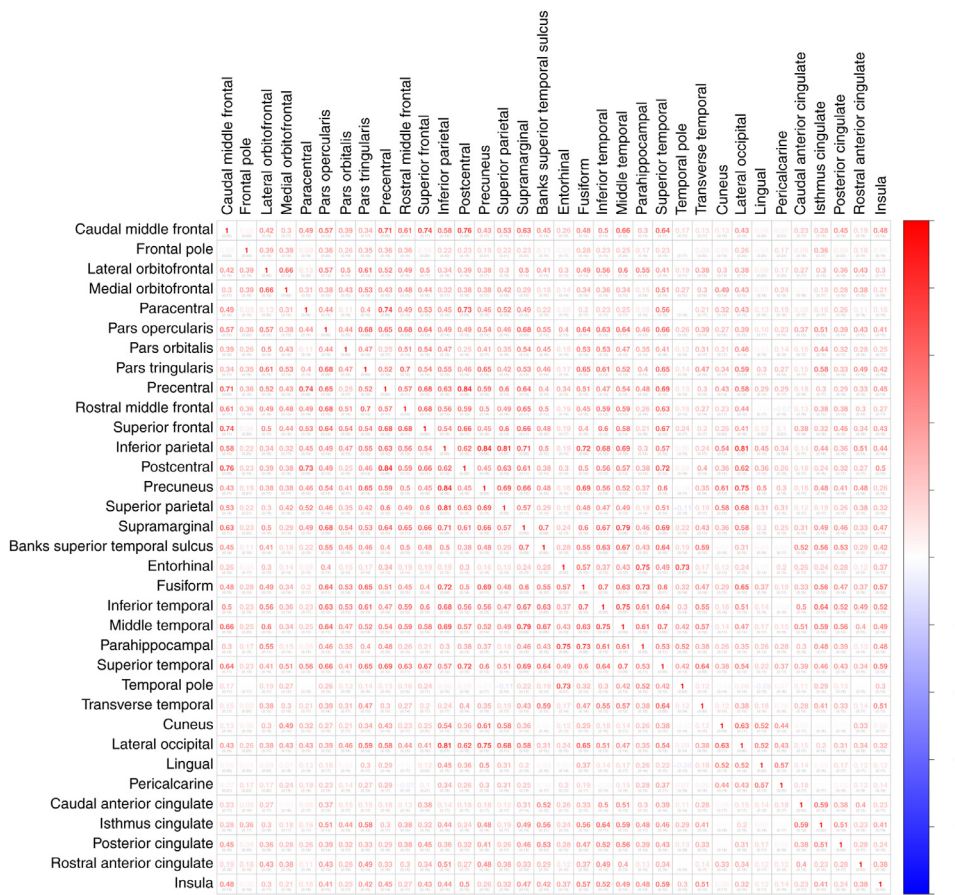
Table 4

Correlations between changes in brain regions and changes in cognitive tests for cortical thickness, surface area, and cortical volume. Standard error of estimates in ().

|	Intelligence (LPS)			Memory			Processing Speed		
	Volume	Area	Thickness	Volume	Area	Thickness	Volume	Area	Thickness
Banks superior temporal sulcus	0.49 (0.15)	0.42 (0.14)	0.41 (0.16)	0.15 (0.21)	0.28 (0.20)	0.02 (0.22)	0.24 (0.15)	0.20 (0.14)	0.20 (0.16)
Caudal anterior cingulate	0.24 (0.17)	0.18 (0.18)	0.10 (0.20)	0.00 (0.20)	-0.16 (0.18)	0.20 (0.22)	-0.06 (0.16)	0.06 (0.15)	-0.16 (0.17)
Caudal middle frontal	0.51 (0.17)	0.32 (0.17)	0.42 (0.19)	0.15 (0.23)	-0.01 (0.23)	0.19 (0.23)	0.38 (0.18)	0.34 (0.15)	0.24 (0.20)
Cuneus	0.09 (0.21)	0.34 (0.18)	-0.16 (0.19)	-0.06 (0.22)	-0.18 (0.23)	0.08 (0.23)	0.34 (0.17)	0.06 (0.18)	0.26 (0.17)
Entorhinal	0.22 (0.16)	-0.05 (0.20)	0.30 (0.14)	0.33 (0.18)	0.19 (0.21)	0.28 (0.18)	0.22 (0.14)	0.11 (0.18)	0.20 (0.14)
Frontal pole	0.32 (0.20)	0.22 (0.19)	0.11 (0.23)	0.24 (0.24)	0.24 (0.22)	-0.04 (0.24)	0.15 (0.18)	0.17 (0.17)	-0.08 (0.23)
Fusiform	0.54 (0.15)	0.37 (0.17)	0.49 (0.18)	0.06 (0.22)	0.11 (0.22)	0.00 (0.23)	0.34 (0.15)	0.21 (0.16)	0.32 (0.17)
Inferior parietal	0.54 (0.14)	0.39 (0.15)	0.43 (0.18)	-0.08 (0.20)	-0.08 (0.21)	-0.04 (0.22)	0.39 (0.16)	0.15 (0.15)	0.42 (0.17)
Inferior temporal	0.44 (0.18)	0.39 (0.16)	0.23 (0.19)	0.19 (0.22)	0.19 (0.20)	0.07 (0.22)	0.24 (0.17)	0.22 (0.16)	0.11 (0.18)
Insula	0.30 (0.16)	0.02 (0.17)	0.48 (0.16)	0.06 (0.18)	0.08 (0.19)	0.00 (0.21)	0.12 (0.16)	-0.14 (0.15)	0.38 (0.17)
Isthmus cingulate	0.26 (0.17)	0.19 (0.18)	0.14 (0.18)	0.14 (0.21)	0.21 (0.21)	-0.04 (0.22)	0.21 (0.16)	0.08 (0.17)	0.19 (0.16)
Lateral occipital	0.39 (0.18)	0.26 (0.19)	0.31 (0.20)	0.02 (0.24)	-0.02 (0.24)	0.04 (0.24)	0.29 (0.18)	0.07 (0.20)	0.31 (0.18)
Lateral orbitofrontal	0.38 (0.20)	0.04 (0.22)	0.48 (0.17)	0.24 (0.22)	0.19 (0.22)	0.16 (0.24)	0.28 (0.18)	0.08 (0.19)	0.32 (0.18)
Lingual	0.31 (0.20)	0.32 (0.19)	0.04 (0.21)	-0.06 (0.21)	0.04 (0.22)	-0.11 (0.24)	0.30 (0.17)	0.13 (0.19)	0.22 (0.18)
Medial orbitofrontal	0.21 (0.21)	0.03 (0.20)	0.26 (0.22)	0.02 (0.22)	0.08 (0.22)	-0.05 (0.22)	0.18 (0.17)	0.18 (0.18)	0.08 (0.19)
Middle temporal	0.37 (0.18)	0.24 (0.19)	0.28 (0.18)	-0.02 (0.24)	-0.10 (0.21)	0.05 (0.22)	0.33 (0.18)	0.15 (0.18)	0.30 (0.18)
Paracentral	0.28 (0.20)	0.03 (0.19)	0.17 (0.19)	-0.01 (0.23)	0.36 (0.20)	-0.22 (0.21)	0.31 (0.18)	-0.04 (0.18)	0.24 (0.17)
Parahippocampal	0.32 (0.15)	0.13 (0.21)	0.29 (0.15)	0.37 (0.16)	0.28 (0.19)	0.27 (0.18)	0.12 (0.15)	-0.27 (0.17)	0.25 (0.14)
Pars opercularis	0.26 (0.19)	0.03 (0.19)	0.30 (0.19)	0.00 (0.22)	0.11 (0.21)	-0.06 (0.23)	0.30 (0.16)	0.12 (0.18)	0.30 (0.17)
Pars orbitalis	0.33 (0.19)	-0.04 (0.20)	0.38 (0.18)	0.08 (0.22)	-0.05 (0.22)	0.13 (0.21)	0.11 (0.18)	-0.02 (0.19)	0.13 (0.20)
Pars tringularis	0.22 (0.20)	0.13 (0.19)	0.16 (0.20)	-0.11 (0.22)	-0.10 (0.20)	-0.06 (0.23)	0.27 (0.18)	0.19 (0.17)	0.17 (0.18)
Pericalcarine	0.27 (0.21)	0.20 (0.20)	0.16 (0.21)	0.00 (0.24)	-0.15 (0.21)	0.07 (0.24)	0.24 (0.19)	0.10 (0.17)	0.20 (0.20)
Postcentral	0.33 (0.21)	-0.17 (0.21)	0.39 (0.21)	-0.08 (0.24)	-0.08 (0.23)	-0.03 (0.24)	0.16 (0.17)	-0.10 (0.17)	0.21 (0.18)
Posterior cingulate	0.40 (0.16)	0.36 (0.16)	0.27 (0.22)	-0.09 (0.19)	0.03 (0.20)	-0.22 (0.21)	0.29 (0.14)	0.28 (0.15)	0.16 (0.17)
Precentral	0.50 (0.16)	0.00 (0.19)	0.46 (0.17)	-0.13 (0.21)	-0.04 (0.22)	-0.10 (0.21)	0.37 (0.15)	-0.13 (0.17)	0.41 (0.16)
Precuneus	0.28 (0.20)	0.15 (0.17)	0.23 (0.22)	-0.12 (0.21)	-0.07 (0.19)	-0.10 (0.23)	0.38 (0.16)	0.14 (0.14)	0.37 (0.18)
Rostral anterior cingulate	0.17 (0.20)	-0.14 (0.18)	0.34 (0.18)	0.06 (0.23)	0.16 (0.24)	-0.11 (0.22)	0.13 (0.18)	-0.05 (0.18)	0.19 (0.20)
Rostral middle frontal	0.25 (0.21)	0.22 (0.19)	0.12 (0.20)	0.14 (0.23)	-0.07 (0.23)	0.19 (0.22)	0.24 (0.19)	0.20 (0.18)	0.12 (0.18)
Superior frontal	0.27 (0.21)	0.01 (0.19)	0.31 (0.23)	-0.07 (0.24)	0.05 (0.22)	-0.12 (0.24)	0.18 (0.19)	0.16 (0.17)	0.08 (0.21)
Superior parietal	0.45 (0.19)	0.30 (0.16)	0.26 (0.21)	-0.14 (0.21)	-0.06 (0.21)	-0.11 (0.21)	0.27 (0.17)	-0.06 (0.16)	0.30 (0.17)
Superior temporal	0.39 (0.18)	0.15 (0.18)	0.41 (0.19)	0.16 (0.18)	0.08 (0.22)	0.16 (0.18)	0.26 (0.17)	0.19 (0.16)	0.23 (0.18)
Supramarginal	0.35 (0.18)	0.21 (0.18)	0.30 (0.18)	0.00 (0.24)	-0.04 (0.22)	0.02 (0.24)	0.33 (0.16)	0.17 (0.15)	0.31 (0.16)
Temporal pole	0.25 (0.16)	0.25 (0.18)	0.12 (0.17)	0.28 (0.19)	0.22 (0.20)	0.24 (0.19)	0.17 (0.13)	0.15 (0.15)	0.11 (0.15)
Transverse temporal	0.12 (0.17)	-0.06 (0.20)	0.15 (0.18)	0.31 (0.18)	0.30 (0.20)	0.10 (0.20)	-0.08 (0.16)	0.08 (0.18)	-0.13 (0.17)
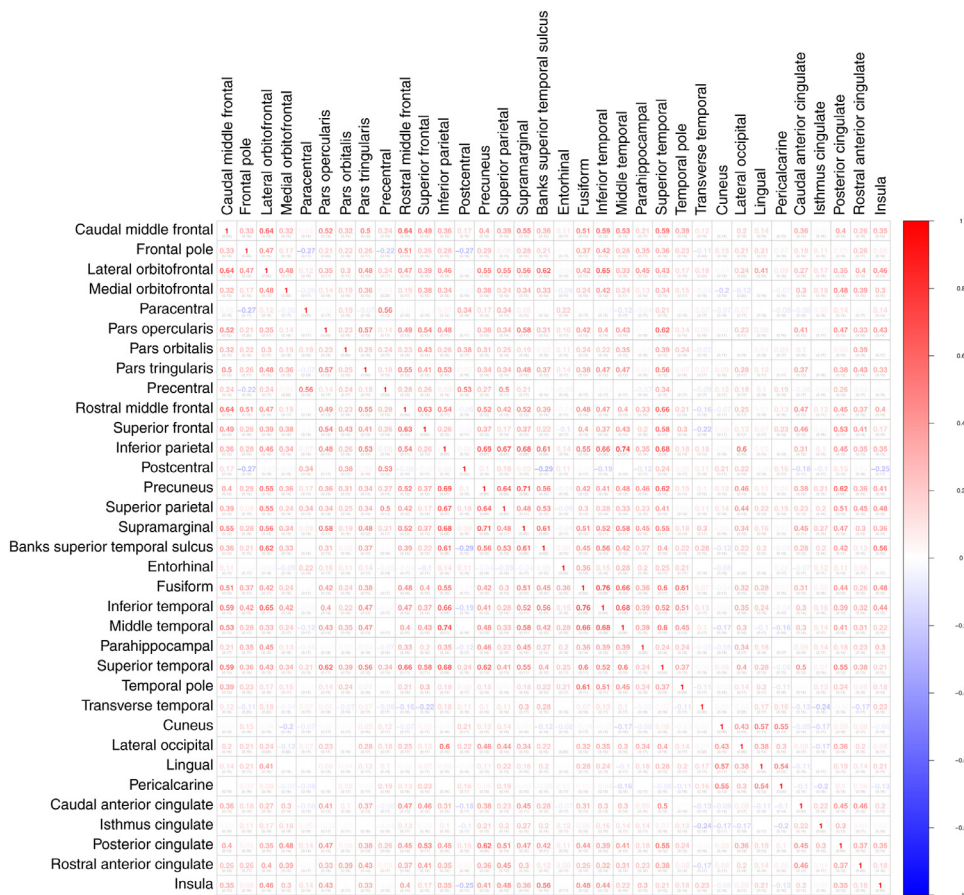
Fig. 4. Correlation pattern of changes in surface area between the different brain regions. Standard error of estimates in ().

Table 5

Correlations between changes in subcortical structures and changes in cognitive tests.

	Intelligence (LPS)	Memory	Processing speed
Accumbens	0.12	0.28	0.08
	(0.20)	(0.22)	(0.17)
Amygdala	0.16	0.46	0.14
	(0.16)	(0.18)	(0.14)
Caudate	-0.03	0.23	0.13
	(0.17)	(0.20)	(0.15)
Cerebellum	0.03	-0.02	-0.17
	(0.21)	(0.24)	(0.20)
Hippocampus	0.24	0.45	0.14
	(0.15)	(0.17)	(0.15)
Pallidum	0.07	-0.03	0.25
	(0.21)	(0.24)	(0.18)
Putamen	-0.02	0.03	0.00
	(0.17)	(0.21)	(0.16)
Thalamus	0.24	0.03	-0.04
	(0.17)	(0.22)	(0.15)

changes in thickness of the insula and changes in LPS scores, and of hippocampus and amygdala with changes in memory scores (Table 5).

3.5. Analyses for the left and the right hemisphere

In addition to the main analyses, part of the analyses were rerun separately for the left and the right hemisphere. The average declines for the regions of the left and the right hemisphere are shown in Supplementary Tables S4–S7. Generally, the two hemispheres showed similar average declines in area and thickness. While we did not directly compare the decline of one hemisphere to the other, there were also some brain regions where the decline seems stronger in one hemisphere. This was more often the case for cortical thickness than area. The subcortical structures showed similar declines in the left and the right hemisphere, with the exception of the accumbens, which declined clearly stronger in the left hemisphere.

The association between changes in thickness, area, and volume for the left and right hemisphere are shown in Supplementary Table S8. The association between thickness and area was in general similar in the left and the right hemisphere with mostly weak to moderate negative correlations.

The hemisphere-specific associations between changes in the anatomical measures and changes in the cognitive tests are shown in Supplementary Tables S9–S12. For area, the association estimates to the cognitive tests were similar between the left and the right hemisphere. For cortical thickness, the two hemispheres showed similar estimates for most regions but there were notable exceptions where the associations were stronger in the right hemisphere (banks superior temporal sulcus, caudal middle frontal gyrus, fusiform gyrus, inferior parietal cortex, inferior temporal cortex, pars orbitalis, superior temporal cortex, supramarginal gyrus). For the subcortical structures, the associations between changes in memory scores and changes in the hippocampus and the amygdala were slightly stronger in the left hemisphere. It is important to note that the uncertainty in these estimates is large, and there were many comparisons involved. More data is needed to confirm these potential differences between the hemispheres.

4. Discussion

In this study, we associated person-specific changes in cortical thickness, area, and volume within and between brain regions, as well as to changes in cognitive test performance. By using a dataset with five re-
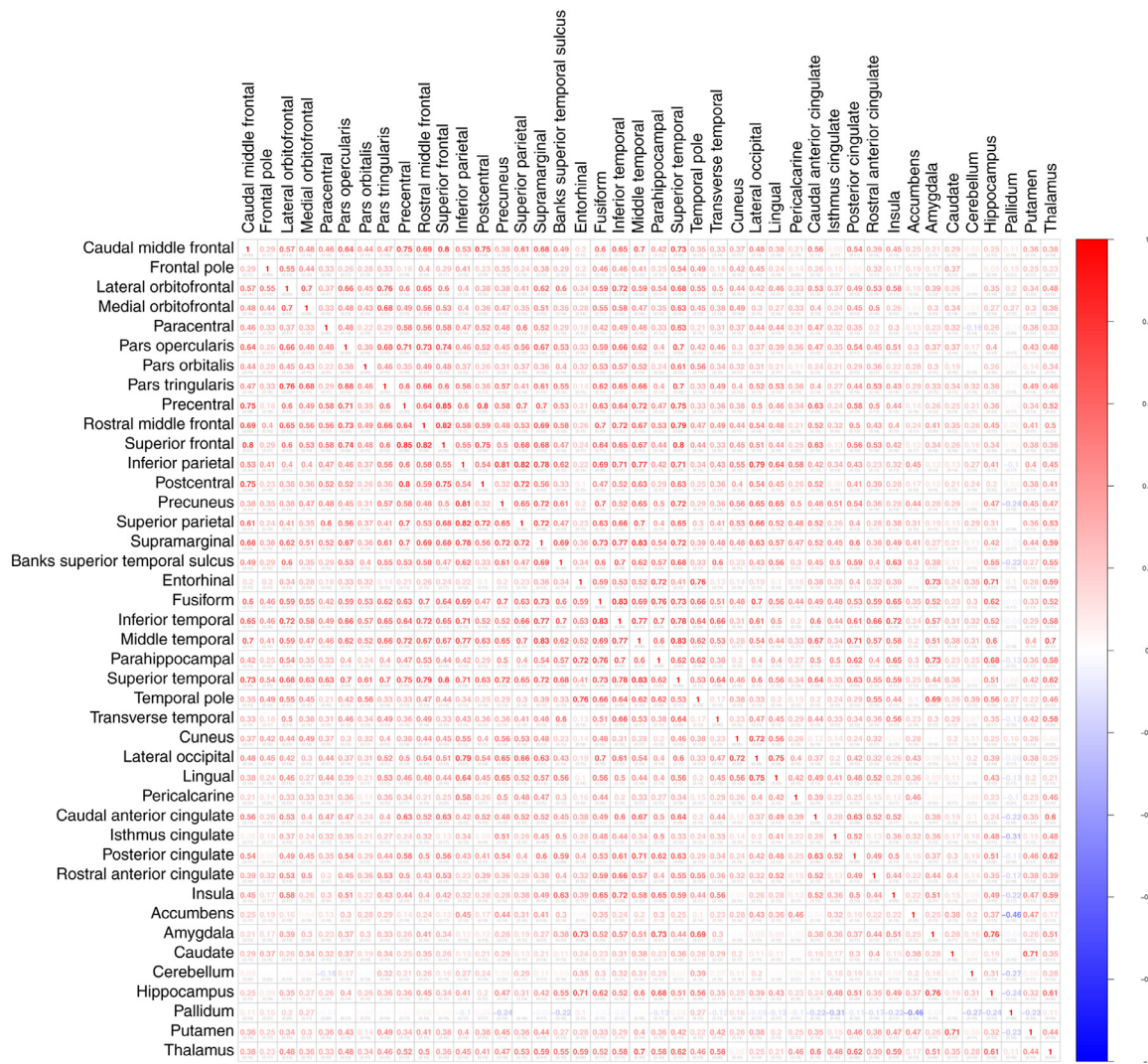
Fig. 5. Correlation pattern of changes in cortical volume between the different brain regions. Standard error of estimates in ().

peated measurement occasions for most subjects and an observational time span of 7 years, we were able to reduce the influence of measurement error on the estimates and gain new insights about the associations (a) between the changes of different brain metrics and (b) between changes in brain metrics and cognitive abilities.

For cortical thickness, most brain regions showed only small declines with no evidence for an increase in steepness in higher age. The average declines typically ranged between 0% and 2% over seven years. Only the entorhinal cortex, the temporal pole, and the parahippocampus showed clearly steeper declines with advancing age. The precentral gyrus showed rather strong but steady thinning. In a recent large-scale analysis of cortical thickness over the life span using cross-sectional data, most brain regions showed a steep decrease during the second and third decades of life and an attenuated or plateaued slope afterwards (Frangou et al., 2020), which is in line with the decelerating decline of cortical thickness over 8 years observed in a longitudinal study with older adults (Rast et al., 2018). In general, our results are consistent with previously reported trajectory patterns. In our sample, the estimated declines were a bit smaller for most brain regions, but the range of values given by the 95%-confidence intervals around our estimates were usually in line with the trajectories of the studies by Franou et al. (2020) and also Shaw et al. (2016), who followed a sample of older adults (age 60 - 66 at baseline) over 12 years. Although it has been repeatedly found that the thickness of the entorhinal cortex and

temporal pole is preserved until the seventh or eight decade of life and shows a steeper decline afterwards (Fjell et al., 2014b; Frangou et al., 2020; Raz et al., 2010; Storsve et al., 2014), a similar pattern for the parahippocampus (as found in our study) has not yet been reported. The anatomical and functional connection between these brain regions renders it plausible that the parahippocampus follows a decline curve in older age similar to those of other medial temporal regions. For patients with Alzheimer disease, a reduction of parahippocampal volumes has been consistently reported (Krumm et al., 2016). Similar to our results, a fast decline of the thickness of the precentral gyrus has been reported in some (Frangou et al., 2020; Lemaitre et al., 2012; Storsve et al., 2014) but not all previous studies (Shaw et al., 2016). In the study by Lemaitre et. al (2012), the fast decline in the precentral gyrus was even provided as a counterexample to the "last in, first out" theory, which proposes that brain structures that mature last are the first to degenerate (Raz, 2000). In general, our subjects do not seem to follow a simple regional decline pattern such as proposed in the "last in, first out" theory, as we did not find evidence for a faster decline of frontal or parietal lobe structures in the observed age range in thickness or area.

Contrary to thickness, area clearly declined in almost all brain regions with slightly steeper declines in higher age. The average declines typically ranged between 1% and 5%. The fastest declines in high age were observed for the rostral anterior cingulate gyrus (which showed strong accelerating decline), the posterior cingulate gyrus, the trans-
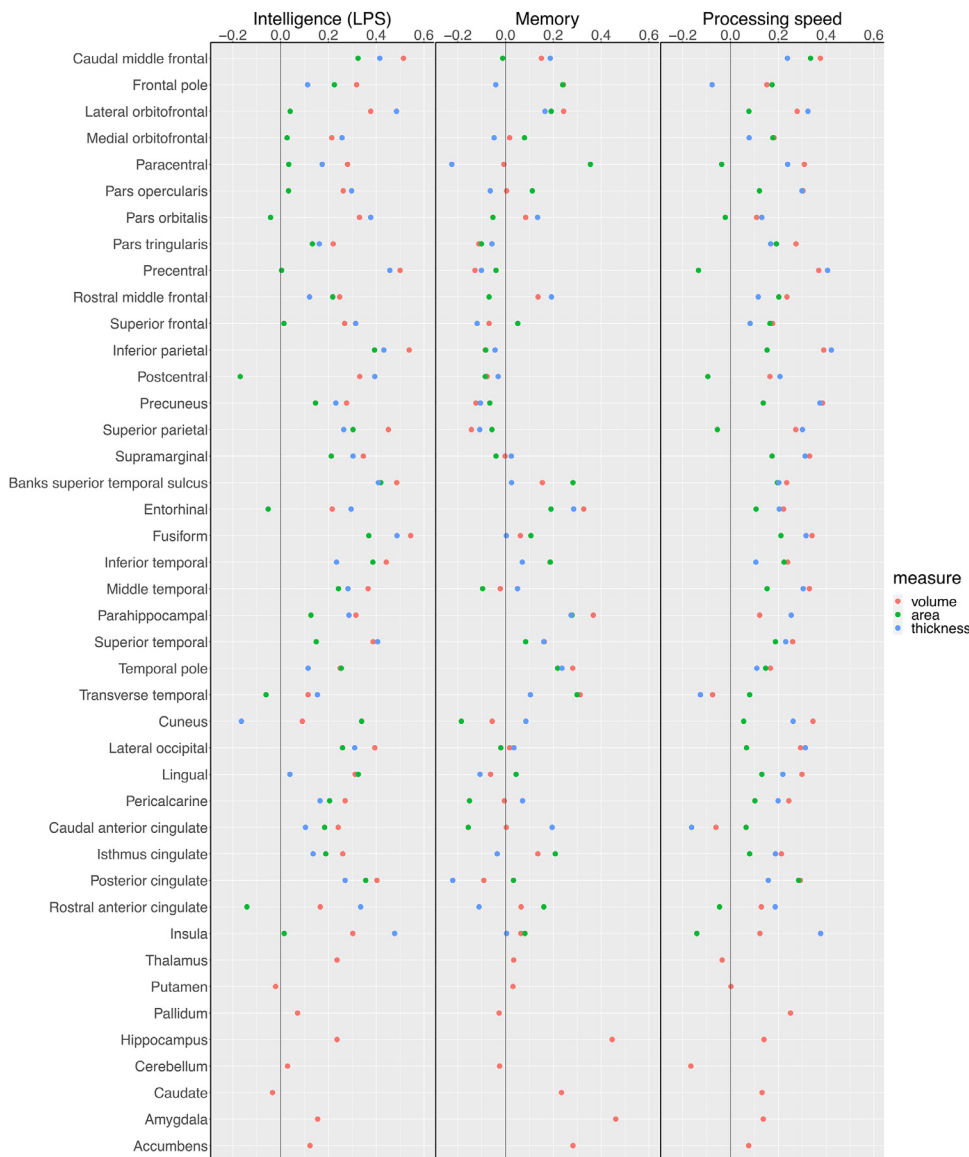
Fig. 6. Correlations between changes in brain regions and changes in cognitive tests.

verse temporal gyrus, and the frontal pole. Literature on area changes in aging is sparse but suggests that area changes are not as strong as thickness changes over the adult lifespan and decline steadily (Hoagey et al., 2019; Storsve et al., 2014). Further support for this comes from brain age prediction studies using machine learning approaches, where surface area carries less information about the age of a person than thickness (Liem et al., 2017; Wang et al., 2014). However, while it is clearly evident that the correlation between area and age is lower than between thickness and age (Lemaitre et al., 2012), the percent changes within each person may be more similar in both metrics over the adult life than the cross-sectional correlations suggest. The reason for this discrepancy can be found in the larger between-person variability of surface area. Therefore, one has to be careful in declaring area as being less susceptible to the effects of aging than thickness. In fact, our data suggest that it may be the other way around in older age. Whereas the decline of area seems steady or even slightly accelerating, the decline of thickness may rather slow down for most brain regions in older age. For both thickness and area, subjects showed substantial variation around the average slope. For area, this means that on one end some subjects are expected to show no or only little decline, while on the other end some subjects are expected to decline about twice as fast as the average slope. For

thickness, where the average decline was not as large, clearly decreasing thickness is expected for some subjects but increasing thickness for other subjects can also be expected over the seven years. The estimated increases in thickness for some people may indicate a more dynamic change pattern in thickness compared to area.

Volume, estimated as the product of thickness and area, showed the largest declines of the three metrics in most brain regions. This can be explained mathematically because area decreases on average in all brain regions and thickness in most brain regions. When both metrics are decreasing, the product of the two shows the largest decreases. Note that this holds true for the average change, independent of the correlation between the metrics.

In a previous study, Storsve et al. (2014) found strong correlations between changes in thickness and changes in volume, but mostly only weak correlations between changes in volume and changes in area. They concluded that the main contributor to volumetric changes within persons are changes in thickness. But it seems that their estimates were strongly biased by the measurement error, which could not be separated from true changes with only 2 repeated measures. By contrast, our data indicate that both measures are important contributors of volumetric changes. Of note, the correlation between changes in volume

and changes in area and thickness neglect the average decrease, which was clearly larger for area than for thickness in the observed age range in most brain regions.

Regarding the interrelations between changes in area and changes in thickness, no evidence for an association between the brain metrics was found for the majority of brain regions. In a cross-sectional study, Hogstrom et al. (2013) found a negative relationship between area and cortical thickness that was stable across young, middle-aged, and old adults. In our data, substantial negative correlations between changes in area and changes in thickness were estimated for some brain regions (paracentral, frontal pole, cuneus, rostral anterior cingulate, pars orbitalis, pre and postcentral, transverse temporal). Thickness and area were also negatively correlated in the study by Storsve et al. (2014) in most of these regions. Other regions such as the temporal pole or lateral occipital gyrus showed a negative correlation only in their study but not in ours. On the other hand, the anterior cingulate showed a negative correlation only in our data. Note that the results are not directly comparable, as our estimates were based on the changes over time separated from the within-subject error, while the estimates by Storsve et al. (2014) included the within-person dynamics but also the measurement error in addition to the changes over time. To obtain reliable association estimates of changes over time, it is important to allow for correlated errors at the same time point (which is only possible with three or more repeated measures) between thickness and area, because both measures are obtained from the same MRI image. Taken together, our data support the view that area and thickness may be affected (at least partially) by different and independent biological processes (Storsve et al., 2014). The negative correlations between changes in area and thickness estimated for some of the regions, however, suggest a more complex interplay between the two measures that may be region-specific (Storsve et al., 2014).

The between-region correlation pattern of changes in thickness was in general strong and homogenous. This means that if a faster-than-average decline is observed in one brain region, we would expect a faster-than-average decline in most other brain regions as well. The correlation pattern of changes in area between brain regions was similar but weaker than the correlation pattern of changes in thickness. For some brain regions (e.g. paracentral, precentral, and postcentral gyrus), area changes were not correlated with area changes of other brain regions. The thickness changes of those regions, by contrast, were strongly correlated with thickness changes of other regions. These results suggest that the factors accelerating changes in thickness may be global mechanisms affecting most brain regions, whereas the mechanisms affecting area may operate more locally. Volumetric changes showed the strongest correlation pattern. Based on the correlation patterns of thickness and area, this is no surprise given that brain regions were usually strongly correlated in thickness and (a bit less) strongly in area, whereas thickness and area within a brain region were more independent. The correlations for volumetric changes were substantially larger in our study than in Raz et al.'s (2005) study. However, the informative value of the estimates in the study by Raz et al. (2005) is limited because the study had only two repeated measurements. To date literature on between-regions volumetric associations is very sparse, but this may be about to change given the amount of longitudinal MRI data currently being collected.

Importantly, MRI studies provide only a very crude image of changes in brain structures and do not provide information regarding the biological underpinnings of these changes. Based on stereological methods, a substantial loss of neurons is not expected during non-pathological aging, and changes in dendritic complexity are subtle and region-specific (Burke and Barnes, 2006). Grey matter changes in learning are believed to stem from a complex interplay of processes such as gliogenesis and structural plasticity of non-neuronal cells; synaptogenesis and changes in dendritic spine morphology; changes in vascular volume; and molecules and transcription factors that are involved in regulating dendritic morphology and development of neurons and glia, while neurogenesis is thought to have only a minor role (Zatorre et al., 2012). Changes

in grey matter may also be related to sub-adjacent changes in white matter (Feczko et al., 2009). In contrast to learning-induced changes found in specific brain regions, aging mechanisms may affect the cortex more globally. However, aging and learning cannot be strictly separated. The human brain needs to adapt to the environment also in older age (Pauwels et al., 2018). Aging mechanisms may lead to an impaired form of learning where the losses slowly outnumber the gains. It is unclear how much of the decline in thickness and area can be actively counteracted and how much is genetically predetermined. The expression of genes specific to CA1 pyramidal cells, astrocytes, and microglia have been related to thinning of the cortex in both development and in aging (Vidal-Pineiro et al., 2020). The small correlations between changes in thickness and changes in area may suggest that if there is a strong influence of an environmental factor (e.g. keeping an active and stimulating lifestyle) it would affect the two measures differently. The correlation matrix of changes indicates that if it would affect area, it may rather be region-specific and more directly related to a specific activity or behavior. If it would affect thickness, it could be affecting the cortex in a more global manner. The small average decreases in thickness and the large variability in person-specific slopes with even slight increases for some subjects may indicate that thickness is more likely than area to be influenced by environmental factors in older age.

In our data, we observed only small declines in cognitive test scores at age 65. However, substantially steeper declines were estimated in all cognitive tests with advancing age. Despite the large measurement error in these tests, there was substantial variation around the average slope of the cognitive tests. The literature reports mostly weak associations between age-related changes in performance on intelligence tests and changes in cortical volume or thickness (Oschwald et al., 2019a). However, these estimates often seem to be biased by the measurement error, which results in an underestimation of true associations. Our data indicate that these associations may be stronger than expected. Another recent longitudinal study also found relatively strong correlations between changes in cognitive abilities (especially verbal fluency) and changes in brain regions (Armstrong et al., 2020). As far as we know, associations between changes in intelligence tests and changes in area have not been addressed in previous studies. Our data indicate that for most regions, changes in thickness are more strongly associated with changes in LPS scores than are changes in area. However, the strongest correlations with changes in LPS scores were found for changes in volume. At least in some brain regions, changes in area also seem to be related to changes in LPS scores. This would be in accordance with the observation that larger-than-average thickness changes are more homogenous across the brain while larger-than-average area changes are more region-specific.

Of particular interest are the medial temporal regions, which have been linked to memory function and are of special focus in Alzheimer's disease research (Fjell et al., 2014b). Although an accelerated decline of volume due to an accelerated decline in thickness is expected with increasing age, subjects showed a large variation around the average slope in these brain regions. The volumetric changes of these regions were strongly associated with each other, with the hippocampus, and with the amygdala but only weakly to moderately with other structures. In addition, our data provided some evidence that changes in hippocampus, amygdala, and medial temporal regions were moderately associated with changes in memory performance. We agree with Fjell et al. (2014b) that a large variation in high age in changes in medial temporal regions is plausible in a healthy aging population and that these changes may be related to memory function independent of Alzheimer's disease.

Predictors of cognitive decline can roughly be divided into biological (genetic) and environmental predictors. Disentangling the different predictors is not a trivial task because a complex interplay of different predictors, brain structure, and brain function is expected. There is some evidence that keeping an active and stimulating environment is important for healthy aging (Nyberg et al., 2020). One may speculate that such an environment keeps the brain integrity (especially of thickness)

intact. The associations between changes in anatomical measures and changes in the cognitive tests support the notion that maintaining the structure of the brain plays an important part in healthy aging.

There are some limitations to the results. First, due to the high number of analyses performed, a higher uncertainty is expected than is given by the estimates of our models. More data from other longitudinal studies is needed to confirm the correlation patterns between brain regions and the relatively strong associations of certain brain regions to the cognitive tests. Second, the estimates regarding accelerating or decelerating average changes with advancing age in brain regions were based on within-subject changes in different subjects. These estimates should contain less noise but are still prone to be influenced by unwanted effects (e.g. selecting exceptionally healthy subjects at very high age). Ideally, these estimates would be based completely on changes within persons. However, this would require a long observed time span and many measurements. The observed time span of seven years is rather low to study the dynamics of changes within a person. Our data indicated that the measurement error of thickness and the cognitive abilities was large compared to the yearly changes, which complicated model fitting and precise estimation. Therefore, particularly for estimation of changes in thickness and changes in the cognitive abilities, more repeated measures and a longer time span would be desirable. Third, practice effects can lead to higher performance on the cognitive tests during repeated measures (Oschwald et al., 2019a). It is expected that a mixture of practice effects and true performance changes results in complex trajectories for the cognitive test scores. Because it is not possible to cleanly disentangle the practice effects from the true performance changes, we did not try to separately model each of these effects. Nevertheless, by allowing for linear and quadratic (random) slopes, the cognitive test score trajectory should be more reasonably captured than by just allowing for linear slopes. From a simplified perspective, practice effects may be seen as another kind of cognitive tests, which should be correlated with the test scores and therefore may have little impact on the estimated associations between the cognitive tests and the brain regions. Fourth, our sample does not represent the whole non-pathological aging population as the IQ of the sample at baseline was rather high. It cannot be expected that our average estimates represent the average person. Nevertheless, we still observed substantial between person variability in the brain and cognitive test metrics in our sample. It can be expected that the variability in these trajectories in the whole non-pathological aging population is even larger. Because we found substantial associations between brain regions and between brain regions and cognitive tests, this should also apply to the normal aging population with correlations that may even be larger.

Author Credit

SM, FL, and LJ contributed to the design, set-up, and maintenance of the Longitudinal Healthy Aging Brain (LHAB) database. SS performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Data availability statement

The analysis code and the associated data tables will be made available by the authors upon reasonable request. The raw MR image data underlying this article are not publicly available.

Ethics statement

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission Zürich (EK 2010-0267/3). The participants provided their written informed consent to participate in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118370.

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