# Ventral striatal atrophy in Alzheimer's disease : exploring a potential new imaging marker for early dementia

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# PART II

## Allometric scaling in brain development and degeneration

# CHAPTER 6

# Allometric scaling of brain structures to intracranial volume: an epidemiological MRI study

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# ABSTRACT

There is growing evidence that substructures of the brain scale allometrically to total brain size, i.e., in a nonproportional and nonlinear way. Here, we examined scaling coefficients of different volumes of interest (VOI) to intracranial volume (ICV) and assessed whether they were allometric or isometric and whether they were significantly different from each other. Furthermore, reproducibility of allometric scaling across different age groups and study populations was investigated. Scaling of VOI to ICV was studied in samples of cognitively healthy adults from the community-based AGES-Reykjavik study ($N = 3883$), the Coronary Artery Risk Development in Young Adults Study (CARDIA) ($N = 709$), and the Alzheimer's Disease Neuroimaging Initiative (ADNI) ($N = 180$). Data encompassed participants with different age, ethnicity, risk factor profile, and ICV and VOI obtained with different automated MRI segmentation techniques. Our analysis showed that 1) allometric scaling is a trait of all parts of the brain, 2) scaling of neocortical white matter, neocortical gray matter, and deep gray matter structures including the cerebellum are significantly different from each other and 3) allometric scaling of brain structures cannot solely be explained by age-associated atrophy, sex, ethnicity, or a systematic bias from study-specific segmentation algorithm, but appears to be a true feature of brain geometry.

# INTRODUCTION

Since the development of (semi-) automated segmentation techniques for brain MRI, a large body of literature has emerged comparing brain volumes of different groups of people in order to find measurable traits distinctive or predictive for certain diseases. Having a good understanding of the physiologic variation in brain geometry is indispensable to discover pathological patterns. Human brain size varies considerably and different adjustment methods are applied to reduce noise stemming from this variation. Despite widespread use of standardization techniques, adjusting for ICV or total brain volume (TBV) when analyzing VOI is complex and controversial. In volumetric studies, ratios of VOI to ICV or TBV, or linear regression-based methods are commonly used. However, a critical evaluation of these techniques showed that each of these adjustment method unmasks different types of relations and result in different magnitude of effects (O'Brien et al. 2011; Voevodskaya et al. 2014). In morphometric studies linear or nonlinear stereotaxic registration of brain MR images are often used. A critical evaluation of these techniques showed that spatial transformation of MR brain images may result in significant opposite group level differences or different proportionality of brain regions compared to those obtained in native space (Allen et al. 2008). Moreover, whether it is necessary to apply head-size adjustment in all types of comparative brain studies was evaluated in a study that investigated the effect of head size on several metrics of the brain, i.e., total brain volume, VOI, cortical thickness and voxel-based morphometry (VBM). It was concluded that head size adjustment should be considered in all volumetric and VBM studies, but not in cortical thickness studies (Barnes et al. 2010).

Probably, part of the inconsistencies in results obtained with different head/brain size adjustment methods can be explained by differences in underlying assumptions of these methods regarding preservation of proportionality of VOI to TBV across the total range of brain size variation in the population. Some techniques, such as ratio-based methods or linear registration, assume isometry of the brain, i.e., proportionality of VOI to TBV is preserved. Other techniques, such as linear regression-based methods or nonlinear registration, allow for allometry to occur in case proportionality is not preserved. Although, these different theoretical underpinnings have been recognized (O'Brien et al. 2011) and caution is called when choosing the adjustment method, it is uncertain whether allometric scaling is true feature of brain geometry.

Some previous studies have provided evidence for allometric scaling of VOI to overall brain size. One study found larger proportions of cerebral WM and smaller proportions of GM in larger TBV compared to lower TBV (Lüders, Steinmetz, and Jancke 2002). Another study that focused on the necessity of head size, age and gender adjustment in MRI studies, found nonlinear relations of cortical GM, hippocampus and putamen to ICV with a power less than 1 (Barnes et al. 2010). Other neocortical metrics such as cortical thickness, total surface area, and sulcal depth have also been found to scale different from what would be predicted based on ICV in case of isometry (Im et al. 2008). Moreover, a recent study examined power law relations of deep GM structures and many regions of cortical GM and found most of them to have nonlinear relation with ICV. Some cortical areas had a power law larger than 1 and others smaller than 1. It was also tested whether prediction error of a statistical model would decrease when ICV correction was based on power-proportion method compared to the commonly used ANCOVA method. Prediction errors with use of power proportion method were slightly lower for structures that had strong nonlinear relations to ICV (Liu et al. 2014).

Although, nonlinearity and nonproportionality in scaling of some VOI to ICV have been reported, results are heterogeneous and little is known on scaling of especially deep GM regions (striatum and thalamus) and cerebellum. Also, it has not been investigated whether scaling coefficients of different brain structures are significantly different from each other. Here, scaling of volumes of frontal, parieto-occipital and temporal cortical GM, cortical WM, medial temporal lobe (MTL), striatum, thalamus, and cerebellum with ICV was studied using automatically segmented MRI brain scans of a large sample of community dwelling older adults ($N = 3883$) who participated in AGES-Reykjavik study. First, we investigated whether and to what extent VOI showed allometric scaling to ICV. Second, we estimated whether scaling coefficients of different VOI were significantly different from each other. Third, we studied whether scaling was similar in different age groups of our sample. Fourth, we set up an experiment to test whether the automated segmentation pipeline of AGES-Reykjavik study could give rise to allometric scaling. Fifth, because allometric scaling would have considerable influence on head/ brain size adjustment methods, the fit of the allometric model on the volumetric data was compared to the linear model. And lastly, since the AGES-Reykjavik study population consisted of older Icelandic individuals, extrapolation of our results to groups of younger individuals and/ or different ethnicity was potentially limited. Therefore, supportive analyses were conducted in two other samples (CARDIA and ADNI) that differed in mean age, source population, and method of automated MR segmentation to estimate brain volumes.

# METHODS

## General design of the AGES-Reykjavik study

The general design and demographics of the AGES-Reykjavik study have been described elsewhere (Harris et al. 2007). The population-based sample of the AGES-Reykjavik study consisted of 5764 men and women, born between 1907–1935. Participants underwent extensive clinical evaluation, including cognitive function testing and brain MRI. All participants signed an informed consent. The AGES-Reykjavik study was approved by the Intramural Research Program of the National Institute on Aging, the National Bioethics Committee in Iceland (VSN00-063), the Icelandic Data Protection Authority, and the institutional review board of the U.S. National Institute on Aging, National Institutes of Health.

## Acquisition and automated segmentation of MRI

MRI was performed at the Icelandic Heart Association on a single study dedicated 1.5T GE Signa Twinspeed EXCITE system MRI scanner. The image protocol, described previously (Sigurdsson et al. 2012), included a T1-weighted 3D spoiled gradient echo (TE 8 ms; TR 21 ms; FA 30°, FoV 240 mm; matrix 256 × 256; 110 slices; slice thickness 1.5 mm), a FSE PD/T2 (TE1 22 ms; TE2 90 ms; TR 3220 ms; echo train length 8; FA 90°, FoV 220 mm; matrix 256 × 256; slice thickness 3.0 mm), and a FLAIR (TE 100 ms; TR 8000 ms; inversion time 2000 ms; FA 90°, FoV 220 mm; matrix 256 × 256; slice thickness 3.0 mm).

A fully automated segmentation pipeline was developed based on the Montreal Neurological Institute processing pipeline (Sigurdsson et al. 2012; Zijdenbos, Forghani, and Evans 2002). The pipeline used a multispectral approach to segment voxels into global tissue classes (cerebrospinal fluid (CSF), GM, WM and white matter hyperintensities (WMH)). Following this, a regional parcellation pipeline –atlas-based segmentation method– was developed to obtain volumes of different substructures of the brain.

## Determination of VOI

The regional tissue segmentation pipeline parcelled the brain in 56 different regions (figure 1 of chapter 5). However, for the present study, we combined regions into a limited amount of 8 VOI known to differ in gross cytoarchitectural features. We separately assessed scaling of neocortical GM and WM to investigate in further detail the previously reported proportional changes as function of TBV. Three regions of neocortical GM were investigated, i.e., frontal (comprising of orbitofrontal and prefrontal GM, precentral gyrus, cingulated gyrus, insula and fornix), temporal (comprising of lateral temporal GM, parahippocampal and fusiform gyrus), and parieto-occipital GM. Cortical WM volume was studied in total and included all lobar WM, corpus callosum, internal and external capsule, and WMH. The medial temporal lobe (MTL), striatum, thalamus and cerebellum were separately studied because of their importance in many studies to neurodegenerative processes. MTL included amygdala and hippocampus (including CA regions I–IV, fimbria, and subiculum of the hippocampus). Striatum included the nucleus accumbens, caudate nucleus, putamen, and globus pallidus. The thalamus included also the hypothalamus. The cerebellum included cerebellar GM and WM. Left and right hemispheres of each structure were combined. Total brain volume (TBV) was calculated as the sum of the neocortical GM and WM, MTL, striatum, thalamus, brainstem and cerebellum. ICV was defined as the sum of TBV and CSF.

## Quality control of MRI segmentation

The quality of the segmentation of the 8 composite VOI was mostly dependent on the performance of the global tissue segmentation into GM, WM, WMH, and CSF, and for a small part dependent on the definition of topographical borders by the regional tissue segmentation. Performance of both global tissue and regional tissue segmentation was evaluated. The quality control of global tissue classification consisted of 3 steps described in (Sigurdsson et al. 2012). In summary these were: 1) visual inspection of the segmentation of 14 a priori selected slices of each subject ($N = 4356$), which led to additional manual editing in 43 cases and rejection of 53 cases and 2) comparison of automated versus manual global tissue segmentation of 5 preselected slices across the brain (including a slice located at the junction of the thalamus and subthalamic structures for reviewing segmentation of the deep gray matter nuclei) in 20 randomly selected cases. Resulting dice similarity index scores (Zijdenbos, Dawant, and Margolin 1994) were 0.82, 0.82, and 0.83 for GM, WM, and CSF respectively. 3) Reproducibility of the entire process of MRI acquisition and post-processing was evaluated by repeated scanning and segmentation (4 times in total) of 32 participants. Excellent intraclass correlation for all global tissue was found ($r > 0.98$, for all). Because the present study relies for an important part on good quality of ICV segmentation, the performance of the automated pipeline was further evaluated specifically on ICV. ICV was manually segmented on the same 20 brain scans used for step 2 of the quality control. Two researchers with extensive neuroradiological experience and blinded for the results of the automated segmentation, segmented ICV on axial 3D T1 weighted images, with correction and editing in sagittal and coronal planes. Resulting ICV were correlated with

ICV obtained by the automated pipeline. Pearson's correlation was 0.97 (0.93–0.99) and Bland-Altmann plot showed a small overestimation of ICV of 31 $cm^3$ on average by the automated segmentation, but no proportional error (figure 1 and 2).

Performance of regional tissue classification was validated against four complete manually labeled scans. Dice similarity index scores per studied region were; frontal GM: 0.83, temporal GM: 0.83, parieto-occipital GM: 0.81, striatum: 0.83, MTL: 0.80, thalamus: 0.92, cerebellum: 0.92, white matter: 0.86.

## Statistical analysis

All statistical analyses were performed with SAS v 9.13 (SAS Institute Inc., Cary, NC, USA) and all graphs were generated with R v 3.1.2 (R Core Team 2014).

### *Analytical sample of AGES-Reykjavik Study*

MR scanning was performed on consenting MR eligible participants, between 2002 and 2006. From the total AGES-Reykjavik sample of 5764 participants, 4726 underwent successful MRI scanning. Global and regional segmentations were successful in 4613 MR scans. We excluded cases of dementia ($n = 202$) and MCI ($n = 422$), assumed to have higher rates of atrophy, and cases for which cognitive function had not been assessed ($n = 106$). Our final study sample consisted of 3883 people with successful brain MRI and segmentation of the images. Demographics and brain structure volumes of the AGES-Reykjavik study population were compared between women and men with $t$-tests for continuous variables and $\chi^2$ tests for categorical variables. All VOI were normally distributed.

### *Estimation of scaling coefficients of different VOI*

Allometric coefficients of VOI with ICV were calculated using the general equation of allometric analyses, $\log(y) = \log(b) + \alpha \times \log(x)$, where x is ICV, y VOI, log(b) intercept, and $\alpha$ represents the allometric coefficient (Harvey 1982), i.e., the slope of the regression between log (ICV) and log (VOI). A coefficient greater than 1.0 is considered a positive allometric coefficient, i.e., VOI increased with a power greater than 1 relative to ICV. A coefficient smaller than 1.0 is seen as a negative allometric coefficient, i.e., VOI increased with a power less than 1 relative to ICV. We chose ICV, instead of TBV, as measure of brain volume to avoid a possible bias towards isometry in estimating allometric coefficients of large VOI. Large structures occupy large volumes in TBV making the range of possible deviations from isometry smaller; this may produce an overestimate of coefficients towards 1 and reduce the ability to estimate allometric

Figure 1: Accuracy of automated segmentation pipeline; Pearson correlation manual versus automated segmentation of ICV

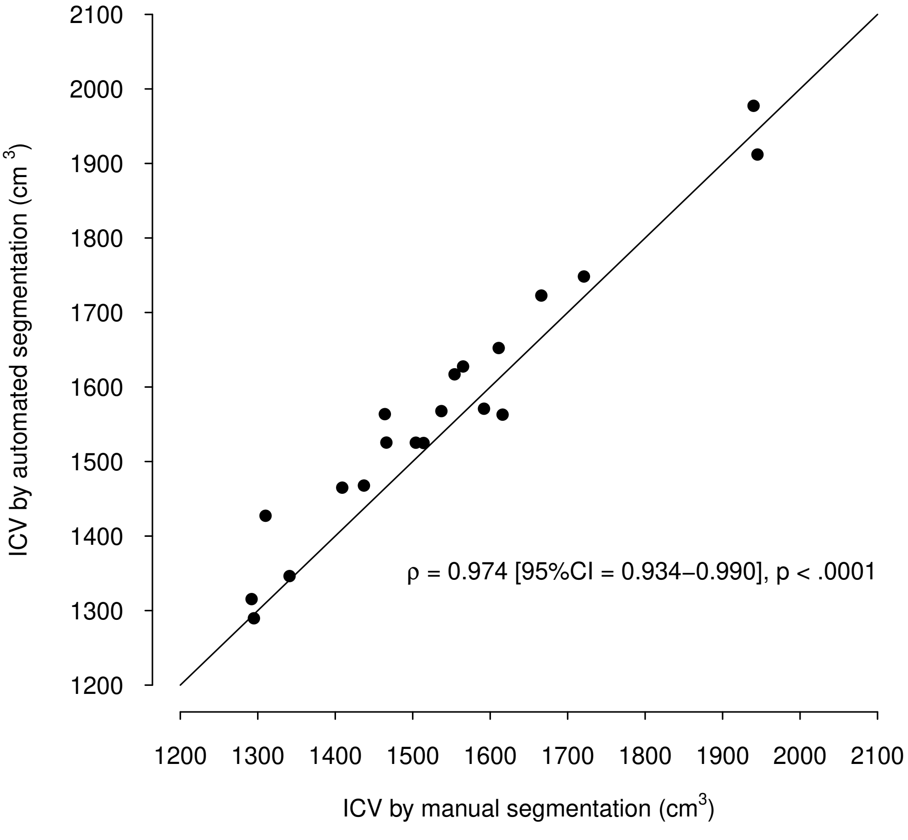
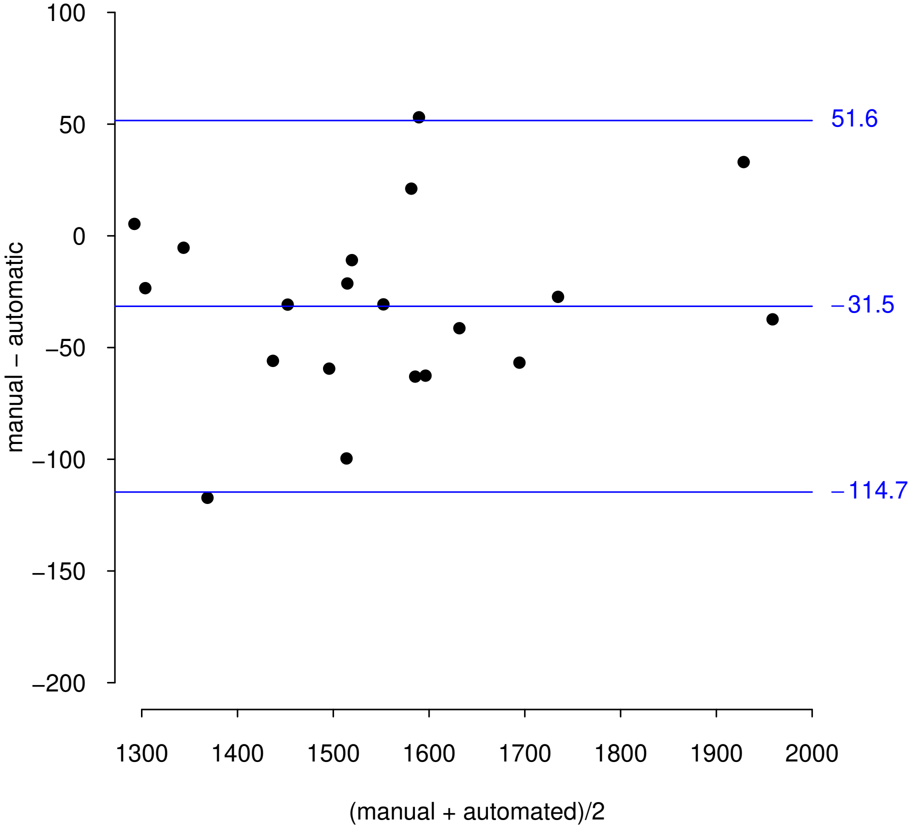


Figure 2: Accuracy of automated segmentation pipeline; Bland-Altman plot manual versus automated segmentation of ICV



coefficients deviant from 1 (Deacon 1990). With the use of ICV none of the structures studied comprised more than 24% (WM) of ICV. Another important reason was that ICV is regarded as a marker for brain volume at its maximum size and therefore a marker of “premorbid” brain size. At time of scanning, brains of most study participants experienced more or less atrophy due to ageing or pathological processes. These are factors we can largely control for in our statistical analyses, whereas it is more difficult to control for differences between current TBV and original TBV. Log-transformed VOI were plotted against log transformed ICV (figure 3). For each VOI, allometric coefficients with ICV were calculated adjusted for age and sex, ($\log(VOI) = intercept + \alpha \times \log(ICV) + \beta_{\text{age}} \times age + \beta_{\text{sex}} \times sex$) and tested against the isometric scaling law of 1:1.

## Comparison of allometric scaling coefficients of different VOI

Allometric coefficients of the different VOI to ICV were compared using a marginal model (PROC MIXED SAS procedure (SAS Institute Inc., Cary, NC, USA) with repeated statement and unstructured correlation matrix), which takes into account the correlations between the VOI. The log transformed VOI were entered as dependent variables and log transformed ICV as independent variable. Interactions of $\log(VOI)$ with $\log(ICV)$ were entered in the model as a cross product together with $\log(ICV)$, $\log(VOI)$, age, and sex. The model was also run with additional independent variables (year of birth, height, achievement of higher education (high school diploma or above), presence of infarct(s), and contrast-to-noise ratio (CNR) between GM and WM and CNR between GM and cerebrospinal fluid), but these did not exert significant effects and were omitted to keep the model parsimonious. A Bonferroni correction was applied to adjust for multiple testing (number of comparisons between slopes in the 3 mixed models = 85) and a $p$-value $< 0.00059$ ($= 0.05/85$) was considered significant. The analysis was performed in the entire sample and repeated for women and men separately. The numerical results of the marginal model are reported in table 2.

## Allometric scaling of VOI in different age groups

To assess whether age influenced scaling of VOI with ICV, scaling coefficients of VOI to ICV were calculated for each quartile of age; the age range of the youngest quartile being 66–71 years, and of subsequent quartiles being, 72–75, 76–79 and 80–95 years. The coefficients were compared among the quartiles by testing whether there was an interaction between the quartiles and ICV.

### Testing the segmentation pipeline with artificially linearly scaled data

To test whether a potential systematic error in the automated segmentation pipeline could introduce allometry in the volumetric data of AGES-Reykjavik study, artificially linearly scaled brain scans were entered into the pipeline and the output was investigated for allometry. Scans of a relatively small (1402 $cm^3$) and relatively large brain (1756 $cm^3$) were skull stripped and linearly scaled by factors ranging from 0.75–1.25 of its original size with steps of 0.01. The resulting sets of scaled images were subsequently processed through the AGES-Reykjavik pipeline. Log transformed volumes of the global tissues GM, WM and CSF were plotted against log transformed ICV and $\alpha$-coefficients were calculated.

### Comparison of allometric model and linear regression model

The fit of the allometric model of the relation of each VOI to ICV on the data was compared to a linear regression model. The line of prediction from the allometric model and linear model were superimposed in the same graph and $R^2$ of each model was calculated. Both models were conducted with adjustments for age and sex.

### Supportive analyses in datasets of CARDIA and ADNI

Supportive analyses were conducted in datasets of CARDIA and ADNI. In both samples the allometric coefficients of VOI with ICV were calculated, corrected for age and sex, and tested against the isometric scaling law of 1:1, similar to the first part of analysis conducted in the AGES-Reykjavik data.

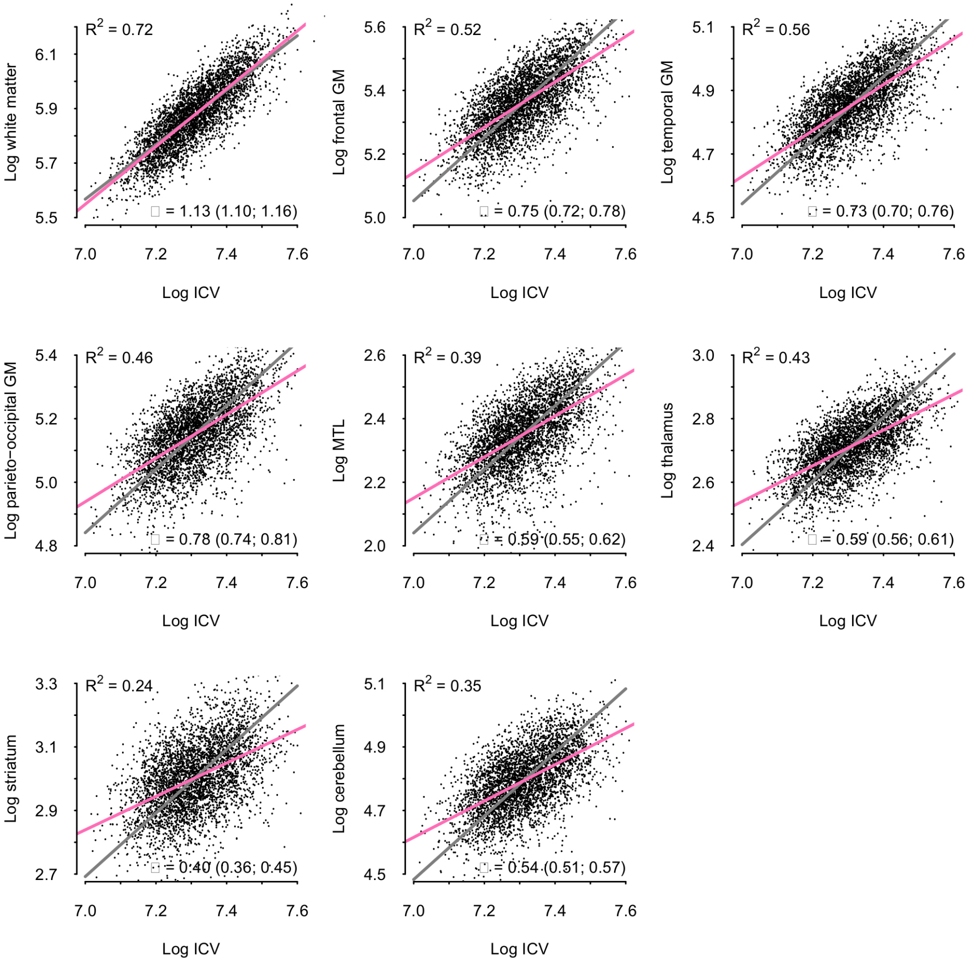
The multicenter prospective cohort CARDIA study was designed to examine the development and determinants of clinical and subclinical cardiovascular disease and its risk factors. Between 1985–1986, 5115 black and white men and women (aged 16–30) were recruited from 4 urban sites across the United States and underwent 8 examination cycles (Friedman et al. 1988). All participants provided written informed consent at each exam, and institutional review boards from each study site and the coordinating center annually approved the study. In 2010–2011, 3498 (72%) of the surviving cohort attended a 25-year follow-up exam. As part of this exam, a subsample of the cohort participated in the CARDIA Brain substudy, designed to investigate the morphology, pathology, physiology and function of the brain with MRI. Exclusion criteria at the time of sample selection, or at the MRI site, were a contraindication to MRI or a body size that was too large for the MRI scanner. Of those who were eligible for the substudy, 719 individuals received whole brain MRI scans. Post-scan image processing was performed by the Section of Biomedical Image Analysis (BIA), Department of Radiology, University of Pennsylvania. MRI scans were inspected and passed through a quality control process. Based on previously described methods (Davatzikos, Tao, and Shen 2003; Goldszal et al. 1998; Lao et al. 2008; Shen et al. 2002; Zacharaki et al. 2008), an automated algorithm was used to segment MRI structural images of supratentorial brain tissue into GM, WM and cerebrospinal fluid. GM and WM were further characterized and segmented as 92 anatomic ROIs in each hemisphere, from which summary VOIs used in the current study were calculated. ICV was calculated as the sum of all supratentorial structures, but not infratentorial.

Some data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Accessed July 1, 2017. http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see http://www.adni-info.org.

For the supportive analysis of our study we used volumetric brain measures derived from the standardized 1.5 T MRI screening dataset in cognitively healthy subjects that was collected between August 2005 and October 2007 and processed using FreeSurfer software (Freesurfer Software website. Cortical Reconstruction and volumetric segmentation (Accessed July 1, 2017. http://surfer.nmr.mgh.harvard.edu).

Figure 3: Allometric coefficients of VOI with ICV



Gray line, isometry line; Red line, line of allometric log-log model between ICV and VOI.

# RESULTS

## Characteristics AGES-Reykjavik sample

The AGES-Reykjavik sample had a mean age of 75.7 (standard deviation = 5.2) years, of which 59.8% were women. ICV ranged from 1116–2162 $cm^3$ in the total sample; from 1116–1868 $cm^3$, in women and from 1232–2162 $cm^3$ in men. Women had on average a lower educational level ($p < 0.0001$), higher BMI ($p = 0.003$), were diagnosed less often with diabetes ($p < 0.0001$), and had smoked ($p < 0.0001$) and drank alcohol ($p < 0.0001$) more sparingly compared to men. Women had lower means of ICV and all VOI compared to men ($p < 0.0001$) (table 1).

## Allometric scaling coefficients of all VOI

All VOI scaled non-isometrically to ICV (figure 3). After correction for age and sex, a positive allometric coefficient of 1.14 (95% confident interval = 1.11–1.17) was estimated for WM volume and negative allometric coefficients were found for frontal GM (0.76 (0.73–0.79)), temporal GM (0.75 (0.72–0.78)), parieto-occipital GM (0.79 (0.76–0.83)), MTL (0.60 (0.56–0.64)), thalamus (0.59 (0.56–0.62)), striatum (0.41 (0.37–0.45)), and cerebellum (0.55 (0.52–0.59)). All were found significantly differently from 1 (1:1 scaling law to ICV ($p < 0.0001$)).

## Significant scaling differences between VOI

Results from the marginal model showed that the $\alpha$-coefficient of WM volume to ICV was significantly different from the $\alpha$-coefficients of all GM VOI (table 2) in the entire sample, and in women and men separately. The $\alpha$-coefficients of the different neocortical GM areas to ICV were not significantly different from each other in women and men separately. Also, the $\alpha$-coefficients of MTL, thalamus, and cerebellum were not significantly different from each other in women and men separately. However, in the entire sample the $\alpha$-coefficient of the MTL was not significantly different from the $\alpha$-coefficient of the parieto-occipital GM, but was significantly different from the thalamus and the cerebellum. The $\alpha$-coefficient of the striatum was significantly different from all other $\alpha$-coefficients except for the $\alpha$-coefficient of the thalamus and cerebellum in the entire sample, and the $\alpha$-coefficient of the cerebellum in men only.

Table 1: General characteristics of the study sample

| Mean (SD) or % (N) | All $N = 3883$ | Women $N = 2307$ | Men $N = 1576$ | $p^a$ |
|---|---|---|---|---|
| Age in years | 75.7 (5.2) | 75.6 (5.3) | 75.8 (5.1) | 0.27 |
| Higher education | 12.2 (473) | 6.52 (150) | 20.6 (323) | <.0001 |
| Smoking status | | | | |
| Never | 41.7 (1619) | 53.2 (1226) | 24.9 (393) | |
| Former | 44.5 (1728) | 34.8 (803) | 58.7 (925) | <.0001 |
| Current | 13.8 (534) | 12.0 (276) | 16.4 (258) | |
| Alcohol intake | | | | |
| Never | 21.5 (829) | 29.3 (671) | 10.1 (158) | |
| Former | 10.8 (418) | 7.78 (178) | 15.3 (240) | <.0001 |
| Current | 67.7 (2608) | 62.9 (1440) | 74.6 (1168) | |
| BMI (kg/m$^2$) | 27.0 (4.3) | 27.2 (4.7) | 26.8 (3.7) | 0.003 |
| Diabetes | 11.1 (430) | 8.76 (202) | 14.5 (228) | <.0001 |
| Stroke | 28.9 (1123) | 23.5 (541) | 36.9 (582) | <.0001 |
| Intracranial volume | 1503 (147) | 1423 (105) | 1619 (121) | <.0001 |
| Total brain volume | 1046 (98) | 1005 (80) | 1105 (91) | <.0001 |
| WM | 360 (45) | 342 (37) | 386 (42) | <.0001 |
| Neocortical gray matter | | | | |
| Frontal | 215 (22) | 207 (19) | 225 (22) | <.0001 |
| Temporal | 129 (13) | 124 (11) | 136 (13) | <.0001 |
| Parieto-occipital | 174 (19) | 169 (17) | 181 (19) | <.0001 |
| Thalamus | 15.1 (1.4) | 14.7 (1.2) | 15.8 (1.3) | <.0001 |
| Medial temporal lobe | 10.6 (1.1) | 10.2 (1.0) | 11.1 (1.1) | <.0001 |
| Striatum | 20.3 (2.3) | 19.5 (2.0) | 21.3 (2.2) | <.0001 |
| Cerebellum | 121.3 (12.0) | 117.4 (10.6) | 126.9 (11.7) | <.0001 |

BMI, body mass index; WM, sum of neocortical white matter; all volumes in cm$^3$.

a $t$-test for continuous variables and $\chi^2$ test for categorical variables.

## Allometric scaling in different age groups

$\alpha$-coefficients of VOI to ICV for each quartile of age are shown in table 3. $\alpha$-coefficients of the both cortical and deep GM structures and cerebellum in the older quartiles appeared somewhat lower compared to the younger quartiles and the $\alpha$-coefficient of WM appeared higher in the older quartiles. However, these differences were nonsignificant, except for temporal GM which was significantly lower in the older quartiles compared to the younger ($p = 0.004$).

Table 2: Comparison of $\alpha$-coefficients of different VOI to ICV, random effects mixed model

| VOI | $\alpha$-coefficient (95%CI) | *p*-values from comparison of $\alpha$-coefficients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | White matter | Frontal | Temporal | Par-occ | MTL | Thalamus | Cerebellum |
| | | | | | All $N = 3883$ | | | |
| White matter | 1.09 (1.06-1.11) | | | | | | | |
| Frontal | 0.740 (0.714-0.766) | <.0001 | | | | | | |
| Temporal | 0.750 (0.724-0.774) | <.0001 | **0.34** | | | | | |
| Par-occ | 0.712 (0.683-0.741) | <.0001 | **0.009** | **0.002** | | | | |
| MTL | 0.672 (0.642-0.702) | <.0001 | <.0001 | <.0001 | **0.02** | | | |
| Thalamus | 0.588 (0.563-0.613) | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | | |
| Cerebellum | 0.598 (0.570-0.627) | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | **0.48** | |
| Str | 0.552 (0.518-0.586) | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | **0.02** | **0.01** |
| | | | | | Women $N = 2307$ | | | |
| White matter | 1.14 (1.11-1.18) | | | | | | | |
| Frontal | 0.748 (0.709-0.787) | <.0001 | | | | | | |
| Temporal | 0.724 (0.687-0.762) | <.0001 | **0.15** | | | | | |
| Par-occ | 0.776 (0.732-0.819) | <.0001 | **0.12** | **0.01** | | | | |
| MTL | 0.591 (0.543-0.639) | <.0001 | <.0001 | <.0001 | <.0001 | | | |
| Thalamus | 0.590 (0.553-0.627) | <.0001 | <.0001 | <.0001 | <.0001 | **0.97** | | |
| Cerebellum | 0.552 (0.508-0.596) | <.0001 | <.0001 | <.0001 | <.0001 | **0.18** | **0.11** | |
| Striatum | 0.380 (0.325-0.434) | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 |

Continued on next page

VOI, volume of interest; White Matter, sum of neo-cortical white matter; Frontal, frontal neo-cortical gray matter; Temporal, temporal neo-cortical gray matter; Par-occ, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.

*p*-value from log-log mixed model adjusted for age and sex.

Bold figures represent non-significant $^{p}$-values ($> 0.00059$) after Bonferroni correction.

Table 2 – continued from previous page

| VOI | $\alpha$-coefficient (95%CI) | *p*-values from comparison of $\alpha$-coefficients | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | White matter | Frontal | Temporal | Par-occ | MTL | Thalamus | Cerebellum |
| | | | | | Men $N = 1576$ | | | |
| White matter | 1.11 (1.07-1.16) | | | | | | | |
| Frontal | 0.761 (0.713-0.809) | <.0001 | | | | | | |
| Temporal | 0.742 (0.696-0.787) | <.0001 | **0.33** | | | | | |
| Par-occ | 0.787 (0.731-0.843) | <.0001 | **0.24** | **0.07** | | | | |
| MTL | 0.589 (0.532-0.645) | <.0001 | <.0001 | <.0001 | <.0001 | | | |
| Thalamus | 0.582 (0.536-0.627) | <.0001 | 0.0004 | <.0001 | <.0001 | **0.81** | | |
| Cerebellum | 0.523 (0.469-0.577) | <.0001 | <.0001 | <.0001 | <.0001 | **0.07** | **0.04** | |
| Striatum | 0.431 (0.367-0.495) | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | **0.01** |

VOI, volume of interest; White matter, sum of neo-cortical white matter; Frontal, frontal neo-cortical gray matter; Temporal, temporal neo-cortical gray matter; Par-occ, parietal and occipital neo-cortical gray matter; MTL, medial temporal lobe.

*p*-value from log-log mixed model adjusted for age and sex.

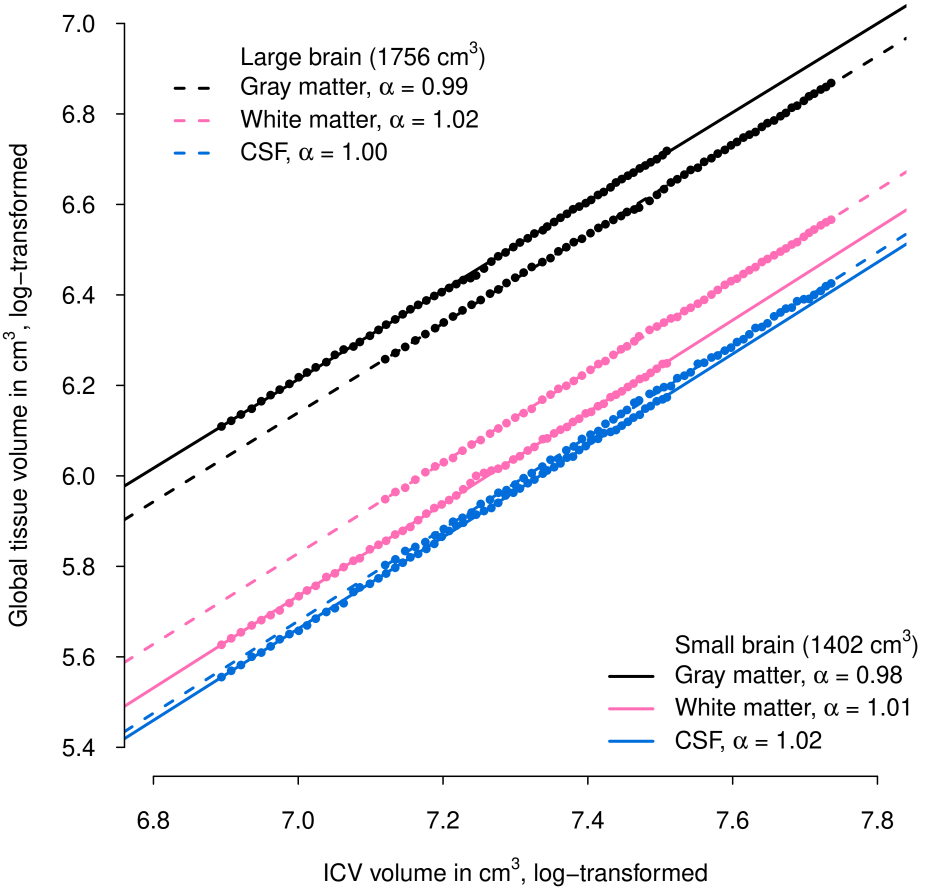
Bold figures represent non-significant *p*-values ($> 0.00059$) after Bonferroni correction.

Table 3: Comparison of $\alpha$-coefficients of VOI to ICV of different quartiles of age

| Volume of interest | $\alpha$-coefficients for quartile of age (95% CI) | | | | *p*[a] |
|---|---|---|---|---|---|
| | Quartile 1 66-71 years | Quartile 2 72-75 years | Quartile 3 76-79 years | Quartile 4 80-95 years | |
| Neocortical white matter | 1.05 (1.01-1.09) | 1.04 (1.00-1.08) | 1.09 (1.04-1.14) | 1.06 (1.02-1.11) | 0.40 |
| Frontal gray matter | 0.74 (0.70-0.79) | 0.71 (0.66-0.75) | 0.72 (0.67-0.77) | 0.66 (0.62-0.71) | 0.11 |
| Temporal gray matter | 0.77 (0.73-0.81) | 0.72 (0.68-0.76) | 0.73 (0.68-0.78) | 0.65 (0.61-0.70) | 0.004 |
| Parietal & occipital gray matter | 0.71 (0.66-0.76) | 0.66 (0.61-0.71) | 0.69 (0.63-0.75) | 0.66 (0.61-0.72) | 0.50 |
| Medial temporal lobe | 0.67 (0.62-0.72) | 0.66 (0.61-0.71) | 0.63 (0.57-0.69) | 0.60 (0.54-0.66) | 0.32 |
| Thalamus | 0.58 (0.53-0.62) | 0.55 (0.51-0.59) | 0.56 (0.51-0.61) | 0.55 (0.51-0.60) | 0.76 |
| Striatum | 0.56 (0.50-0.62) | 0.52 (0.46-0.57) | 0.53 (0.46-0.60) | 0.48 (0.42-0.55) | 0.38 |
| Cerebellum | 0.58 (0.53-0.63) | 0.57 (0.52-0.62) | 0.57 (0.51-0.62) | 0.55 (0.50-0.61) | 0.90 |

[a] linear regression with volume of interest as dependent variable and intracranial volume, quartile of age and their interaction term. *p*-value from the interaction term between ICV and quartile of age.

Figure 4: Accuracy of automated segmentation pipeline; scaling of artificially linearly scaled data



## Little allometry introduced by segmentation pipeline

Figure 4 displays log of global tissue volumes plotted against log ICV obtained by the automated segmentation pipeline based on the artificially linearly scaled data set of a relatively large and small brain. The $\alpha$-coefficients were 0.99 for GM, 1.02 for WM, and 1.00 for CSF for dataset based on the relatively large brain and 0.98 for GM, 1.01 for WM, and 10.2 for CSF for the dataset based on the relatively small brain. Because of the almost perfect fit of the points and the regression line these $\alpha$-coefficients were significantly different from the isometric scaling law of 1.0 (all $p$-values $< 0.0001$), except for the CSF in the large brain.

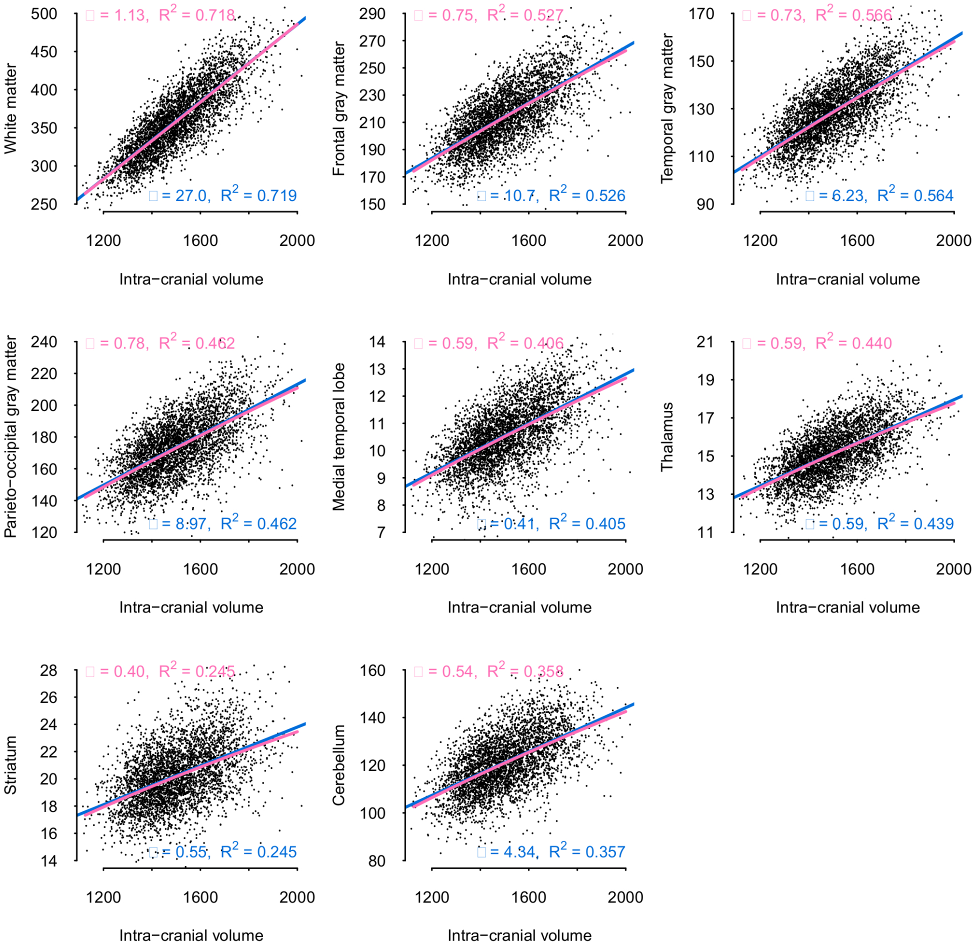
## Comparable fit of allometric and linear regression models

Figure 5 superimposes the line of prediction of the allometric model (and associated $\alpha$-coefficient and $R^2$) with line of prediction of the linear model (and associated $\beta$-coefficient and $R^2$). Compared to the $R^2$ of the linear model, the $R^2$ of the allometric model was a few per mill smaller for cerebellar, cortical and deep GM structures and a few per mill larger for WM. Thus, the models have a comparable fit and can substitute each other.

## Allometric scaling in CARDIA and ADNI

The CARDIA sample consisted of individuals with a mean age of 50 (3.5) years, of which 52.9% were women. ICV in the CARDIA sample, including only supratentorial areas, varied from 999–1643 cm$^3$. The ADNI sample consisted of individuals with a mean age of 76 (5.0) years, of which 49.4% were women. ICV in the ADNI sample varied from 1116–1985 cm$^3$. We found the highest allometric coefficients for WM volume in both CARDIA ($\alpha = 1.05$) and ADNI ($\alpha = 1.00$). All GM areas had negative allometric coefficients with the lowest coefficients in the deep GM areas (table 4). Roughly, results suggest similar trends compared with those found in the AGES-Reykjavik data. However, important differences were 1) allometric coefficients of the neocortical GM areas to ICV in CARDIA with values between 0.90–0.94 were higher, compared with those in the AGES-Reykjavik and ADNI samples, and 2) WM volume in the ADNI data set seemed to increase isometrically with ICV.

Figure 5: Comparison of allometric log-log model to linear model of VOI to ICV



Red line, line of the allometric log-log model between the ICV and the VOI;
Blue line, line of the linear model between the ICV and the VOI.

Table 4: Comparison of $\alpha$-coefficients in study populations of AGES-Reykjavik, ADNI, and CARDIA

| Volume of interest, M (SD) | AGES ($N = 3883$) | | ADNI ($N = 180$) | | CARDIA ($N = 709$) | |
|---|---|---|---|---|---|---|
| | Vol, M (SD) | $\alpha$ ($R^2$) | Vol, M (SD) | $\alpha$ ($R^2$) | Vol, M (SD) | $\alpha$ ($R^2$) |
| Intracranial volume | 1503 (147) | NA | 1532 (156) | NA | 1208 (133)$^a$ | NA |
| Total brain volume | 1046 (98) | NA | 1000 (101) | NA | 983 (107)$^a$ | NA |
| Neocortical white matter | 360 (44) | 1.13 (0.72) | 443 (57) | 1.00 (0.67) | 462 (59) | 1.05 (0.84) |
| Frontal GM | 215 (22) | 0.75 (0.52) | 159 (16) | 0.72 (0.59) | 197 (22) | 0.90 (0.76) |
| Temporal GM | 129 (13) | 0.73 (0.56) | 122 (13) | 0.81 (0.67) | 156 (17) | 0.91 (0.73) |
| Parietal and occipital GM | 174 (19) | 0.78 (0.46) | 114 (12) | 0.81 (0.60) | 124 (14) | 0.94 (0.79) |
| Thalamus | 15.1 (1.4) | 0.59 (0.39) | 12 (1.4) | 0.76 (0.53) | 14 (1.5) | 0.50 (0.26) |
| Medial temporal lobe | 10.6 (1.1) | 0.59 (0.43) | 9.9 (1.2) | 0.49 (0.31) | 10 (1.1) | 0.61 (0.36) |
| Striatum | 20.3 (2.3) | 0.40 (0.24) | 20 (2.2) | 0.62 (0.30) | 20 (2.1) | 0.59 (0.48) |
| Cerebellum | 121 (12) | 0.54 (0.35) | 123 (12) | 0.50 (0.36) | NA | NA |

M (SD), mean (standard deviation); volumes are displayed in $cm.^3$ AGES, Age, Gene, Environment/ Susceptibility - Reykjavik Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; CARDIA, Coronary Artery Risk Development in Young Adults Study; Vol., volume; GM, gray matter.

$\alpha$, allometric coefficient derived from $(\log(VOI) = intercept + \alpha \times \log(ICV) + \beta_{\text{age}} \times age + \beta_{\text{sex}} \times sex)$.

a includes supratentorial areas only

# DISCUSSION

## Allometric scaling of WM, cortical and deep GM

One goal of the present study was to assess and compare scaling coefficients of different VOIs to ICV in the AGES-Reykjavik dataset. We found all VOI to scale allometrically with ICV. One could roughly discern three patterns of scaling, i.e., WM scaling, neocortical GM scaling and deep GM scaling. First, neocortical WM was the only structure to proportionally increase in larger ICV with a positive allometric coefficient of 1.14. Scaling of WM was found significantly different from all GM structures and cerebellum. Second, negative allometric coefficients were found for frontal (0.76), temporal (0.74), and parieto-occipital (0.79) cortical GM structures. Scaling of neocortical GM structures (frontal, temporal, and parieto-occipital) was not significantly different from each other, but was significantly larger than in deep GM structures when women and men were separately assessed. Also, scaling of MTL (0.60), thalamus (0.59), and the cerebellum (0.55) was not significantly different from each other in women and men separately. The scaling coefficient for striatal volume (0.41) was relatively most invariant over the range of ICV and was significantly different from all other structures, except the cerebellum.

Allometric scaling cannot solely be explained by age, sex, ethnicity or a systemic bias from segmentation pipeline. One important limitation of our study was that the sample consisted of older individuals, who have experienced various amounts of brain atrophy. Therefore, the observed scaling exponents cannot be extrapolated to younger samples. After stratifying the AGES-Reykjavik sample into quartiles of age, we found most structures to have similar scaling coefficients except for temporal GM (not including the MTL), which had lower $\alpha$-coefficients in older individuals. We do not have an explanation for the significant difference in scaling found for temporal GM, but it prompted us not to rule out the possibility that allometric scaling of sub structures of the brain may vary with age in a way that we could not detect in the age span of our sample. Nonetheless, the findings of this analysis show that allometric scaling is a feature of the brain in the older population, which cannot be accounted for by adjusting for age when performing brain comparative studies.

A second important limitation was that all participants were Icelandic and the sample was genetically relatively homogeneous. Ancillary analyses in ADNI and CARDIA, with participants of younger age and different ethnicities, also showed that WM proportionally increased with increasing ICV, followed by proportionally decreases in GM, with greatest decreases in the deep GM structures, similar to our observations in the AGES-Reykjavik study. Still, there were also differences in the results between the studies. The allometric coefficients of the cortical GM areas to ICV in CARDIA seemed higher compared to those in the AGES-Reykjavik and ADNI samples. A potential explanation could be that "ICV" in CARDIA was constructed from supratentorial structures only, and as a result allometric coefficients were higher. Another explanation could be that in the relatively young sample of the CARDIA allometric scaling is less pronounced. Further studies are needed to specifically examine this hypothesis. A second difference between the results of the additional analyses and our primary analyses in AGES-Reykjavik study was that WM volume in the ADNI data set seemed to increase isometrically with ICV. This may be explained by differences in tissue segmentation between GM and WM, as suggested by the higher mean volume of WM and lower mean volume of GM in ADNI compared with AGES-Reykjavik. Depending on how border voxels are assigned to the GM and WM tissue classes, the difference between allometric coefficients may differ. Because of these differences in scaling coefficients among the study samples, it is at the moment not possible to establish fixed reproducible allometric coefficients for the human brain and more studies are needed.

A third potential limitation of the study was the use of an automated MR segmentation technique. Systematic errors, such as improper skull stripping, incorrect intensity thresholds, difficulty in segmenting sulcal CSF, or imprecise template warping could all be possible sources of finding allometric correlations between VOI to ICV. However, when we fed artificially linearly scaled scans in the segmentation pipeline, the scaling coefficients of the output only showed small deviations from the isometric scaling law of 1, at maximum in the order of 2%. This could not explain the much larger deviations from 1 of the different scaling laws of VOI in the study sample. Therefore, we did not find evidence for a possible systematic error in the segmentation pipeline that could explain the allometry.

## Allometric scaling as true feature of brain geometry

Differences in geometric or cytoarchitectural properties of different brain structures may underlie differences and similarities in scaling to ICV. We observed similar scaling coefficients of different neocortical GM areas, which suggest they preserve proportionality to one another regardless of ICV. However, cortical GM and WM had significantly different scaling coefficients, indicating they do not preserve proportionality with varying brain size. This can be explained by differences in topology, where GM can be regarded as a surface of neural tissue covering an associated volume of WM (Dale, Fischl, and Sereno 1999). The different lobes of the neocortex are similarly organized in repetitive cortical columns (Mountcastle 1997). Assuming a stable thickness of the neocortical GM "surface" across various brain sizes, as suggested by several studies (Hofman 1985; Hofman 1988; Mountcastle 1997), neocortical GM to WM should scale by an exponent of 2/3 (square-cube). If we focus on the results based on the AGES-Reykjavik study sample, we can observe that scaling coefficients of neocortical white to gray matter range from 0.65 to 0.70 (0.76/1.14 for frontal GM, 0.74/1.14 for temporal GM, and 0.79/1.14 for parieto-occipital GM), which approximates the geometric square-cube scaling law. Nevertheless, we did not establish the same results in the younger sample of CARDIA or the smaller sample of the ADNI and caution should be taken to apply a purely square-cube scaling law to the architecture of neo cortex. In a previous study slight increases of neocortical thickness (scaling of 0.2) with increase in ICV were observed (Im et al. 2008). Another recent study showed the neocortical GM to have a more extensive gyrification, i.e., to be "twistier", in larger brains compared to smaller ones (Germanaud et al. 2012). Also, for other parameters, such as cell soma size or amount of supporting glial cells, the extent to which they vary with increasing brain size is unclear. Some studies have also pointed to possible constraints in WM expansion, which should lead to scaling factors of white to gray that are higher than the square-cube law of 2/3. It has been proposed that hemispheric specialization increases with increasing brain volume, which would lead to a decrease in interhemispheric connections and thus a decrease in WM volume (Ringo et al. 1994). However, the coefficients reported in the present study for the AGES-Reykjavik study provide no evidence for such a limitation on WM expansion

The disproportionally lower scaling coefficients of deep GM structures to ICV compared to the cortex are not readily explained. The cortex gives rise to connections with striatum and thalamus, thus these structures could be expected to expand with neocortical GM volume. However, we found no evidence for preserved proportionality of the striatum and thalamus with cortical GM with scaling. Possibly, the structures are more strongly influenced by other factors during brain development than neocortical growth. Brain structures grow in asynchronous patterns from birth through early adulthood and the striatum has been shown, together with frontal brain areas, to undergo more extensive developmental changes relatively late in early adulthood compared to other brain areas (Sowell et al. 1999). Also, genetic factors could influence variation in regional brain volumes and lead to disproportional neocortical and deep GM volume increases with ICV, especially for the striatum. One twin study showed that the volume of the striatum, thalamus, and cerebellum were significantly more influenced by genetic factors compared to neocortical structures that were influenced more by environmental factors (Yoon et al. 2011). And another twin-study concluded the phenotypic covariance of the striatal structures, hippocampus, and thalamus was primarily due to patterns of genetic covariance (Eyler et al. 2011).

## Implications for methods of head/ brain size adjustment

Knowledge on allometric scaling of regional brain volumes is important for the discussion of adjustment methods for normal variation in comparative brain studies. Allometric scaling implies both nonproportionality and nonlinearity of scaling. Our results contribute to the understanding why certain methods should not be used. Ratios of brain structure volume over ICV or stereotaxic normalization by means of linear affine transformation assume isometric scaling of the brain, i.e., proportionate scaling, which may lead to over- or underestimation of results. Therefore the use of these methods should be avoided, except when studying disproportionality is the purpose. The erroneous effect of linear spatial normalization on groups with differences in ICV was illustrated in a study comparing neocortical thickness differences in stereotaxic and native space between men and women (Lüders, Narr, et al. 2006). The normalized data showed a disproportionately increased neocortical thickness in women compared to men, which was considerably attenuated in the unscaled data. Another important finding of our study was that allometric scaling was most apparent in deep GM structures. Unwanted effects of spatial registration therefore may be expected to be especially problematic in deep gray matter structures. Previously, a study reported that spatial-transformation based methods indeed produce significantly different proportions in smaller structures such as the hippocampus (Allen et al. 2008). Lastly, we compared the fit of the allometric model to a linear model in predicting the relation of VOI to ICV. We found very small differences in $R^2$, which implies the allometric model and linear model could substitute each other in the range of total brain size variation among humans. Therefore, we conclude that it is important in brain comparative studies to adjust for nonproportionality, but not for nonlinearity.

## CONCLUSION

In summary, our study found allometric scaling of WM, neocortical GM and deep GM structures to ICV in large samples of adult humans with different age, sex and ethnicity. A positive allometric coefficient was found for WM and negative allometric coefficients for neocortical and deep GM structures, with smallest scaling coefficients for deep GM. Furthermore, our analysis showed that the allometric scaling could not solely be explained by age, sex, ethnicity, or a possible systematic bias arising from the automated segmentation algorithm. We therefore conclude allometry is a true feature of the brain geometry.

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