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Consistent neuroanatomical age-related volume differences across multiple samples

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Abstract

Magnetic resonance imaging (MRI) is the principal method for studying structural age-related brain changes *in vivo*. However, previous research has yielded inconsistent results, precluding understanding of structural changes of the aging brain. This inconsistency is due to methodological differences and/or different aging patterns across samples. To overcome these problems, we tested age effects on 17 different neuroanatomical structures and total brain volume across five samples, of which one was split to further investigate consistency (883 participants). Widespread age-related volume differences were seen consistently across samples. In four of the five samples, all structures, except the brainstem, showed age-related volume differences. The strongest and most consistent effects were found for cerebral cortex, pallidum, putamen and accumbens volume. Total brain volume, cerebral white matter, caudate, hippocampus and the ventricles consistently showed non-linear age functions. Healthy aging appears associated with more widespread and consistent age-related neuroanatomical volume differences than previously believed.

Keywords: MRI morphometry; Age; Cortex; White matter; Cerebellum; Ventricles; Hippocampus; Amygdala; Thalamus; Basal ganglia

1. Introduction

Brain changes are inevitable in aging. Still, core questions remain a matter of debate: What structures change, when do they start aging, at what rates, and are some structures spared? Many cross-sectional studies have demonstrated neuroanatomical age-related volume differences *in vivo* by the use of magnetic resonance imaging (MRI) (Allen et al., 2005; Blatter et al., 1995; Courchesne et al., 2000; Fotenos et al., 2005; Good et al., 2001; Head et al., 2004, 2005; Jernigan et al., 1991, 2001; Luft et al., 1999; Mu et al., 1999; Raz et al., 2000, 2004a,b, 2005, 2007; Raz and Rodrigue, 2006; Salat et al., 2004; Sullivan et al., 1995, 2004; Taki et al., 2004; Tisserand et al., 2002; Walhovd et al.,

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2005a). Some structures are found to decline substantially, while others appear better preserved (Raz and Rodrigue, 2006). Different age trajectories have been observed, with some brain areas declining linearly from early in life, whereas others continue to increase in volume before eventually beginning to deteriorate (Allen et al., 2005; Good et al., 2001; Luft et al., 1999; Raz et al., 2004b; Walhovd et al., 2005a). Unfortunately, the results diverge much across studies, and differences in segmentation procedures and demarcation criteria complicate comparisons. Discrepant findings have been reported for most structures. Adding to this problem, in most studies only a few structures are segmented, making it difficult to assess the relative vulnerability of different structures to age.

The aim of the present paper was to overcome these problems. Data from five samples (one split-half making a total of six groups for analysis) were processed with the same segmentation tools, and the stability of age effects across samples was assessed for 16 subcortical structures as well as cortical volume and total brain volume. Three questions were asked: (1) Which structures show significant age-related volume differences across samples? (2) Which structures undergo the most prominent age-related changes, and which are relatively preserved? (3) Which structures are volumetrically changed in a linear fashion, and which show curvilinear (quadratic) age relationships?

Main findings from previous MRI studies on age-related differences in neuroanatomial volumes are summarized in the following. Further reviews can be found elsewhere (Raz and Rodrigue, 2006). It should be noted that the vast majority of studies reviewed below are of a cross-sectional nature, and unless longitudinal designs are explicitly noted, what is observed are age differences, rather than age changes. There is consensus that gray matter (GM) volume/thickness is smaller with higher age (Blatter et al., 1995; Courchesne et al., 2000; Fotenos et al., 2008; Good et al., 2001; Jernigan et al., 1991, 2001; Murphy et al., 1996; Pfefferbaum et al., 1994; Raz et al., 1997; Resnick et al., 2000; Salat et al., 2004; Sullivan et al., 1995, 2004; Walhovd et al., 2005a), and that this effect is seen early in life (Courchesne et al., 2000; Giedd, 2004; Giedd et al., 1999, 1996; Lebel et al., 2008). Based on cross-sectional investigations, there generally appears to be somewhat greater GM loss in the cortex than in subcortical structures (Jernigan et al., 2001; Walhovd et al., 2005a). However, a longitudinal study has indicated at least as much shrinkage of the caudate and cerebellum as in the lateral frontal and orbitofrontal cortex (Raz et al., 2005). Aging of different parts of the cortex is highly heterogeneous, and cortical volume is included in the present study mainly to allow comparisons with subcortical structures. Detailed analyses of cortical thickness are reported elsewhere (Fjell et al., in press).

Less consistent results have been reported for the relationship between age and white matter (WM) volume. Some studies have found no age differences (Abe et al., 2008; Blatter et al., 1995; Good et al., 2001; Jernigan et al., 1991; Pfefferbaum et al., 1994; Sullivan et al., 2004), while others have found that total WM volume is negatively related to age (Allen et al., 2005; Guttmann et al., 1998; Jernigan et al., 2001; Walhovd et al., 2005a). Samples of varying ages may be a reason for the discrepant findings, and studies including the oldest participants tend to report age effects. One study (Courchesne et al., 2000) reported white matter to be negatively related to age only from 70 years of age onwards, and this age range has not been consistently included in aging studies. Jernigan and colleagues (Jernigan et al., 2001; Jernigan and Gamst, 2005) found that despite its later onset, white matter loss was more rapid than gray matter loss, and ultimately exceeded it. In recent years, there has been increased focus on the possibly curvilinear nature of age change in WM volume (Allen et al., 2005; Jernigan and Gamst, 2005; Walhovd et al., 2005a), with gains until middle age followed by later decrease. Non-linear fits tend to significantly increase the proportion of variance in WM volume explained by age. As for gray matter, results indicate somewhat less age-related loss in deep subcortical regions than in the cerebral lobes (Jernigan et al., 2001). For instance, although some decline has also been observed in brainstem volume (Walhovd et al., 2005a), several studies have reported no effect of age on volume of the pons (Luft et al., 1999; Raz et al., 1998, 2001, 1992; Van Der Werf et al., 2001).

In the following, age effects on different subcortical brain structures from 31 cross-sectional studies are reviewed (details are presented in Table 1). All studies tested effects of age on the volume of at least one of the subcortical structures/compartments included in the present study, and a short presentation of the main results from this literature is given below:

Hippocampus: The variability among studies is high. Nine of 15 studies reviewed here found that hippocampus shrank with age (Allen et al., 2005; Greenberg et al., 2008; Jernigan et al., 2001; Lupien et al., 2007; Mu et al., 1999; Raz et al., 2004a; Scahill et al., 2003; Schuff et al., 1999; Walhovd et al., 2005a), while five found no change (Du et al., 2006; Liu et al., 2003; Sullivan et al., 1995, 2005; Van Petten, 2004). In one study, age effects on hippocampal volume were found for men but not women (Pruessner et al., 2001). In addition, age effects on hippocampal volume normalized to global GM loss were not observed in a very large study (Good et al., 2001). Notably, three of the studies found non-linear effects of age (Allen et al., 2005; Lupien et al., 2007; Walhovd et al., 2005a), and one longitudinal study reported accelerated age-related hippocampal shrinkage (Raz et al., 2005). Part of the discrepant findings may thus stem from failure to account for non-linearity.

Amygdala: There have been fewer studies of age effects on the amygdala, but in sum, the reports indicate smaller age effects on the amygdala than on the hippocampus. Three studies found smaller volume of amygdala with higher age (Allen et al., 2005; Mu et al., 1999; Walhovd et al., 2005a), while two did not (Jernigan et al., 2001; Pruessner et al.,

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Table 1
Overview of studies of age effects on subcortical brain structures.

Study	*N*	Age range	Segmentation method	Normalization	Age effects (Pearson's *r*)	Non-linear effects	Not age effects
Krishnan et al. (1990)	39	24–76	Manual	None	Caudate ($R = -.69$)		
Jernigan et al. (1991)	55	30–70	Semi-automated	Supratentorial cranium	Caudate (−.49)		Diencephalic structures (including thalamus)
Gur et al. (1991)	69	18–80	Semi-automated	ICV	Ventricular CSF, Sulcal CSF (r only provided for total CSF; .76)		
Cohen et al. (1992)	54	20–70	Semi-automated	None	CSF (r not provided)		
Sullivan et al. (1995)[a]	72	21–70	Semi-automated	ICV	Temporal lobe sulcal CSF LH (.57) and RH (.54), Lat Vent LH (.33) and RH (.33), 3rd Vent (.47)	Quadratic: Temporal lobe sulcal CSF LH, Lat Vent LH & RH; Cubic: Temporal lobe sulcal CSF RH	Hippocampus
Gunning-Dixon et al. (1998)	148	18–77	Manual	None	Caudate (−.32), Putamen (−.41)		Globus pallidus
Coffey et al. (1998)	330	66–96	Manual	ICV	Lat Vent, 3rd Vent, sulcal CSF (men only) (*r* not provided)		Sulcal CSF (women only)
Luft et al. (1999)	48	20–73	Semi-automated	ICV		Exponential: Cerebellum	Globus pallidus
Schuff et al. (1999)	24	36–85	Manual	ICV	Hippocampus ($r = -.64$)		
Mu et al. (1999)	619	40–90	Manual	ICV	Hippocampus (−.93), Amygdala (−.92)		
Sullivan et al. (2000)	61	23–72	Semi-automated	None	Cerebellum GM LH (−.39) and RH (−.45)		Cerebellum WM
Xu et al. (2000)	331	30–79	Manual	ICV	Thalamus (*r* not provided)		
Good et al. (2001)	465	18–79	VBM	ICV/global GM loss	Global CSF	Quadratic: Global CSF (women only)	Amygdala, hippocampus, Lat. thalamus
Pruessner et al. (2001)	80	18–42	Manual	None	Hippocampus (for men only, LH $r = -.47$, RH $r = -.44$)		Hippocampus (women), amygdala
Raz et al. (2001)	190	18–81	Manual	None	Cerebellar hemispheres GM (−.32), Vermian lobules (−.24 to −.32)		Vent pons
Jernigan et al. (2001)[b]	78	30–99	Semi-automated	Cranial vault	Hippocampus (−.65), Caudate (−.35), Nucleus accumbens (−.33), Cortical sulcal CSF (.83), Cerebral Vent CSF (.74), Cerebellar CSF (.75)		Amygdala, thalamus, basomesial diencephalon, lenticular nucleus (putamen, globus pallidus), Substantia nigra
Van Der Werf et al. (2001)	57	21–82	Manual	ICV & Brain size	Thalamus (−.71)		
Scahill et al. (2003)		39	Semi-automated	ICV	Hippocampus, ventricles (*r* not provided)		
Raz et al. (2003)	53	20–77	Manual	ICV	Caudate ($r = -.41/-.47$ baseline/5 year follow-up), Putamen ($r = -.46/-.47$ for baseline/follow up)		Globus pallidus (significant reduction in 5-year longitudinal data)

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Table 1 *(Continued)*

Study	*N*	Age range	Segmentation method	Normalization	Age effects (Pearson's *r*)	Non-linear effects	Not age effects
Liu et al. (2003)	90	14–77	Manual/ semi-automated	ICV	Cerebellum (−.37)		Hippocampus
Van Petten (2004)	48	65–85	Manual	Cranial vault			Hippocampus
Raz et al. (2004a)	200	20–80	Manual	Body height	Hippocampus (−.42)		
Sullivan et al. (2004)	100	23–72	Manual	None	Thalamus (men: −.53, women: −.59)		Pontine
Sullivan et al. (2005)	128	20–85	Manual/ semi-automated	None			Hippocampus
Walhovd et al. (2005a)	73	20–88	Automated	ICV	Hippocampus (−.40), Amygdala (−.47), Thalamus (−.78), Accumbens (−.65), Caudate (−.69), Putamen (−.47), Brainstem (−.35), Cerebellar GM (−.61), Cerebellar WM (−.56), Lat Vent (−.70), Inf lat Vent (.57), 3rd Vent (.74)	Quadratic: Hippocampus, Pallidum, Brainstem, Cerebellar GM, Cerebellar WM, Lat Vent, Inf lat Vent, 3rd Vent; Cubic: Putamen	Pallidum, 4th Vent
Allen et al. (2005)	87	22–88	Manual	None	Hippocampus (−.38)[c], Amygdala (−.42)	Cubic: hippocampus	
Du et al. (2006)	42	58–87	Semi-automated	None			Hippocampus (cross-sectional, reductions at follow-up)
Lupien et al. (2007)	177	18–85	Manual	None (sex as covariate)	Hippocampus (*r* not known)	Quadratic: hippocampus	
Nunnemann et al. (2007)	133	29–80	VBM	None	Putamen (men: −.6)		Putamen (women)
Hasan et al. (2008)	33	19–59	Manual	ICV	Caudate (−.55)		
Greenberg et al. (2008)	82–146	60–85	Manual	None	Caudate RH (−.19) and LH (−.24), Putamen RH (−.22) and LH (−.27), Hippocampus RH (−.36) and LH (−.27), Vent CSF (.39), Nonvent CSF (.37)		

The table does not necessarily encompass all studies of possible relevance. Studies were only included if they reported cross-sectional data for at least one of the structures included in the present paper, except cortical volume, white matter volume, or whole-brain volume. In several of the cases, r was not reported, and was then calculated here based on other information (e.g. R^2). This may lead to slight inaccuracies due to rounding errors, etc. Very different measures are used for correcting ICV/head size/brain size/body size, and the statistical procedures used for the corrections are also often different (e.g. ratio scores, residuals from regression analyses, entered as covariate, showed not to affect the data and then left out of the final analyses). In several of the studies where normalization was not used, ICV or a proxy for ICV was calculated, but for different reasons not used (e.g. did not interact with any variables of interest), or only the results of the analyses without the correction were reported in detail. Not all studies tested for non-linear relationships, and when done, not all tested for cubic relationships. Correlations are Pearson's *r*, unless stated otherwise (the type used was not stated explicitly in all studies). $p \leq .05$ is regarded as significant, regardless of the chosen threshold in each study. LH: Left Hemisphere; RH: right hemisphere; CSF: cerebrospinal fluid; GM: gray matter; WM: white matter; VBM: voxel based morphometry; Vent: ventricles; Lat: lateral.

[a] Men only.

[b] Spearman's rho.

[c] Calculated from R^2 from the cubic regression.

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2001), and in one age effects relative to global GM loss were not observed (Good et al., 2001).

Thalamus/diencephalic structures: Four studies found smaller volume with higher age (Sullivan et al., 2004; Van Der Werf et al., 2001; Walhovd et al., 2005a; Xu et al., 2000), while two did not (Jernigan et al., 1991, 2001). In addition, one study found lack of age effects on the lateral thalamus relatively to global GM loss (Good et al., 2001).

Caudate: Caudate is the only structure where all the relevant studies are in coherence, with eight studies finding linear negative relationships with age (Greenberg et al., 2008; Gunning-Dixon et al., 1998; Hasan et al., 2008; Jernigan et al., 1991; Jernigan et al., 2001; Krishnan et al., 1990; Raz et al., 2003, 2005; Walhovd et al., 2005a).

Putamen: Four studies found age effects (Greenberg et al., 2008; Gunning-Dixon et al., 1998; Raz et al., 2003; Walhovd et al., 2005a). Additionally, in one study, age effects were found for men, but not for women (Nunnemann et al., 2007). Age effects were not found on the lenticular nuclei in one study (Jernigan et al., 2001), but these include the globus pallidus in addition to the putamen, and the latter may explain why effects were not found.

Pallidum: None of the four studies reporting on pallidum volume in relation to age found linear negative relationships (Gunning-Dixon et al., 1998; Jernigan et al., 2001; Luft et al., 1999; Raz et al., 2003), while a quadratic relationship was found in a fifth study (Walhovd et al., 2005a).

Accumbens area: Only two studies have been reported, and both found linear negative relationships with age (Jernigan et al., 2001; Walhovd et al., 2005a).

Brainstem: Smaller volume of the brainstem with higher age was found in one study (Walhovd et al., 2005a), while the ventral pons has been found to be well preserved in another (Raz et al., 2001), and no significant age change was observed in pontine structures in a third study (Sullivan et al., 2005).

Cerebellum: Five studies have found negative age relationships for total cerebellar volume, cerebellar GM, cerebellar WM, or other cerebellar compartments (Jernigan et al., 2001; Liu et al., 2003; Luft et al., 1999; Raz et al., 2001; Sullivan et al., 2000; Walhovd et al., 2005a). In one study, no effects on cerebellar WM (Sullivan et al., 2000) were found, in contrast to a more recent study (Walhovd et al., 2005b). One study observed that the age changes were best described by an exponential fit (Luft et al., 1999). Longitudinal findings of age-related decline in cerebellar volume have been more dramatic than cross-sectional, and comparable to the declines in the association cortices and the caudate nucleus (Raz et al., 2005)

CSF: There is agreement across studies that CSF compartments increase in volume with age (Coffey et al., 1998; Cohen et al., 1992; Good et al., 2001; Greenberg et al., 2008; Gur et al., 1991; Jernigan et al., 2001; Scahill et al., 2003; Sullivan et al., 1995; Walhovd et al., 2005a). Some studies have also found non-linear age changes (Good et al., 2001; Sullivan et al., 1995; Walhovd et al., 2005a).

The differences observed across studies may be related to sample characteristics, segmentation procedures, demarcation criteria, and procedures for intracranial volume (ICV) corrections. Based on the above findings, the following set of hypotheses could be made:

H1. Caudate nucleus, nucleus accumbens, and cerebellar volume will be negatively related to age in all samples, while CSF/ventricular volume will be positively related.

H2. Hippocampus, amygdala, putamen, thalamus volume will generally decline with age, but not consistently across all six samples.

H3. Pallidum and brainstem volume will not be consistently related to age, and age effects will be found only in a minority of the samples.

These hypotheses are strictly based on the previous findings, assuming the results of the present multi-sample study would most likely to be representative of previous findings. However, to the extent that standardizing segmentation and analysis techniques has effect, such empirical hypotheses may not be confirmed, and greater consistency may be found.

2. Methods

2.1. Samples

The details of each of the samples are described in Table 2 and Supplementary Tables 1 and 2, where key publications with in-depth inclusion criteria are provided, including description of approvals by the relevant ethical committees. The total *n* of the samples was 883, with an age range of 75 years (18–93 years). All samples were screened for neurological conditions. It is likely that effects on the volume of the different brain structures largely can be attributed to the influence of normal aging.

2.2. MR acquisition

All participants were scanned on 1.5 T magnets, but from two different manufacturers (Siemens, Erlangen, Germany; General Electric CO. [GE], Milwaukee, WI), and four different models (Siemens Symphony Quantum, Siemens Sonata, Siemens Vision, GE Signa). With the exception of the data from Samples 4a and 4b, the separate sample data sets are from different scanners. All participants within each sample were scanned on the same scanner. The measurements were conducted on T1 weighted sequences were acquired (3D magnetization prepared gradient-echo for the Siemens scanners, and 3D spoiled gradient recalled pulse sequence for GE). Slice thickness varied between 1.5 mm (Sample 1) and 1.25 mm (Samples 4 and 5), with acquisition matrices of 256×192 (Samples 1, 3 and 5) or 256×256

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Table 2
Sample characteristics.

Sample	Country	*N* (% F)	Age mean (range)	Education mean (range)	Key publications	Main screening instruments/inclusion criteria
1	Nor	69 (57)	51.3 (20–88)	15 (7–20)	Walhovd et al. (2005a)	Health interview, MMSE >26, BDI <16, IQ >85, RH only
2	Nor	208 (71)	46.8 (19–75)	14 (9–22)	Espeseth et al. (2008)	Health interview, IQ >85
3	Swe	106 (32)	41.6 (19–56)	14 (9–22)	Jonsson et al. (2006), Nesvag et al. (2008)	Health interview, DSM-III-R, WASI vocabulary >16[a]
4a	USA	155 (65)	44.5 (18–93)	3.5 (1–5)[c]	Marcus et al. (2007)	Health interview, CDR = 0[b], MMSE >25[b], RH only
4b	USA	154 (61)	44.4 (18–94)	3.4 (1–5)[c]	Similar to Sample 4a	Similar to Sample 4a
5	USA	191 (60)	47.3 (18–81)	15.7 (12–21)	Raz et al. (2004a)	Health interview, BIMCT >30, GDQ <15, RH only, neuroradiology

Nor: Norway; Swe: Sweden; F/M: the ratio of females to males; MMSE: Mini Mental Status Exam (Folstein et al., 1975); BDI: Beck Depression Inventory (Beck and Steer, 1987); BIMCT: Blessed Information-Memory-Concentration Test (Blessed et al., 1968); CDR: clinical dementia rating (Berg, 1984, 1988; Morris, 1993); GDQ: Geriatric Depression Questionnaire (Auer and Reisberg, 1997); RH: right handed; WASI: Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

[a] Available for 70 participants.

[b] Available for participants ≥60 years only.

[c] Available for all participants ≥60 years, and sporadically for the rest. 1: less than high school grad., 2: high school grad., 3: some college, 4: college grad., 5: beyond college.

(Samples 2, 4a, and 4b). In three of the samples (Samples 1, 2, 4a, and 4b), multiple scans were acquired within the same scanning session, and averaged to increase the signal-to-noise ratio. The details of the sequences used in each are presented in Supplementary Table 2. Examples of the scan quality from each sample are presented in Supplementary Fig. 1.

2.3. Volumetric analyses

The automated procedures for volumetric measures of the different brain structures were performed with FreeSurfer version 4.0.1, which can be freely downloaded (http://surfer.nmr.mgh.harvard.edu/). The segmentation for cerebrum from the average brain from Sample 2 is shown in Fig. 1. The 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 (Fischl et al., 2002). 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 aging. The technique has previously been shown to be comparable in accuracy to manual labeling (Fischl et al., 2002, 2004). A newly developed atlas-based normalization procedure was used. This has been shown to increase the robustness and accuracy of the segmentations across scanner platforms (Han and Fischl, 2007). It should be mentioned that the cortical volume estimates from the whole-brain segmentation approach in FreeSurfer are probably less accurate than the estimates from the surface-based thickness calculations. Still, the results of the whole-brain procedure were used here because this approach was used for all the other structures analyzed in this paper. Estimated intracranial volume (ICV) was used to correct the volumetric data. This was calculated by the use of an atlas-based normalization procedure, where the atlas scaling factor is used as a proxy for ICV, shown to correlate highly with manually derived ICV ($r = .93$) (Buckner et al., 2004). This procedure has recently been shown to overestimate intracranial volume with increasing atrophy in a longitudinal study of semantic dementia (Pengas et al., 2009). Although this may not be a similar problem with normal aging, ICV values were examined with a special focus on a possible problem of overestimation. No obvious outliers were detected among the ICV estimates, and

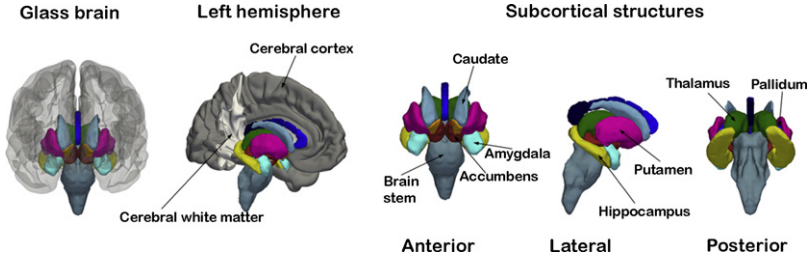

Fig. 1. Whole-brain segmentation. The figure shows the segmentation results from the average brain of Sample 2. The three-dimensional renderings illustrate the shape, extension, and relative position within the brain of the different neuroanatomical structures.

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ICV estimates correlated negatively, rather than positively with age ($r = -.07, -.24, .01, -.25, -.20$, and $-.04$ in Samples 1, 2, 3, 4a, 4b, and 5, respectively). In Sample 2, 4a and 4b, these negative correlations reached significance ($p < .05$), in keeping with a cohort effect (Haug, 1984), rather than possible overestimations, which could lead to a positive ICV–age correlation.

2.4. Statistical analyses

Unless stated otherwise, all analyses were done separately for each sample. An ANCOVA with 13 structures ×2 hemispheres, with age as between subjects factor and with sex and sample as covariates, yielded no age × hemisphere interaction ($F[75,806] = .88$, $p = .75$) and no age × hemisphere × structure interaction (F $[206.48,2218.99] = 1.10$, $p = .16$). The sum of left and right hemisphere volume was thus used in the analyses. First, the average raw volumes of the total sample were calculated per decade, and percent change per decade was estimated based on these. Average percent linear change per decade was also calculated based on the ICV-corrected volumes for each sample. Multiple regression analyses with age and age^2 as simultaneous predictors of the ICV-corrected volumes (the residuals after each volume was regressed on ICV) were performed to test for linear and non-linear age effects in each sample. These regression analyses were repeated for the total sample after the effects of sample were regressed out. ANOVAs with each neuroanatomical structure in turn as dependent variable was performed to test effects of sample × age interactions (sample as fixed factor).

3. Results

3.1. Relationships with age

The mean volumes of the different anatomical structures are shown per decade for the total sample in Table 3. Table 4 shows the estimated percentage volumetric change in each structure per decade based on the raw volumes of the total sample. Average percent linear change per decade based on the ICV-corrected volumes for each sample is shown in Supplementary Table 3. An illustration of the age effects on the morphometry of the three-dimensional segmentations of each structure is given in Supplementary Fig. 2. Table 5 shows linear and quadratic effects of age on ICV-corrected volume of each of the brain structures for each sample separately and for the total sample. Scatter plots for select structures are shown in Fig. 2. All neuroanatomical volumes, with the exception of the 4th ventricle and the brainstem, were robustly related to age in at least five of the six samples, with smaller neuroanatomical structures and greater ventricular/CSF compartments in higher age. For twelve of the ICV-corrected volumes, including total brain volume, significant age relationships were found in all six samples. The strongest relationships were observed for the cerebral cortex, with the amount of variance explained by age ranging from 34% to 71% for the linear components. There was large overlap of results across samples. Sample 3 stood out as the one in which the weakest age effects were seen. Generally, the quadratic term significantly increased the amount of explained variance. Cerebral WM, lateral ventricles, inferior lateral ventricles, 3rd ventricle, caudate, hippocampus, and total volume showed a non-linear pattern in five samples. The accumbens area, thalamus, and fourth ventricle did not show a non-linear component in any of the samples, whereas amygdala and cerebellar cortex showed a non-linear component in one sample only. The rest of the structures displayed a mix of linear and non-linear effects across samples. Fig. 4 shows the strength of the age relationships across groups, sorted by the median explained variance, where both the linear and the non-linear (where significant) contributions to the amount of explained variance are included.

3.2. Effects of sample

To test whether sample influenced the strength of the relationship between neuroanatomical volume and age, ANOVAs were conducted with each brain structure in turn as dependent variable, sample as fixed factor, and age as covariate (d.f. = 5, error = 871 for all analyses). Significant interactions between age and sample were found for the cerebral cortex ($F = 4.30$, $p < .001$), cerebral WM ($F = 14.09$, $p < 10^{-12}$), cerebellar cortex ($F = 3.56$, $p < .01$), caudate ($F = 2.88$, $p < .05$), putamen ($F = 2.34$, $p < .05$), pallidum ($F = 4.18$, $p < .001$), amygdala ($F = 6.02$, $p < .0001$), accumbens ($F = 3.73$, $p < .005$), third ventricle ($F = 2.41$, $p < .05$), and total brain volume ($F = 3.60$, $p < .005$), whereas a trend was found for hippocampus ($F = 1.95$, $p = .084$). In contrast, no sample × volume interactions were observed for the lateral ventricles ($F = .65$), inferior lateral ventricles ($F = .11$), cerebellum WM ($F = 1.42$), thalamus ($F = 1.60$), fourth ventricle ($F = .30$), brainstem ($F = 1.41$), and CSF ($F = .89$) (Fig. 3).

3.3. Age effects in the total sample

Regression analyses with age and age^2 on residuals with the effects of sample regressed out generally confirmed the age patterns observed in the subsamples. However, largely due to increase in statistical power due to increase in the sample size ($n = 883$), all structures now showed significant age effects, and a quadratic age component was significant for a few additional structures, a total of 13. Reduction in the magnitude of age differences at older age suggesting age-related deceleration was observed for the cerebral cortex, caudate, putamen, pallidum, the lateral and inferior lateral ventricles, and the 3rd and 4th ventricle. On the other hand, increase in age-related differences suggesting acceleration of age effects on volume in the latter part of the lifespan was observed for cerebral WM, cerebellar WM, hippocampus and the brain-

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Table 3
Mean volume of the different neuroanatomical structures per decade.

	Total sample ($N = 883$)													
	18–29 years ($N = 262$)		30–39 years ($N = 109$)		40–49 years ($N = 159$)		50–59 years ($N = 100$)		60–69 years ($N = 110$)		70–79 years ($N = 105$)		80–95 years ($N = 38$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cerebral Cor	517426	66685	489079	69076	484994	73159	446856	60459	419190	68791	393507	58007	389445	39685
Cerebral WM	448369	55455	465638	59881	473373	70145	451591	57500	427932	59294	393931	53765	360263	53355
Lat Vent	12659	6902	15046	9093	16152	9943	17472	9330	24566	12949	34205	17344	41336	17985
Inf Lat Vent	651	363	724	434	705	432	712	401	1045	671	1742	1130	2499	1191
Cerebel WM	28320	3506	28543	3444	28410	3747	27360	3587	25787	3544	24452	3198	22862	4006
Cerebel Cor	109909	13173	108925	12313	107773	13778	101211	13572	97125	13010	90332	13464	90595	9440
Thalamus	14002	1518	14037	1431	13624	1600	12749	1449	12241	1513	11510	1358	10931	1182
Caudate	7848	981	7319	887	7139	901	6939	850	6853	1011	6975	972	7285	1269
Putamen	12507	1400	11312	1360	10707	1136	10206	1127	9640	1034	9520	1158	9035	1209
Pallidum	3638	452	3395	481	3236	394	3051	435	2981	485	2889	336	2646	466
Hippocampus	8214	889	8319	941	8368	1044	8101	1027	7467	1106	6865	979	6201	730
Amygdala	3540	459	3442	467	3400	495	3216	477	3025	524	2766	440	2679	507
Accumbens	1492	266	1263	244	1175	199	1142	229	1060	178	1013	181	1038	180
3rd Vent	1032	286	992	361	1033	356	1173	406	1419	526	1813	574	1927	708
4th Vent	1979	576	1945	640	1801	514	1847	491	2016	666	2126	664	2077	665
Brainstem	21456	2385	22186	2413	22206	2696	21444	2594	21277	2732	20179	2565	19086	2455
CSF	1195	241	1241	338	1273	269	1245	281	1412	330	1542	654	1606	496
Total volume	1176723	125178	1163458	130877	1164404	151413	1093865	126705	1034578	135408	963939	120410	922066	98074
ICV	1586302	161092	1615561	173216	1610050	185966	1552345	157821	1534473	159132	1538938	175808	1488398	171561
	Females ($N = 528$)													
	18–29 years ($N = 154$)		30–39 years ($N = 58$)		40–49 years ($N = 83$)		50–59 years ($N = 64$)		60–69 years ($N = 72$)		70–79 years ($N = 67$)		80–95 years ($N = 30$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cerebral Cor	490631	57077	460475	53466	453442	57940	425692	52015	398916	59567	378820	49812	389744	38415
Cerebral WM	427040	46766	439966	43353	439631	52271	424193	40860	406040	47102	378277	50723	357302	46707
Lat Vent	11262	4941	13202	6490	15018	10420	14436	6368	23399	12715	30458	16178	38390	16059
Inf Lat Vent	639	307	651	364	682	472	625	379	972	667	1578	1066	2154	967
Cerebel WM	27375	2757	27404	3238	27310	3104	26208	3219	25006	2956	24148	3370	22853	3588
Cerebel Cor	104270	9742	103237	9566	101066	10112	95664	10922	93178	11080	87705	12021	89267	7308
Thalamus	13367	1257	13468	1140	13018	1411	12282	1224	11643	1136	11190	1388	10805	822
Caudate	7576	883	7072	709	6931	851	6649	630	6597	904	6830	863	7288	1072
Putamen	12060	1278	10832	1261	10385	1033	9882	1003	9382	903	9093	759	9134	1148
Pallidum	3477	418	3216	452	3075	381	2916	304	2857	496	2807	298	2624	398
Hippocampus	7889	737	8075	904	7954	870	7896	994	7182	837	6726	890	6166	688
Amygdala	3396	439	3241	365	3169	395	3039	379	2862	445	2655	358	2598	357
Accumbens	1461	246	1202	237	1154	206	1108	215	1030	186	1005	180	1035	154

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3rd Vent	978	231	912	293	978	343	1061	300	1327	485	1646	534	1708	482
4th Vent	1889	499	1834	567	1706	500	1819	475	1959	710	2051	687	2033	704
Brainstem	20518	2021	21265	2092	21205	2238	20505	2165	20353	2201	19394	2095	18910	2166
CSF	1136	226	1184	351	1186	255	1132	201	1365	334	1451	761	1480	369
Total volume	1119061	102916	1099454	87918	1088340	107907	1036033	96939	985044	108815	928650	104816	917726	85065
ICV	1510744	125832	1533802	131432	1531369	157510	1471598	101797	1465030	124339	1468898	140686	1451682	130944

Males ($N = 355$)

	18–29 years ($N = 108$)		30–39 years ($N = 51$)		40–49 years ($N = 76$)		50–59 years ($N = 36$)		60–69 years ($N = 38$)		70–79 years ($N = 38$)		80–95 years ($N = 8$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cerebral Cor	555635	60678	521609	70846	519452	72801	484482	56517	457605	69402	419400	62870	388322	47000
Cerebral WM	478784	52778	494832	62998	510222	68864	500298	50339	469412	58311	421531	48060	371369	76358
Lat Vent	14650	8630	17144	11052	17389	9305	22870	11242	26776	13270	40812	17563	52386	21551
Inf Lat Vent	670	431	807	493	729	386	868	396	1184	666	2031	1196	3791	1097
Cerebel WM	29669	3999	29838	3233	29612	4030	29409	3316	27268	4098	24988	2833	22897	5611
Cerebel Cor	117948	13288	115394	11957	115097	13564	111071	12250	104604	13240	94963	14741	95572	14625
Thalamus	14909	1397	14684	1462	14285	1538	13580	1460	13374	1503	12074	1111	11403	2064
Caudate	8235	989	7599	988	7366	904	7455	950	7338	1036	7231	1105	7272	1938
Putamen	13145	1324	11858	1270	11059	1145	10781	1118	10129	1100	10273	1351	8664	1439
Pallidum	3868	396	3599	433	3411	330	3291	526	3216	365	3034	355	2727	693
Hippocampus	8677	884	8597	913	8821	1035	8466	996	8006	1343	7111	1089	6331	908
Amygdala	3744	407	3672	468	3652	471	3530	476	3336	526	2962	503	2985	835
Accumbens	1536	288	1333	235	1197	191	1202	244	1118	146	1027	184	1050	269
3rd Vent	1108	337	1083	409	1092	362	1372	492	1593	562	2107	527	2749	843
4th Vent	2108	651	2070	698	1904	512	1895	523	2124	569	2257	608	2244	493
Brainstem	22794	2229	23233	2343	23299	2741	23113	2473	23029	2808	21564	2752	19747	3433
CSF	1279	239	1307	312	1367	252	1445	295	1503	305	1703	356	2079	643
Total volume	1258945	107088	1236248	134276	1247473	148899	1196677	107274	1128433	132181	1026159	122167	938339	143108
ICV	1694042	143966	1708541	168946	1695978	177193	1695896	136681	1666049	133301	1662430	164399	1626083	238950

Units are number of voxels (1 mm^3). Cor: cortex; WM: white matter; Lat: lateral; Inf: inferior; Vent: ventricles; CSF: cerebrospinal fluid; Total volume: the sum of all the other structures (CSF and ventricles not included).

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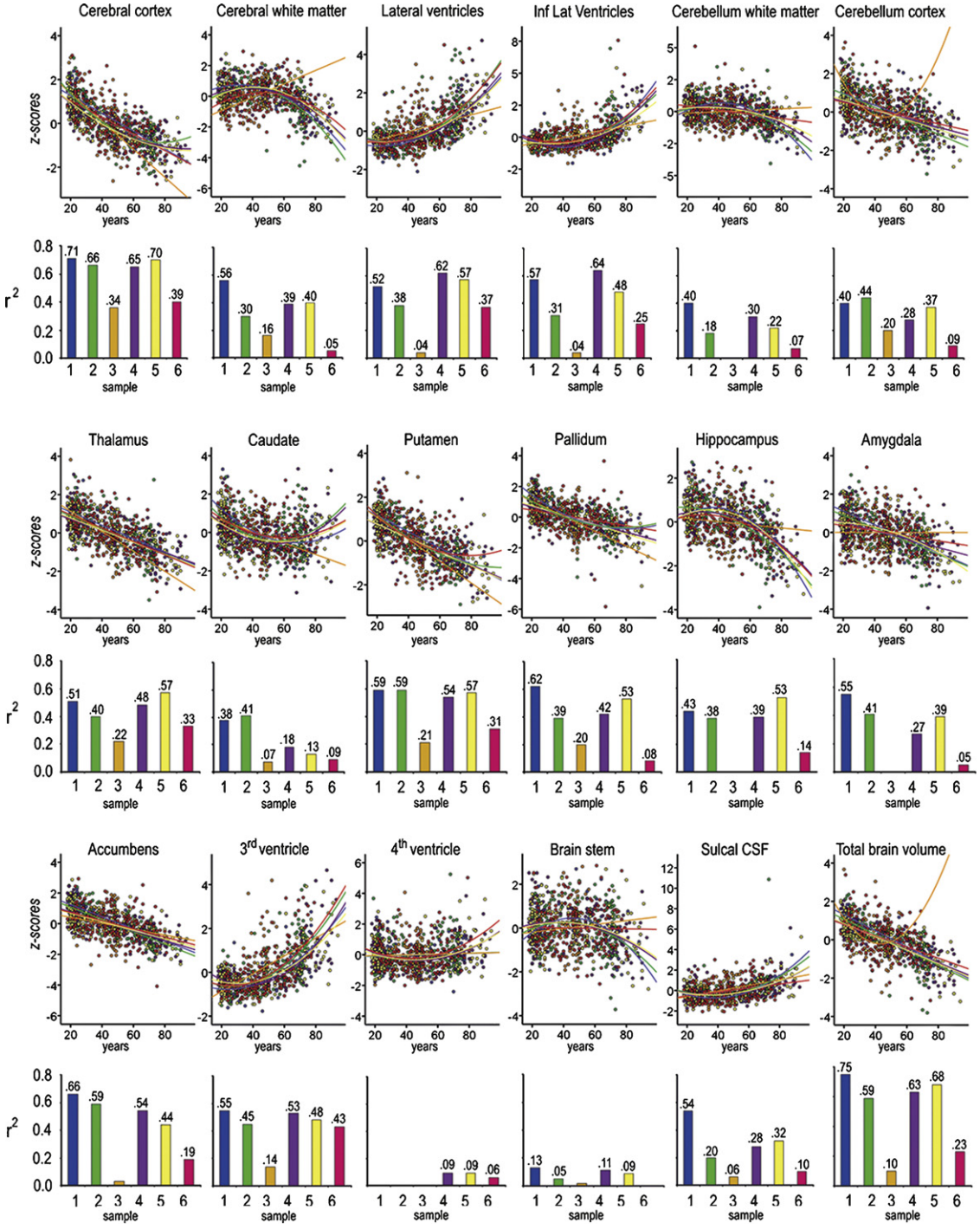

Fig. 2. Scatter plots. The scatter plots depict the individual data points in the relationship between age and the volume of each of the examined brain structures in each of the samples (color coded). All volumes were corrected for intracranial volume, and the standardized residual values are shown on the *y*-axis (*z* scores). Regression lines for each sample are shown. If a non-linear (quadratic) component significantly increased the amount of explained variance, this curve is shown instead of the linear one. That does not mean that the exact quadratic fit shown depicts the true age function, and these fits should not be used to interpret the exact timing of peaks and dips in the age functions. For purpose of comparison, the age fits for each sample is calculated for the same, total age range (18–94) across samples. However, the actual age range differs across samples, and no age function should be interpreted beyond the actual age range of the sample in question. In particular, Sample 3 has a relatively narrow age range extending only to 56 years of age, and the age fits should not be interpreted beyond this age. Above each scatter plot a three-dimensional rendering of the relevant Freesurfer-segmentation from the average brain from Sample 2 is shown. Below each scatter plot is a bar chart showing the amount of variance in brain structure explained by age in each sample. If the quadratic component significantly contributed, the R^2 corresponds to the total contribution from the linear and non-linear components. If the quadratic component did not contribute significantly, the R^2 corresponds to the contribution from the linear component only. If $p \leq .05$, the coefficients are given above each bar.

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Table 4
Percentage change per decade for the total sample based on raw volumes.

	18–29 to 30–39	30–39 to 40–49	40–49 to 50–59	50–59 to 60–69	60–69 to 70–79	70–79 to 80–95	18–29 to 80–95
Cerebral Cor	−5.5	−.8	−7.9	−6.2	−6.1	−1.0	−24.7
Cerebral WM	3.9	1.7	−4.6	−5.2	−7.9	−8.5	−19.7
Lat Vent	18.9	7.4	8.2	40.6	39.2	20.8	226.5
Inf Lat Vent	11.2	−2.6	1.0	46.8	66.7	43.5	283.9
Cerebel WM	.8	−.5	−3.7	−5.7	−5.2	−6.5	−19.3
Cerebel Cor	−.9	−1.1	−6.1	−4.0	−7.0	.3	−17.6
Thalamus	.2	−2.9	−6.4	−4.0	−6.0	−5.0	−21.9
Caudate	−6.7	−2.5	−2.8	−1.2	1.8	4.4	−7.2
Putamen	−9.6	−5.3	−4.7	−5.5	−1.2	−5.1	−27.8
Pallidum	−6.7	−4.7	−5.7	−2.3	−3.1	−8.4	−27.3
Hippocampus	1.3	.6	−3.2	−7.8	−8.1	−9.7	−24.5
Amygdala	−2.8	−1.2	−5.4	−5.9	−8.6	−3.1	−24.3
Accumbens	−15.3	−7.0	−2.8	−7.2	−4.4	2.5	−30.4
3rd Vent	−3.9	4.1	13.6	21.0	27.8	6.3	86.7
4th Vent	−1.7	−7.4	2.6	9.1	5.5	−2.3	5.0
Brainstem	3.4	.1	−3.4	−.8	−5.2	−5.4	−11.0
CSF	3.8	2.6	−2.2	13.4	9.2	4.2	34.4
Total volume	−1.1	.1	−6.1	−5.4	−6.8	−4.3	−21.6

Cor: cortex; WM: white matter; Lat: lateral; Inf: inferior; Vent: ventricles; CSF: cerebrospinal fluid; Total volume: the sum of all the other structures (CSF and ventricles not included).

Table 5
Effects of age on structures corrected for intracranial volume. The age relationships were all negative, with the exception of ventricular and CSF volumes, for which positive relationships were observed. For the total sample, the effects of sample were regressed out.

	Sample 1 (R^2)		Sample 2 (R^2)		Sample 3 (R^2)		Sample 4a (R^2)		Sample 4b (R^2)		Sample 5 (R^2)		Total Sample (R^2)	
	Age	Age^2	Age	Age^2	Age	Age^2	Age	Age^2	Age	Age^2	Age	Age^2	Age	Age^2
Cerebral Cor	**.71**	.72	**.63**	**.66**	**.34**	.36	**.63**	**.65**	**.68**	**.70**	**.39**	.40	**.54**	**.56**
Cerebral WM	**.48**	**.56**	**.21**	**.30**	**.16**	.17	**.27**	**.39**	**.20**	**.40**	.00	**.05**	**.12**	**.21**
Lat Vent	**.49**	**.52**	**.33**	**.38**	*.04*	.04	**.52**	**.62**	**.52**	**.57**	**.34**	**.37**	**.37**	**.41**
Inf Lat Vent	**.37**	**.57**	**.27**	**.31**	*.04*	.04	**.41**	**.64**	**.39**	**.48**	**.18**	**.25**	**.27**	**.34**
Cerebel WM	**.24**	**.40**	**.13**	**.18**	.00	.00	**.22**	**.30**	**.18**	**.22**	**.07**	.07	**.13**	**.16**
Cerebel Cor	**.40**	.41	**.44**	.44	**.18**	**.20**	**.28**	.28	**.37**	.37	**.09**	.10	**.27**	.27
Thalamus	**.51**	.51	**.40**	.41	**.22**	.25	**.48**	.48	**.57**	.57	**.33**	.33	**.40**	.40
Caudate	**.33**	**.38**	**.11**	**.41**	**.07**	.09	.03	**.18**	**.06**	**.13**	**.07**	**.09**	**.08**	**.13**
Putamen	**.59**	.60	**.58**	**.59**	**.21**	.21	**.54**	.55	**.57**	.57	**.29**	**.31**	**.45**	**.46**
Pallidum	**.59**	**.62**	**.38**	**.39**	**.20**	.21	**.42**	.42	**.53**	.54	**.08**	.08	**.32**	*.32*
Hippocampus	**.33**	**.43**	**.37**	**.38**	.00	.04	**.33**	**.39**	**.40**	**.53**	**.12**	**.14**	**.26**	**.29**
Amygdala	**.55**	.55	**.41**	.41	.00	.00	**.27**	.27	**.36**	**.39**	**.05**	.05	**.23**	.23
Accumbens	**.66**	.66	**.59**	.59	.03	.04	**.54**	.55	**.44**	.44	**.19**	.19	**.39**	.39
3rd Vent	**.51**	**.55**	**.40**	**.45**	**.14**	.15	**.37**	**.53**	**.41**	**.48**	**.38**	**.43**	**.36**	**.40**
4th Vent	.00	.01	.00	.02	.00	.01	.01	**.09**	*.03*	**.09**	.02	**.06**	**.01**	**.04**
Brainstem	.04	**.13**	*.02*	**.05**	.01	.02	**.08**	**.11**	**.06**	**.09**	.00	.00	**.03**	**.05**
CSF	**.40**	**.54**	**.15**	**.20**	*.06*	.08	**.20**	**.28**	**.24**	**.32**	**.10**	.11	**.16**	**.20**
Total volume	**.75**	.75	**.59**	.59	**.06**	**.10**	**.63**	.63	**.68**	.69	**.23**	.23	**.47**	.47

Cor: cortex; WM: white matter; Lat: lateral; Inf: inferior; Vent: ventricles; CSF: cerebrospinal fluid; Total volume: the sum of all the other structures (CSF and ventricles not included); ICV: intra cranial volume.
The numbers in the age^2 columns indicate amount of explained variance for the model consisting of age + age^2. They are printed in bold/italic if adding a quadratic age term significantly ($p < .01/.05$) increased the amount of explained variance (R^2), not whether the total expression is significant. **Bold**: $p < .01$; *Italic*: $p < .05$.

stem. The R^2 for the different volumes and age in the total sample are shown in Fig. 4.

4. Discussion

For most neuroanatomical volumes, age effects were observed across samples. Of the 18 neuroanatomical volumes tested, including total brain volume, 12 showed age effects in all six samples, while four showed effects in five of the samples. Only the 4th ventricle (related in three samples) and the brainstem (related in four of the samples) were not related to age in a consistent fashion. The first hypothesis based on previous reports was that caudate nucleus, nucleus accumbens, and cerebellum compartments would be negatively related to age in all samples, while CSF compartments would be

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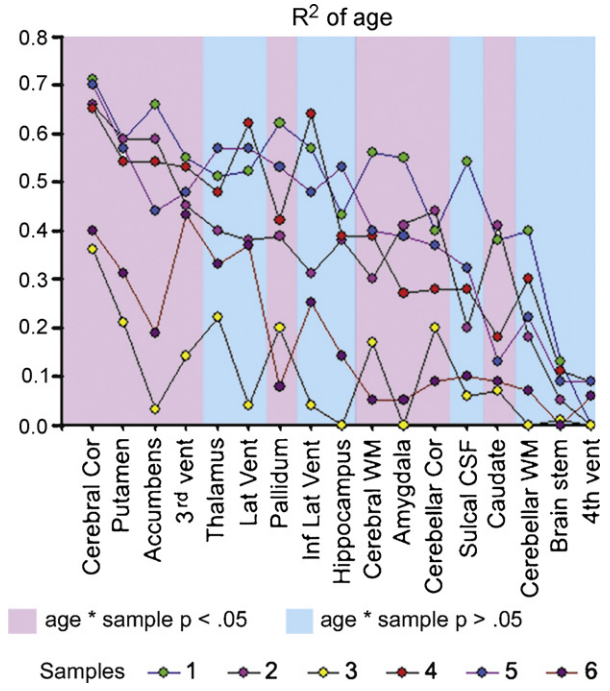

Fig. 3. Amount of age-explained variance for each structure in the separate samples. The figure shows the R^2 (amount of explained variance) of age for each of the tested structures in each sample separately. Pink background: structures for which a significant ($p < .05$) age × sample interaction was found. Blue background: structures for which no significant ($p > .05$) age × sample interaction was found.

positively related. This was mainly confirmed, in that significant age relationships were found in five of the samples for accumbens and effects on the caudate, cerebellar cortex, cerebellar WM and all CSF-measures except the 4th ventricle were found in all six samples. The second empirically based hypothesis was that hippocampus, amygdala, putamen and thalamic volume would be generally, but less consistently

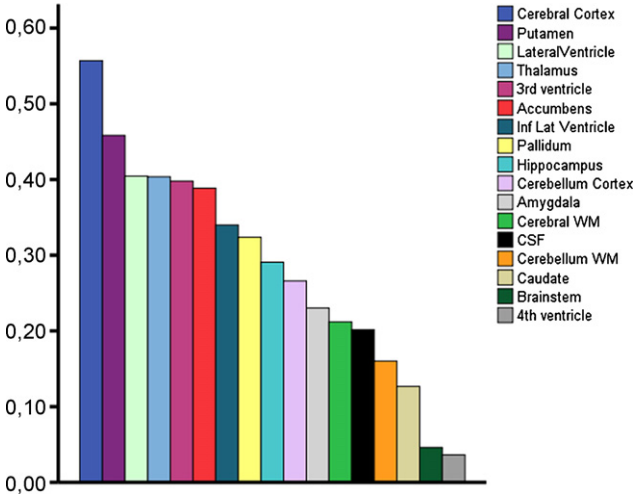

Fig. 4. Amount of age-explained variance for each structure in the total sample. The bars show the percentage volumetric variance explained by age in the total sample for each of the neuroanatomical structures. The effect of sample was regressed out.

related to age. This was not confirmed; putamen and thalamic volume were related to age in all six samples, while the two other volumes showed age effects in five of six. Finally, we predicted that pallidum and brainstem volume would not be related to age, or related only in a minority of the samples. Pallidum volume was related to age in all samples, while volume of the brainstem showed age effects in only three. Thus, the various structures showed age effects in a more stable manner across samples than what would be expected from previous literature. In addition, all structures were significantly affected by age in the total sample analyses, indicating that when statistical power is sufficiently high, age effects are observed throughout the human brain. The present data may be useful as a reference for other researchers if they would like to see e.g. how their control group at a given age may compare to a larger sample of controls. However, we caution against using these data as a normative reference for clinical use, since this must be further validated.

The present results indicate that age affects brain structures globally, but with substantial differences in the amount of variance explained by age. Of the specific structures, the cerebral cortex showed the greatest amount of variance explained by age in all samples. Cerebral WM showed relative preservation with age, which fits with previous reports of WM increase until middle age (Allen et al., 2005; Bartzokis et al., 2003; Walhovd et al., 2005a). However, after middle age, WM volume appeared to show an accelerating decrease in volume. Hippocampus is a structure vulnerable to many cerebral insults and known to be affected at the early stages of AD. A multi-component model of brain aging (Buckner, 2004; Head et al., 2005; Raz, 2000) proposes that whereas the medial temporal lobes are affected by AD, a separate process with an anterior-to-posterior gradient affects normal aging and may underlie the executive problems often observed in late adulthood. Striatum changes have been implicated in reduced executive function in healthy aging (Rubin, 1999). The present analyses showed that hippocampal volume decreased as a function of age in five of the six samples, with a median explained variance of 38%. This result is consistent with reported longitudinal findings (Raz et al., 2005), and indicates that hippocampus is far from spared in normal aging. However, hippocampus was not especially vulnerable to the effects of age either.

The striatal structures showed a strikingly heterogeneous aging pattern, in that pallidum and putamen volume was relatively severely affected by age (explained variance in the total sample of 46% and 32%, respectively), while caudate seemed to be among the best preserved structures with an age-explained variance of 13%, and only 7.2% shrinkage from the 20s to 80s/90s, even though age effects were identified in all striatal structures in all samples. Taken together, striatum and hippocampus seem to age at about the same speed, but there appears to be considerable heterogeneity in the aging of the striatal structures. In addition to the cerebral cortex, pallidum and accumbens volume showed relatively large age effects. The accumbens was the structure for which

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the largest estimated percentage age difference was observed (an estimated loss of 30.4% from the 20s to the 80s/90s), and pallidum also showed large volumetric age effects (about 5% per decade). Thus, cross-sectional findings across the samples suggest that basal ganglia have significant vulnerability to aging. This view is consistent with longitudinal findings, although the latter suggest greater shrinkage of the caudate nucleus than the rest of the striatum (Raz et al., 2003, 2005).

Quadratic relationships were found for several structures consistently across samples, confirming previous reports (Allen et al., 2005; Jernigan and Gamst, 2005; Walhovd et al., 2005a). Cerebral WM, lateral ventricles, inferior lateral ventricles, 3rd ventricle, caudate, hippocampus, and total volume showed a non-linear pattern of age-related differences in five samples, while the volumes of accumbens, thalamus, and the fourth ventricle were linearly related to age. These results are interesting for several reasons. An implication is that even though age-related differences in brain morphometry seem to be global, they are heterogeneous. Different parts of the brain not only age at different rates, but also in qualitatively different ways. Some structures, such as the hippocampus and cerebral WM, showed initial increase in volume, before accelerated volume loss sets in. Other structures, like the caudate, showed initial volumetric decrease followed by less prominent loss. These trends were found across five or six samples. The curvilinear nature of age relationships was also confirmed in the total sample analysis, where the majority of structures showed significant quadratic components. Diminishing effects of age in higher age ranges were observed for the cerebral cortex, caudate, putamen, and pallidum, along with a flatter rate of expanding CSF compartments (lateral, inferior lateral, 3rd and 4th ventricles). An acceleration of effects of age on neuroanatomical volumes in the latter part of the lifespan, on the other hand, was observed for cerebral WM, cerebellar WM, hippocampus and the brainstem. The significant curvilinear relationship for the cerebral cortex appeared to be due to a greater initial volume loss in the 20s rather than a true flattening late in life. However, the additional variance in cortical volume explained by the quadratic component in the total sample was on the order of 2% only. The non-linear patterns also indicate that age effects on brain structures should be studied as continuous processes, and only a part of the story is captured if distinct age ranges are compared. The effects of age on brain morphometry are continuous, but they are not uniform throughout the adult lifespan.

The age-related differences found in the present study tended to be stronger and more consistent than that in most often previously reported studies. This is especially notable since the data were obtained from five independent projects, with five different scanners, in three different countries, thus presupposing several possible sources of variability. It is likely that the use of identical segmentation procedures for all the scans greatly reduced the inconsistency. When formally tested, sample exerted an influence on the relationship between volume and age for several structures. However, sample effects were strongest for the structures most affected by age. Hence, sample differences did generally not determine whether an effect was present, but modulated the strength of the effect. This indicates that much of the variability in previous research may be accounted for by differences in segmentation approaches and definition of ROIs. The present study used an automated segmentation technique, which has previously been shown to be comparable in accuracy to manual methods (Fischl et al., 2002, 2004). The correlation between hippocampal volume and age obtained in a manual morphometry study (almost identical to Sample 6) (Raz et al., 2004a) was −.42, compared to −.35 in the present study, indicating that the automated segmentation approach used did not overestimate age effects. The data from Samples 3 and 6 were based on a single T1 scan, while the data from the other samples were based on multiple runs optimized for automated segmentation techniques. The larger estimated hippocampus volume in Samples 3 and 6 may indicate slight problems with automatic labeling of this region in these samples. As can be seen in Fig. 1, the gray/white contrast in the acquisitions from Samples 1, 2, and 4/5 is different than the contrast from Samples 3 to 6. This may have contributed to the lower correlations in these samples. As the atlas used for segmentation has been built from data acquired on a Siemens platform, segmentation accuracy is probably higher with Siemens scanners (Samples 1, 2, 4a,b) than GE scanners (Samples 3, 5) (Han and Fischl, 2007). Still, a newly developed atlas normalization procedure was used, which has been shown to increase the robustness and accuracy of the segmentations also on data from GE scanners (Han and Fischl, 2007). Also, all segmentations were visually inspected for accuracy, ensuring that no obvious segmentation errors were included.

The observed differences across samples are likely also in part due to true differences across populations, which can theoretically be due to sampling methods and criteria as well as societal differences. It is important in this regard not to conflate effect sizes such as R^2 with the degree of estimated volume loss observed. For instance, Sample 1, drawn from a Norwegian study, tended to show the strongest age relationships, yet not the highest percentage volume change per decade. This means that age is a strong predictor of neuroanatomical variance in the population, but not necessarily that the absolute magnitude of the age declines is great. This may for instance happen if the population is homogeneous with respect to other characteristics than age. Norway and Sweden tend to be characterized by more homogenous public health care and education than the US. One might speculate that this type of homogeneity could simultaneously make biological variables such as age a stronger predictor. However, while age was a strong predictor in Norwegian Samples 1 and 2, it was a less strong predictor in Swedish sample 3. Further, volunteer participants in these kinds of studies tend to have higher education and better health than the average population, which may diminish national differences in access to health care and education. Hence, scan parameters appear

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a more likely factor of influence in this regard than sample characteristics.

Generally, Sample 3 showed the weakest age relationships. This could be related to the analysis of one instead of two scans per participant, a smaller age range with an upper age limit of 56 years, or to the fact that a lower percentage of the participants were females. Some studies have found evidence for steeper age functions for males than females (Chung et al., 2006; Coffey et al., 1998; Cowell et al., 1994; Good et al., 2001; Gur et al., 2002; Murphy et al., 1996; Nunnemann et al., 2007; Pruessner et al., 2001; Raz et al., 2004a; Resnick et al., 2000; Riello et al., 2005; Sowell et al., 2007; Xu et al., 2000), though this is a controversial issue (Greenberg et al., 2008; Salat et al., 2004; Sowell et al., 2007). However, this does not seem to be the case for the present samples (Fjell et al., in press). Thus, it is hard to pinpoint the exact reason for the somewhat weaker age effects for Sample 3.

Importantly, however, the results were largely replicable across the different samples. An implication of the findings is, in line with a recent reliability study (Jovicich et al., 2009), that multi-site studies can obtain a high degree of consistency and sensitivity, in this case, to age effects. The amount of explained variance in the total sample was generally somewhat lower than the amount of variance explained in single samples. Indeed it would be surprising if this was not the case when pooling studies where no attempts have been made to standardize imaging parameters. However, all age relationships were significant in the total sample due to the increased power, so the benefits of increasing samples by including additional sites may not be substantially contradicted by the noise introduced. This will likely apply especially if efforts are made to standardize scanning parameters. The detection of age effects throughout the brain in the present study, in areas where age effects have generally not been detected, such as the brainstem, is first and foremost dependent on the large sample size. For instance, age significantly accounted for 1% of the variance of 4th ventricle volume, corresponding to a correlation of .10. The relatively large effect sizes for some of the structures where age effects have most often previously been found, e.g. the putamen, may depend on the consistent application of a robust segmentation technique (Fischl et al., 2002; Jovicich et al., 2009). Automated methods may have some undesirable features, in that without proper quality check they may potentially allow erroneous segmentation, especially if gross anatomical anomalies that violate the assumptions inherent in the atlas used are present. However, automated methods also have several advantages over manual methods. They require minimal intervention by highly trained personnel, allow processing of many brains in a reasonable time frame and are characterized by high reliability and repeatability of measures (Fischl et al., 2002). It would be practically impossible to undertake the present study with manual segmentation, as it would require years of work.

In conclusion, the present cross-sectional study shows that age affects brain volumes globally, but the various structures are influenced in both quantitatively and qualitatively different ways.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2009.05.013.

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