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Effects of age on volumes of cortex, white matter and subcortical structures

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Abstract

The effect of age was investigated in and compared across 16 automatically segmented brain measures: cortical gray matter, cerebral white matter, hippocampus, amygdala, thalamus, the accumbens area, caudate, putamen, pallidum, brainstem, cerebellar cortex, cerebellar white matter, the lateral ventricle, the inferior lateral ventricle, and the 3rd and 4th ventricle. Significant age effects were found for all volumes except pallidum and the 4th ventricle. Heterogeneous age responses were seen in that age relationships for cortex, amygdala, thalamus, the accumbens area, and caudate were linear, while cerebral white matter, hippocampus, brainstem, cerebellar white, and gray matter, as well as volume of the lateral, inferior lateral, and 3rd ventricles showed curvilinear relationships with age. In general, the findings point to global and large effects of age across brain volumes.

Keywords: MRI; Morphometry; Age; Cortex; White matter; Cerebellum; Ventricles; Hippocampus; Amygdala; Thalamus; Accumbens area; Striatum; Pons

1. Introduction

Several studies have examined the effects of age on different brain volumes, among them total gray or cortical gray matter [3,5,12,16,17,22,23,25,28,29,35,36], white matter [5,12,14,23,28,36], hippocampus [17,21,22,35], amygdala [17,21], thalamus [36,36], pons [20,24,26,36], caudate nucleus [17,19,27], putamen [27], globus pallidus [27], cerebellum [8,17,24,26,32], and ventricular spaces [27,21,28]. While semi-automated techniques for the quantification of global gray and white matter are often used (e.g. [5,12]), exact measurements of specific subcortical structures are typically obtained by manually tracing their boundaries in MR images. This requires high technical and neuroanatomical skills, and is quite time consuming. Thus, morphometric reports are usually limited to one or a few such structures. Knowledge of the relative age decline of different brain volumes is, therefore, limited by the use of different samples, scanning protocols and volumetric techniques.

The present study utilizes automatic labeling of all of the above mentioned brain structures in an adult lifespan sample. The results of manual labeling using the validated techniques of the Center for Morphometric Analysis [4,11,18,32] are used to automatically extract the information required for automating the segmentation procedure [9]. The effects of age is investigated in, and compared across, cortical gray matter, cerebral white matter, hippocampus, amygdala, thalamus, the

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accumbens area, caudate, putamen, pallidum, the brainstem, cerebellar cortex, cerebellar white matter, the lateral ventricle, the inferior lateral ventricle, and the 3rd and 4th ventricle. The nature of each measure's relationship with age is investigated with respect to linear, quadratic, and cubic components.

In the following, some previous findings on the presently studied structures' relationship with age are briefly discussed. Many studies have given valuable information on these topics. However, the present study is targeted at comparison of several structures within the same pool of participants, more than the study of different structures in isolation. Thus, the discussion below is designed to provide a brief background only and is not intended to be exhaustive with respect to previous relevant literature.

1.1. Age changes in cortical gray matter and subcortical structures

There is consensus that gray matter is reduced with age [3,5,12,16,17,22,23,25,28,29,35,36], and this reduction seems to start at a very early point in life [5]. On average, there appears to be somewhat greater gray volume loss in the cortex than in subcortical structures [17], and studies of the latter vary in the extent of age differences found. In one of the few studies comparing age effects on a number of different structures, Jernigan et al. [17] found no relationship between age and the volumes of amygdala and thalamus, modest age-related volume loss in the caudate nucleus and nucleus accumbens, and evidence for markedly greater hippocampal reduction, with accelerated loss relative to the cerebral cortex. No age decline was found in the lenticular nucleus. In another study comparing age decline in the caudate, putamen, and pallidum, a decrease of equal magnitude was found for the caudate and putamen cross-sectionally as well as longitudinally, while age decline in the pallidum was only found by longitudinal measurement [27]. Absence of age decline in the thalamus [16], as well as significant age decline in the caudate nucleus (e.g. [16,19]) and hippocampus (e.g. [21,22]) have been observed in other samples too. However, there is also conflicting evidence regarding age effects on subcortical structures. For instance, contrary to the above, thalamic age decline has been reported [25,26,37], one large-scale study [21] found that the amygdala is significantly reduced with age, and one study with a somewhat younger male sample [35] found no hippocampal age decline. Further, in a very large-scale study [12], preservation relative to other gray matter areas was found in the amygdala and hippocampus. Differences such as these may at least partly be attributed to varying sample characteristics – in particular, whether the full age range is sampled, including persons above 70 years and older.

1.2. Cerebral white matter and age

Reports on the relationship between age and white matter volume seem less consistent than those on gray matter. Some studies have reported no age changes in white matter volume [3,12,16,23,36], while others have found that total white matter volume [14,17] is reduced with age. There have also been findings of white matter decline in parts of the brain [12,25,30]. As for gray matter structures, samples of varying ages may be a reason for the discrepant findings, and studies including the oldest participants tend to report an age-related decline. One such recent study [5] found white matter decrease only from 70 years of age onwards. This is in accordance with another study [17], in which it was also found that despite its later onset, white matter loss was more rapid, and ultimately exceeded that of gray matter. As for gray matter, results indicate somewhat less age-related loss in deep subcortical regions than in the cerebral lobes [17], and several studies have reported no age reduction of the pons [20,24,26,36].

1.3. Cerebellar volume and age

Cerebellar volume also seems to decline with age (e.g. [17,24,26,34], though discrepant findings have been reported also here [8]. When cerebellar gray and white matter have been measured separately, age effects have been observed only for gray matter in one study [34], but age reductions in both, comparable to the decline found in cerebral gray and white matter, have recently been reported [17].

1.4. Changes in ventricular volume with age

Age-related volume loss is typically seen in the form of increased CSF spaces, and expansion of ventricular spaces has been found in healthy elderly persons [17,21,28]. In a study comparing age effects on cortical and subcortical gray and white matter as well as CSF compartments [17], the greatest age effect was seen in the form of increased cortical sulcal, cerebral ventricular, and cerebellar CSF. No significant difference was observed in rate of change across the different compartments.

2. Methods

2.1. Sample

Volunteers were recruited by advertisements placed on campus and in local newspapers. Participants were required to be right-handed, feel well and healthy, have normal or corrected to normal vision, not use a hearing aid, and not suffer from diseases or conditions known to affect central nervous system functioning (e.g. hypothyroidism, multiple sclerosis, Parkinson's disease, stroke, head injury). Those satisfying these criteria were further screened for health problems and cognitive problems by a structured interview, Beck depression inventory (BDI) [1], the mini-mental state examination (MMSE) [10], and the Wechsler abbreviated intelligence scale (WASI) [39]. Participants scoring above 14 on the BDI, below 26 on the MMSE, or more than one

Table 1
Sample characteristics ($n = 73$)

	Young ($n = 25$)			Middle aged ($n = 23$)			Old ($n = 25$)		
	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.	Range
Age	27.3	5.2	20–41	56.0	7.0	43–66	74.3	4.8	67–88
Edu	15.8	2.1	13–18	15.8	2.7	9–20	14.1	3.2	7–19
IQ	114.0	7.2	102–128	114.8	9.2	93–129	112.0	13.4	85–134
MMSE	29.1	.8	28–30	29.2	.8	28–30	28.3	1.2	26–30
BDI	2.7	3.1	0–9	3.3	3.0	0–11	6.4	3.2	1–14

Beck depression inventory (BDI) was included at a later stage, and is reported for only a part of the sample ($n = 65$) (Edu: years of formal education).

standard deviation below the population mean on the IQ test, were excluded from the study. This led to the exclusion of three participants. The remaining sample consisted of 73 persons (40 *F*) aged 20–88 years. For a subsample of 54 persons, age correlations for three of the measures (cortical, cerebral white matter, and hippocampal volume) have been reported in a separate paper [38] in relation to normal memory capability. Characteristics of the sample divided in three age groups (young, middle-aged, and old) are shown in Table 1. One-way ANOVA showed that there was no significant difference in IQ across groups ($p = .613$), but there were significant ($p < .05$) group differences in education, MMSE, and BDI. Age differences on these measures are to be expected in the normal population (e.g. [2,13]. In hindsight, however, another measure than the BDI should ideally have been chosen. The BDI includes responses to somatic complaints, and the increased prevalence of such complaints with age probably results in higher scores [2].

2.2. MRI scanning

A Siemens Symphony Quantum 1.5 T MR scanner with a conventional head coil was used. The pulse sequences used for morphometric analysis were: two 3D magnetization prepared gradient echo (MP-RAGE), T1-weighted sequences in succession (TR/TE/TI/FA = 2730 ms/4 ms/1000 ms/7°, matrix = 192 × 256, FOV = 256 mm), with a scan time of 8.5 min per volume. Each volume consisted of 128 sagittal slices with slice thickness = 1.33 mm, and in-plane pixel size of 1 mm × 1 mm. The image files in DICOM format were transferred to a Linux workstation for morphometric analysis.

2.3. MRI volumetric analyses

The automated procedures for volumetric measures of the different brain structures are described by Fischl et al. [9]. This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. The training set included both healthy persons in the age range 18–87 years and a group of Alzheimer's disease patients in the age range 60–87 years, and the classification technique employs a registration procedure that is robust to anatomical variability, including the ventricular enlargement typically associated with neurological diseases and aging. Briefly, the segmentation is carried out as follows. First, an optimal linear transform is computed that maximizes the likelihood of the input image, given an atlas constructed from manually labeled images. Next, a nonlinear transform is initialized with the linear one, and the image is allowed to further deform to better match the atlas. Finally, a Bayesian segmentation procedure is carried out, and the maximum a posteriori (MAP) estimate of the labeling is computed. The segmentation uses three pieces of information to disambiguate labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. This latter term represents a large number of constraints on the space of allowable segmentations, and prohibits label configurations that never occur in the training set (e.g. hippocampus is never anterior to amygdala). The technique has previously been shown to be comparable in accuracy to manual labeling. The segmentations were visually inspected for accuracy. None were discarded. A sample of the segmentation is shown in Fig. 1. Intracranial volume (ICV) was calculated based on proton density (PD) weighted low-flip angle FLASH scans obtained during the same scanning session as the scans used for automatic labeling. A deformable template procedure, similar to the "Shrink Wrapping" procedure described by Dale and colleagues [6,7], was used to obtain an estimate of the smooth surface surrounding the intracranial space (containing cerebrum and cerebellum, CSF, meninges, and brainstem to a level immediately below the pons).

2.4. Statistical analyses

For each neuroanatomical volume, the summed values of the left and right hemisphere were regressed on ICV, and the standardized residuals were used in the analyses reported here. This method was deemed appropriate since the topic of investigation was age differences regardless of gender, and there was no relationship between ICV and age in the present sample ($r = -.01$, n.s.), but a significant difference in the mean ICV of women and men (M (mm^3) = 14995, S.D. = 9837 and M (mm^3) = 21762, S.D. = 125011, respectively, $p = .000$). Regression analyses were performed with all measures separately as the criteria variables and age as the predictor variable. The analyses were repeated with age^2 as an additional predictor variable in order to assess possible

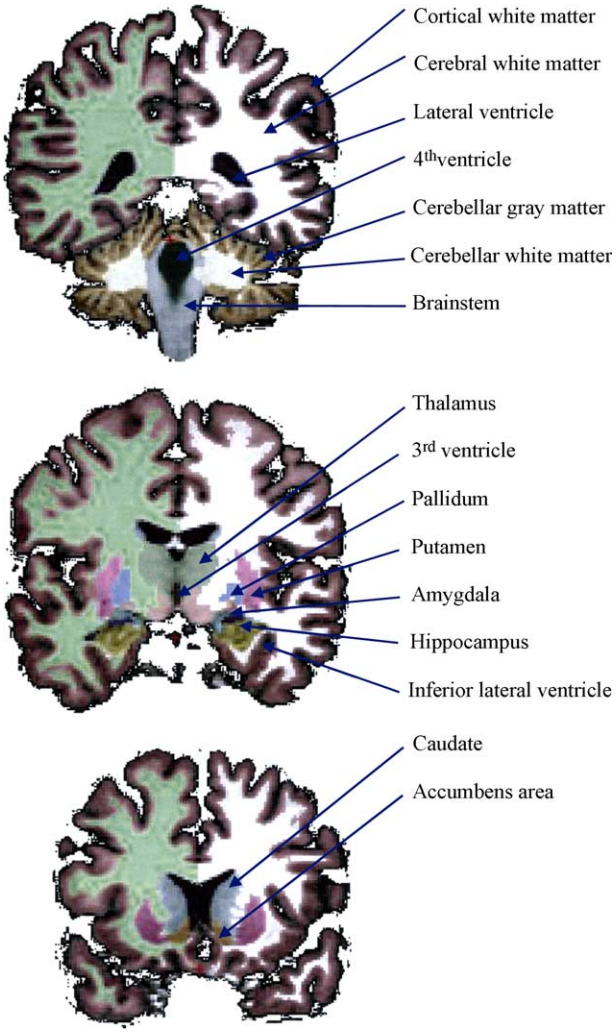

Fig. 1. A sample of the automated labeling of the brain of a young male participant. From top to bottom, slice 105, 135, and 160 in the coronal view are shown, respectively. The different structures have unique color codes. The arrows here are all pointed at the structures of the left hemisphere.

quadratic components, and again with age^3 as a third predictor variable, to assess possible cubic components. For purpose of comparison with the study of Jernigan et al. [17], Spearman's correlations were also calculated for all brain measures and age. Further, the volume percentages of the ICV were calculated for measures of cortical gray matter, white matter, subcortical structures, pons, and ventricular volumes. Note that this is different from percentage of the supratentorial cranial vault (STCV), which was used by Jernigan et al. [17]. The linear estimates of volume changes from age 20 to 90 were then calculated.

3. Results

3.1. Relationships between age and brain measures

The number of voxels in each raw volume measured is shown in Table 2. The regression equations, F and p values for all the structures predicted by age, as well as the R^2 change when age^2 was included as a multiple regressor are shown in Table 3. When introducing age^3 as a third regressor, additional unique variance ($p < .05$) was explained in only one structure, the putamen, for which R^2 increased from .283 to .333. The regression plots for all gray, subcortical, and white matter volumes are shown in Fig. 2, and plots for ventricular measures are shown in Fig. 3. As seen, there were significant effects of age on most brain measures. Age decline was found in all white matter structures, and in all gray matter and subcortical structures, with the exception of pallidum, which only showed a marginally significant negative relationship

Table 2
Number of voxels (mm^3) in each raw volume measured

	Mean	S.D.
Cortical gray matter	462,043	60,831
Cerebral WM	387,080	55,660
Hippocampus	7,345	924
Amygdala	3,534	480
Thalamus	13,375	1,631
Accumbens area	1,322	236
Caudate	7,957	1125
Putamen	10,985	1,068
Pallidum	4,192	470
Brainstem	20,776	2,346
Cerebellar cortex	103,610	14,729
Cerebellar WM	26,327	4,000
Lateral ventricles	27,162	16,388
Inferior lateral ventricles	1,301	716
3rd ventricle	1,377	675
4th ventricle	2,233	567
ICV	1,582,681	137,447

Table 3
Regression equations with each volume as a function of age (linear component, beta$_1$) when entered as a single regressor[a]

Y	Beta$_1$	F	p	R^2	R^2w/age^2
Cortical gray	−.779	109.286	.000	.606	.616
Cerebral WM	−.508	24.674	.000	.258	**.404**
Hippocampus	−.398	13.377	.000	.159	**.315**
Amygdala	−.469	20.015	.000	.220	.256
Thalamus	−.780	110.399	.000	.609	.619
Accumbens area	−.652	52.539	.000	.425	.428
Caudate	−.692	65.300	.000	.479	.498
Putamen	−.473	20.511	.000	.224	**.283**
Pallidum	−.229	3.926	.051	.052	**.064**
Brainstem	−.353	10.136	.002	.125	**.242**
Cerebellar cortex	−.605	40.908	.000	.366	**.401**
Cerebellar WM	−.557	31.855	.000	.310	**.437**
Lateral ventricles	.695	66.379	.000	.483	**.555**
Inferior lateral ventricle	.567	33.727	.000	.322	**.552**
3rd ventricle	.741	86.365	.000	.549	**.603**
4th ventricle	.210	3.268	.075	.044	.065

The R^2 when age^2 (quadratic component) was entered as a multiple regressor is shown (bold characters indicate $p < .05$ for age^2. All quadratic relationships significant at $p < .05$ were also significant at the Bonferroni-corrected p-value of $p < .003$, with the exception of putamen ($p = .019$) and cerebellar cortex ($p = .047$)).

[a] All linear relationships significant at $p < .05$ were also significant when Bonferroni-corrected for multiple comparisons, $p < .003$.

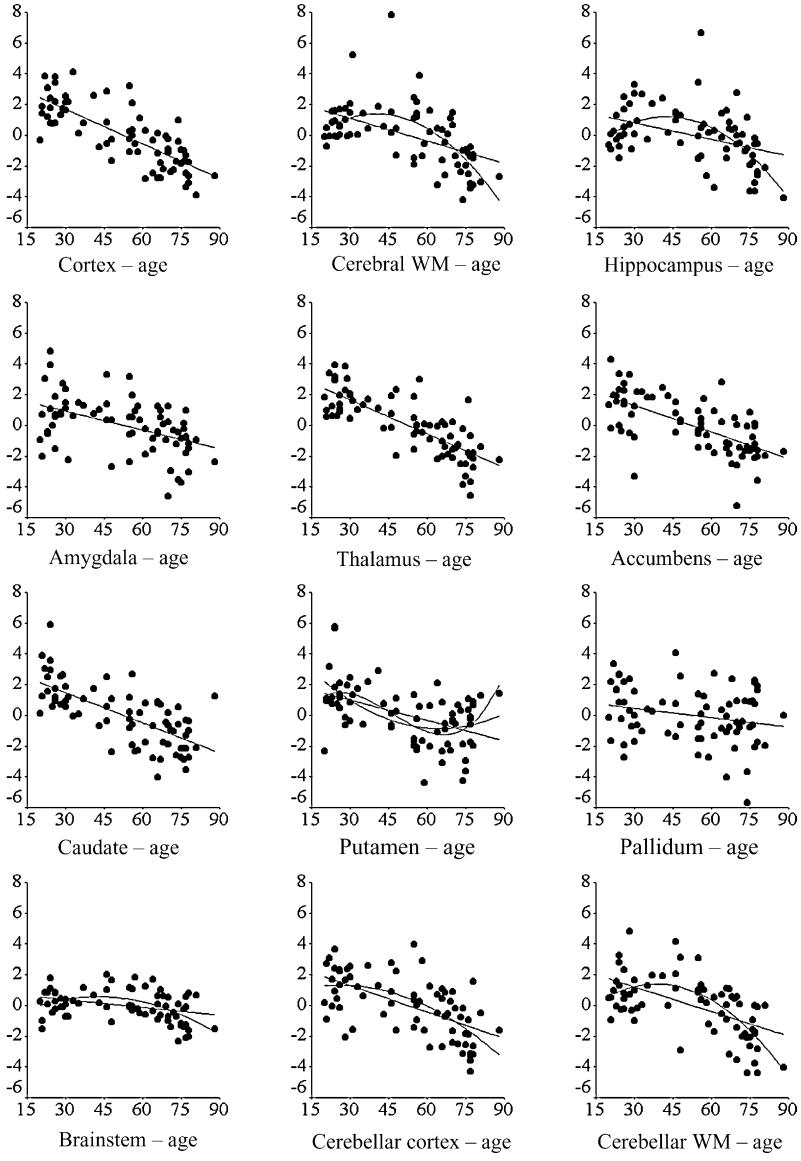

Fig. 2. Regression plots showing the relationships between age and the volume of cortical gray matter, cerebral white matter, hippocampus, amygdala, thalamus, accumbens, caudate, putamen, pallidum, brainstem, cerebellar cortex and cerebellar white matter. With the exception of pallidum, all the relationships are significant ($p < .05$). Only where age^2 or age^3 made a unique contribution to the amount of explained variance, is a quadratic or cubic regression function shown.

with age. The volumes of the lateral, inferior lateral, and 3rd ventricles were positively related to age, but the relationship between the 4th ventricle and age did not reach significance. Significant quadratic components were found for all white matter structures: cerebral and cerebellar white matter, and the brainstem. The relationship between age and hippocampus, putamen, and cerebellar cortex, were also best described by a adding a curvilinear component. As seen from Fig. 2, with the exception of putamen, these volumes appear to initially remain stable or increase with age, but then start to decline in the 40 s. Based on the regression equation, the volume of the putamen appears to initially increase until the 30 s, when it declines, whereupon a new increase is seen in the late 60 s. Expansion of the volume of the 3rd ventricle and the lateral and inferior lateral ventricles followed a curvilinear pace. As seen from Fig. 3, these ventricular volumes appear initially to be stable, but later accelerate. However, volume of the 4th ventricle was not significantly related to age.

3.2. Outlier analyses

Upon inspection of the regression plots, some outliers were evident in the material. Thus, outliers in the data set were identified by use of studentized deleted residuals. The deleted residual is the residual value for the respective case, had it not been included in the regression analysis. If the deleted residual differs greatly from the respective standardized residual value, then this case is possibly an outlier because its exclusion changed the regression equation. All analyses were rerun excluding, regression-by-regression, cases with studentized

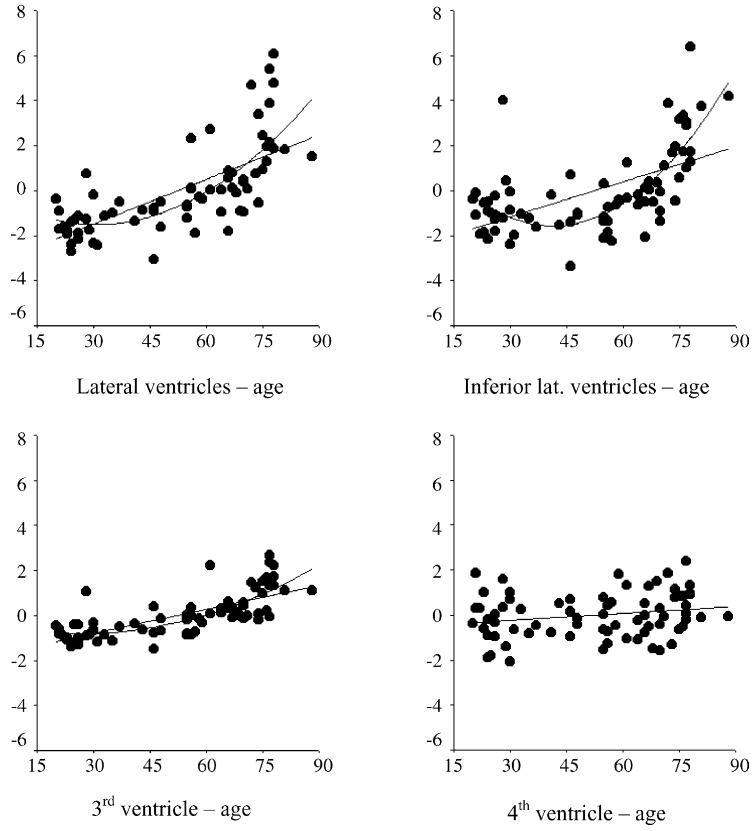

Fig. 3. Regression plots showing the relationship between age and the volume of the lateral, inferior lateral, 3rd and 4th ventricles. With the exception of the 4th ventricle, all the relationships are significant ($p < .05$). Only where age^2 made a unique contibution to the amount of explained variance, is a curvilinear regression function shown.

deleted residuals exceeding ±2.0. The results without the outliers and the number of participants excluded per analysis are shown in Table 4. For the linear regressions, R^2 increased in 13 of 16 cases when outliers were excluded, it decreased in two cases, and remained stable for pallidum. In general, the changes were not dramatic. However, a marked increase in explained variance of nearly 10% was seen for both hippocampus and the 3rd ventricle. For the analyses including age^2 as a multiple regressor, an increase in explained variance was observed in 12 of 16 cases, decrease in three cases, and the amount for the 4th ventricle remained stable. Again, the changes were generally not marked, but an increase

Table 4
Regressions with each volume as a function of age, as shown in Table 3, but with outliers excluded (studentized deleted residuals >2.0)[a]

Y	*n* excluded age (+age^2)	Beta$_1$	*F*	*p*	R^2	R^2w/age^2
Cortical gray	3 (4)	−.816	135.332	.000	.666	.671
Cerebral WM	3 (4)	−.585	35.367	.000	.342	**.465**
Hippocampus	3 (4)	−.506	23.350	.000	.256	**.374**
Amygdala	5 (5)	−.461	18.580	.000	.212	**.247**
Thalamus	3 (4)	−.825	147.315	.000	.681	**.690**
Accumbens area	3 (3)	−.677	59.270	.000	.458	.460
Caudate	4 (4)	−.740	82.528	.000	.548	.552
Putamen	5 (5)	−.423	15.060	.000	.179	.224
Pallidum	3 (3)	−.227	3.814	.055	.052	.076
Brainstem	5 (2)	−.396	12.623	.001	.157	**.284**
Cerebellar cortex	4 (3)	−.671	55.814	.000	.451	**.459**
Cerebellar WM	5 (4)	−.586	35.118	.000	.344	**.436**
Lateral ventricles	4 (6)	.704	65.854	.000	.496	**.612**
Inferior lateral ventricles	3 (3)	.633	46.128	.000	.392	**.654**
3rd ventricle	5 (4)	.803	120.169	.000	.645	**.702**
4th ventricle	2 (3)	.232	3.914	.052	.054	.065

[a] Bold characters indicate $p < .05$ for age^2.

in explained variance of nearly 10% was observed for the 3rd ventricle. The quadratic component of the relationship between age and putamen became marginally insignificant ($p = .051$). However, the quadratic components for amygdala and CSF became significant only upon exclusion of the outliers. The analyses including age^3 as a third regressor did not yield any additional significant cubic relationships when performed without the outliers, but the cubic component of the age–putamen relationship remained significant ($p < .01$), and R^2 increased from .333 to .352. In order to determine whether there was something unusual about the deleted cases, the number of outliers accounted for by each excluded participant in the linear regressions was calculated. It was found that having at least one outlier observation was the rule, rather than the exception, since 48 of the 73 participants were excluded in one or more of the 16 outlier analyses. Five of these 48 accounted for 2 outlier observations, 4 accounted for 3, 3 accounted for 4, and 1 accounted for 5 outlier observations. The scans of the 13 persons that accounted for multiple outliers were re-inspected, but erroneous segmentations were not apparent. The characteristics of participants with multiple outlier observations were then compared to those of the remaining participants. Independent samples T-tests showed that the groups did not differ ($p > .05$) with respect to IQ (outliers: $M = 113.3$, S.D. = 8.9 versus others $M = 113.6$, S.D. = 10.5), MMS (outliers: $M = 29.1$, S.D. = .9 versus others: $M = 28.8$, S.D. = 1.0), age (outliers: $M = 48.9$, S.D. = 22.1 versus others: $M = 53.2$, S.D. = 20.3) or sex. Thus, there was no obvious reason why these participants were outliers, and no obvious reason to exclude them from analyses. However, the results for analyses performed also without the outliers are presented here in order to minimize the possibility that rare data points exert undue influence, and to enable evaluation of the robustness of the observed fits.

3.3. Spearman's correlations and estimates of percentage change from age 20 to 90

Spearman's correlations of all brain measures with age are presented in Table 5. Where applicable, Spearman's correlations from another study [17] comparing age differences in several brain measures are also reported. That study was performed on a sample of comparable size ($n = 78$) and gender distribution (41 *F*), but somewhat older age range (30–99 years) than the present. With the exception of hippocampus and cerebral white matter, the relationships found in the present study are stronger. The most striking differences are seen in much stronger age relationships for the thalamus, followed by amygdala, the accumbens area, and caudate. The only age effects of comparable size (an absolute difference in Spearman's rho of less than .20) are seen for cerebral and cerebellar white matter, and cerebellar cortex/gray matter. Linear estimates of percentage changes from age 20 to 90 for gray, white, subcortical, and ventricular volumes are shown in Table 6. The estimated proportional age loss was ultimately greatest in the accumbens area, followed by caudate, cortex, cerebellar cortex, thalamus, and cerebellar white matter.

Table 5
Spearman's rho correlations between brain measures and age[a]

Cortical gray	**−.78**	(**−.53**)
Cerebral WM	**−.56**	(**−.63**)
Hippocampus	**−.42**	(**−.65**)
Amygdala	**−.47**	(−.08)
Thalamus	**−.79**	(−.13)
Accumbens area	**−.68**	(**−.33**)
Putamen	**−.41**	(.00)
Pallidum	−.18	
Caudate	−.70	(**−.35**)
Brainstem	−.38	
Cerebellar cortex	−.62	(**−.56**)
Cerebellar WM	−.58	(**−.49**)
Lateral ventricles	.77	
Inferior lateral ventricles	.61	
3rd ventricle	.80	
4th ventricle	.22	

Where applicable, results from Jernigan et al. [2] are reported in parentheses (data were reported for the lenticular nucleus, rather than for the putamen and pallidum separately).

[a] Bold characters indicate $p < .05$.

4. Discussion

The present results indicate significant age differences in all neuroanatomical volumes, with the exception of pallidum, which followed the same trend, but showed marginally non-significant differences. Age differences were also observed in the lateral, inferior lateral, and 3rd ventricle. A similar trend was observed for the 4th ventricle, but this was marginally insignificant. In sum, the data for these 16 brain measures suggest almost globally smaller neuroanatomical volumes and larger CSF compartments in older, relative to younger persons. We cannot with certainty conclude that this is due to a reduction of brain tissues and expansion of CSF compartments with age. It is well known that cohort effects exist for mental abilities [31], and one may reason that these can be partly based in structural brain differences. For instance, the known secular acceleration of body height and weight comes with an accompanying increase in brain weight [15], which may be confused with aging effects. Fortunately, there was no relationship between ICV and age in the present sample, so there is not reason to believe that the present data are much influenced by this cohort effect. Longitudinal MR studies on normal age changes are naturally scarce, but some data exist and these do not completely concur with cross-sectional findings. However, the magnitude of longitudinal change with age in the striatum has been found to be greater, not smaller, than predicted from cross-sectional studies [27], and 1 year longitudinal age changes have also been observed for ventricular volume [28]. Thus, it seems reasonable to conclude that the presently observed age differences do, at least partly, represent age-related changes, i.e. tissue volume loss. For reasons

Table 6
Linear estimates of volume changes from age 20 to 90

	Proportion of ICV		%Change of ICV	%Change of 20-year-old volume
	x = 20 years	x = 90 years		
Cortex	.331540	.246140	−8.54	−25.76
Cerebral WM	.265296	.220202	−4.51	−17.00
Hippocampus	.004957	.004282	−.07	−13.60
Amygdala	.002403	.002028	−.04	−15.59
Thalamus	.009494	.007268	−.22	−23.45
Accumbens	.000975	.000676	−.03	−30.65
Caudate	.005727	.004245	−.14	−25.88
Putamen	.007393	.006468	−.09	−12.54
Pallidum	.002738	.002557	−.02	−6.62
Brainstem	.013796	.012381	−.14	−10.30
Cerebellar cortex	.073652	.056264	−1.74	−23.61
Cerebellar WM	.018574	.014422	−.42	−22.35
Lateral ventricles	.006394	.029270	+2.29	+357.79
Inferior lateral ventricles	.000411	.001298	+.09	+215.74
3rd ventricle	.000387	.001422	+.10	+267.41
4th ventricle	.001300	.001546	+.02	+18.90

of convenience we refer to the observed age differences as age changes.

4.1. Global volume loss

Of all the studied volumes, thalamus and cortical gray matter were the most negatively associated with age, while the volumes of the lateral and 3rd ventricle were about equally strongly positively associated (all rhos > .75). More moderate, but robust relationships (rhos = .38–.70) were observed for the caudate, the accumbens area, hippocampus, putamen, cerebellar cortex and cerebellar white matter, cerebral white matter, brainstem, and the inferior lateral ventricles. It is noteworthy that the present data generally suggest greater and more global neuroanatomical age changes than previously found. Absence of a relationship between thalamic volume and age has previously been reported [16,17], while a relationship has been found in other studies [36,37], and this is among the strongest age relationships found in the present study. Further, pontine volume has also been reported not to decline with age [20,24,26,36], and inconsistent and negative findings have been reported for the hippocampus and amygdala [12,21,35]. Smaller, and insignificant age differences in the volume of the pallidum are, however, not surprising, and are in line with previous cross-sectional results [17,27].

The observed differences across studies may partly be due to age differences in the samples. Younger, but also older samples have previously been employed. The apparently different and larger age effects for hippocampus and cerebral white matter found by Jernigan et al. [17] is likely influenced by the inclusion of several participants in the 20s in the present study, whereas Jernigan et al.'s [17] sample included participants from 30 years and up. It is evident from the regression plots that both hippocampus and cerebral white matter continue to increase in volume into the 30s and 40s, followed by a subsequent age decrease. Jernigan et al.'s results probably reflect this later age decrease to a greater degree, especially for hippocampus and cerebral white matter. Based on the present data, these structures, along with pons, cerebellar white matter, and cerebellar cortex, seem to decline only from around the 40s. It is less clear whether sample differences across studies can explain the larger age effects on other subcortical structures in the present study, as presented in Table 5. For instance, larger age effects were found for amygdala, thalamus, accumbens and caudate as well as cortex. It is known that there is postadolescent maturational age reduction in cortical and subcortical volumes [33], and such reduction among the participants in their 20 s may have influenced the present findings. However, age effects on all of the above-mentioned volumes were found to be linear, so that there is no apparent break point between maturational reductions and further age decreases. The inclusion of participants in the 20s may increase the percentage reduction of volumes seen up to 90 years, and may also increase the variance so that effect sizes could become somewhat stronger in the present sample. However, in our opinion, when evident in the Spearman correlations with age in a sample with a lower age limit of 20 years, this linear decrease should be nearly as evident in samples with a lower age limit of 30 years. It, therefore, does not seem likely that the increased age variance in the present study may account for all of the larger age effects in a systematic way.

4.2. Heterogenic aging patterns across structures

It is evident that more or less global age reductions were found across the studied brain structures in the present sample. However, as mentioned, some have rather pointed to the regional variability of neuroanatomical volume loss (e.g. [17]). The present data also emphasize heterogenic age responses of various brain volumes, in that some structures, i.e. cortex, amygdala, thalamus, the accumbens area, and

caudate, show linear relationships, while other structures, i.e. cerebral white matter, hippocampus, brainstem, cerebellar white and gray matter, as well as volumes of the lateral, inferior lateral and 3rd ventricles, show curvilinear relationships with age. The fact that age decline in these latter volumes were best described by curvilinear functions, may limit their potential value as diagnostic markers. Since normal age change in these volumes is normally steeper over some parts of the life span, it may be more difficult to delineate what an observed accelerated volume reduction means, and whether it is a sign of normal aging or pathology. A steep reduction in structures characterized by a linear age function, on the other hand, such as cortical or thalamic volume, would more likely be a sign of abnormality. Heterogenic aging is also seen in differential percentages of volume reduction across the studied structures. As seen in Table 6, the greatest estimated proportional reduction between the ages of 20 and 90 is seen for the accumbens area, caudate, cortex, thalamus, and cerebellum, and this is accompanied also by large proportional increases of the lateral, inferior lateral and 3rd ventricles. Smaller proportional volume changes (i.e. less than 20%) are estimated for the remaining volumes, including hippocampus and cerebral white matter.

Differential age changes were seen across different neuroanatomical volumes in the present data in the form of linear versus curvilinear relationships with age, as well as somewhat different proportional age changes in the various volumes.

4.3. Limitations and reasons for discrepancies across studies

As discussed above, the type and magnitude of age changes found likely depend on the age range studied. The present study includes a broad age range, and should as such yield data representing nearly the entire adult lifespan. Further, the sample is fairly similar to that of Jernigan et al. [17], comparing several of the same structures with different results. However, that study did involve an older age range (30–99), so that, as noted above, some structures in the present study are likely more influenced by an early increase in volume and accompanying non-monotone age relationships. Our results also differ markedly from those of the large-scale study of Good et al. [12], who for instance found little or no age effect on the amygdala and hippocampus. A possible explanation for this discrepancy could be the analysis methods used. Especially, Good et al. only reported regionally specific changes within the gray matter compartment *over and above* global gray matter change, whereas most other studies, including the present, report changes without covarying out global gray matter volume. With their method, Good et al. then reported relative preservation of hippocampus and amygdala with age. This need not necessarily be in conflict with the present study, since our data indicate a relatively larger effect size of age for the volume of cortex than for both hippocampus and amygdala.

The present sample is of well-above average IQ, and this suggests that the strong age effects are most likely not due to below-normal function or characteristics of the participant pool. It is also noteworthy that the observed effects are not due to the presence of deviant participants in the sample, since most relationships strengthened when outliers were excluded. As in other in vivo imaging studies, the quality of the scans may have influenced the results. However, two successive T1-weighted sequences were used to ensure high scan quality. A main difference between this and most studies is that an automatic segmentation and labeling technique was employed. This may have influenced the results. However, the automatic labeling procedure has been shown to be of comparable accuracy to manual labeling. Thus, we find it likely that besides age variations in the studied samples and applied segmentation and labeling techniques, the observed discrepancies across studies may reflect the real and, by other means, well-documented heterogeneity of aging [31]. This indicates that individual differences comprise the norm, not the exception, and that the normal range of cognitive capabilities widens across the age range. Such individual variability may partly be reflected in brain morphology. Given a magnitude of normal individual differences, different MR studies may incidentally capture different versions of normal age changes. A wide range of normal variation in any measure poses huge challenges for the use of that measure in clinical settings. That being said, it is perhaps more likely that studies not observing relationships are more prone to incidental variations than studies that do observe strong and consistent relationships. For instance, the present regression plots of age and cortex, thalamus, and caudate show very dense, strong and straightforward relationships. The fact that such relationships can be identified by the use of automated and cost-efficient labeling gives hope that volumetric measurement of neuroanatomical structures may be a fruitful approach in delineating normal as well as abnormal age changes.

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