Behavioral/Systems/Cognitive

Minute Effects of Sex on the Aging Brain: A Multisample Magnetic Resonance Imaging Study of Healthy Aging and Alzheimer's Disease

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Age is associated with substantial macrostructural brain changes. While some recent magnetic resonance imaging studies have reported larger age effects in men than women, others find no sex differences. As brain morphometry is a potentially important tool in diagnosis and monitoring of age-related neurological diseases, e.g., Alzheimer's disease (AD), it is important to know whether sex influences brain aging. We analyzed cross-sectional magnetic resonance scans from 1143 healthy participants from seven subsamples provided by four independent research groups. In addition, 96 patients with mild AD were included. Estimates of cortical thickness continuously across the brain surface, as well as volume of 17 subcortical structures, were obtained by use of automated segmentation tools (FreeSurfer). In the healthy participants, no differences in aging slopes between women and men were found in any part of the cortex. Pallidum corrected for intracranial volume showed slightly higher age correlations for men. The analyses were repeated in each of the seven subsamples, and the lack of age × sex interactions was largely replicated. Analyses of the AD sample showed no interactions between sex and age for any brain region. We conclude that sex has negligible effects on the age slope of brain volumes both in healthy participants and in AD.

Introduction

More than 50 magnetic resonance imaging (MRI) studies of sex effects on brain structures have been published, partly motivated by observations of small, but consistent, sex differences in cognitive abilities (Halpern and Tan, 2001; Jones et al., 2003). More importantly, as brain morphometry emerges as a valuable tool in prediction and diagnosis of age-related neurological disorders, e.g., Alzheimer's disease (AD) (Fischl et al., 2002; Dubois et al., 2007; Colliot et al., 2008), it is increasingly important to understand the factors that influence volumetric changes with increasing age. Although much is known about the general pattern of age effects on brain morphometry from cross-sectional studies (Courchesne et al., 2000; Jernigan et al., 2001; Raz et al., 2004b, 2007; Salat et al., 2004; Fotenos et al., 2005; Walhovd et al., 2005a,b; Fjell et al., 2009), the role of sex in brain aging is still controversial. Although extremely valuable longitudinal studies of aging exist (Resnick et al., 2003; Raz et al., 2004a), the age spans sampled are small, and the present paper will focus on cross-sectional studies. Some studies have found more age-related regional volume differences in men than in women (Cowell et al., 1994; Murphy et al., 1996; Coffey et al., 1998; Resnick et al., 2000; Xu et al., 2000; Good et al., 2001; Pruessner et al., 2001; Gur et al., 2002a; Raz et al., 2004b; Riello et al., 2005; Chung et al., 2006; Sowell et al., 2007; Nunnemann et al., 2009), while others have found no sex differences (Salat et al., 2004; Lemaître et al., 2005; Sowell et al., 2007; Greenberg et al., 2008), or a heterogeneous

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Table 1. 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)	Nesvåg et al. (2008)	Health interview, DSM-III-R, WASI vocabulary > 16[a]
4	USA	155 (65)	44.5 (18–93)	3.5 (1–5)[b]	Marcus et al. (2007)	Health interview, CDR = 0[c], MMSE > 25[c], RH only
5	USA	154 (61)	44.4 (18–94)	3.4 (1–5)[b]	Similar to sample 4	Similar to sample 4
6	USA	191 (60)	47.3 (18–81)	15.7 (12–21)	Raz et al. (2004b)	Health interview, BIMCT > 30, GDQ < 15, RH only, neuroradiology
7	Nor	260 (57)	48.8 (20–93)	15.5 (8–23)[d]	Fjell et al. (2008)	Health interview, neuropsychological evaluation, BDI < 16, IQ > 85, RH only
8[e]	USA	96 (59)	76.6 (62–96)	2.8 (1–5)[b]	Similar to sample 4	Health interview, CDR ≥ 0.5, RH only

Nor, Norway; Swe, Sweden; % f, percentage of female participants; MMSE, Mini Mental Status Exam (Folstein et al., 1975); BDI, Beck Depression Inventory (Beck, 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 all participants ≥ 60 years, and sporadically for the rest. 1, Less than high school graduate (grad.); 2, high school grad.; 3, some college; 4, college grad.; 5, beyond college.

[c]Available for participants ≥ 60 years only.

[d]Missing for one participant.

[e]Alzheimer patients.

pattern across different brain structures (Murphy et al., 1996; Gunning-Dixon et al., 1998; Pruessner et al., 2001; Gur et al., 2002a; Cowell et al., 2007). The inconsistencies may be caused by differences in sample characteristics, scan quality, segmentation approach, or statistical procedures. Limited attempts to replicate the pattern of sex difference in regional brain aging in samples drawn from the same population using the same equipment were unsuccessful (Raz et al., 1997, 2004b). We tested whether age affects the brains of women and men differentially by addressing these sources of variation. A total of 1143 healthy participants from seven cross-sectional life-span samples were included in the combined sample. In addition, 96 AD patients were included in a separate sample. This made it possible to account for sample- and scan-related factors that could influence the results. We tested how sex influences the magnitude and direction of age effects on cortical thickness and the volumes of 17 different subcortical brain structures. No previous studies have tested effects of sex in healthy aging or AD on such a large number of subcortical and cortical structures simultaneously.

Materials and Methods

Samples. Age correlations across six of the seven healthy samples (n = 883) have been reported previously (Fjell et al., 2009), without analyses of sex effects. The details of each of the subsamples are described in Table 1, as well as in a previous publication from the project (Fjell et al., 2009). The current sample consisted of 1143 participants (676 women, 467 men), with an age range of 76 years (18–94 years, mean = 46.8, SD = 19.2). All the healthy samples were well screened for diseases and history of neurological conditions, and for cognitive deficits/dementia by standardized tests. Ninety-six AD patients (59 women/37 men) were included from the Open Access Series of Imaging Studies (OASIS) database (www.oasis-brains.org), with an age range of 34 years (62–96 years, mean = 76.6, SD = 7.1). Details of recruitment and screening procedures for the AD group were given by Marcus et al. (2007). AD participants underwent the Washington University Alzheimer Disease Research Center's full clinical assessment, yielding Clinical Dementia Rating (CDR) (Berg, 1984, 1988; Morris, 1993; Morris et al., 2001). CDR of 0.5 or higher was taken to indicate mild or moderate AD.

MR acquisition. All scans were obtained from 1.5 T magnets from two different manufacturers [Siemens and General Electric (GE)], and from five different models (Siemens Avanto, Symphony, Sonata, and Vision and GE Signa). All participants within each sample were scanned on the same scanner. T1-weighted sequences were acquired [three-dimensional (3D) magnetization-prepared gradient echo for Siemens/3D spoiled gradient recalled pulse sequences for GE]. In five of the samples (samples 1, 2, 4, 5, and 7) multiple scans were acquired within the same scanning session and averaged to increase the signal-to-noise ratio. The details of the sequences are presented in Table 2.

MRI analysis. All datasets were processed and analyzed with FreeSurfer 4.01 (http://surfer.nmr.mgh.harvard.edu/) at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with the additional use of computing resources from the ~4000-central-processing-unit Titan grid cluster (http://hpc.uio.no) run by the Research Computing Services Group at USIT (Universitetets senter for informasjonsteknologi), University of Oslo. The automated procedure for volumetric measures of the different brain structures is described in detail by Fischl et al. (2002, 2004). A label was automatically assigned to each voxel in the 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 AD patients in the age range 60–87 years, and the classification technique used a registration procedure that is robust to anatomical variability, including the ventricular enlargement typically associated with aging. The technique has been shown to be comparable in accuracy to manual labeling (Fischl et al., 2002, 2004). We also applied a newly developed atlas normalization procedure, which has been shown to increase the robustness and accuracy of the segmentations across scanner platforms (Han and Fischl, 2007). Two limitations must be mentioned: the segmentation labeled "CSF" in FreeSurfer represents CSF in an area superior to the brainstem, inferior to the fornix, and posterior to the third ventricle. An example of the segmentation is presented in supplemental Figure 1 (available at www.jneurosci.org as supplemental material). However, it is important to note that this is less validated than the other CSF measures (ventricles), and that strong conclusions should thus not be drawn regarding CSF based on this measure. The measure is included in the whole-brain segmentation (the FreeSurfer label "CSF"), and we therefore report results for it. Second, the cortical volume estimates from the whole-brain segmentation approach are probably less accurate than the surface-based thickness calculations. However, to ease comparison with the subcortical volumes, the whole-brain procedure was used for estimating all volume (but not thickness) data. Intracranial volume (ICV) was calculated by use of an atlas normalization procedure described by Buckner et al. (2004).

Cortical thickness was obtained by reconstructing representations of the gray/white matter boundary (Dale and Sereno, 1993; Dale et al., 1999) and the cortical surface, and the distance between these surfaces at each point across the cortical mantle was calculated. This method uses both intensity and continuity information from the entire 3D MR volume in segmentation and deformation procedures to construct representations of cortical thickness. The maps were created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The

Table 2. MRI parameters

Sample	MRI scanner	MRI protocol
1	Siemens Symphony Quantum	Two 3D MP-RAGE T1-weighted sequences TR/TE/TI/FA = 2730 ms/4 ms/1000 ms/7° Matrix = 192 × 256 Scan time: 8.5 min per volume Each volume consisted of 128 sagittal slices (1.33 × 1 × 1 mm)
2	Siemens Sonata	Two 3D MP-RAGE T1-weighted sequences TR/TE/TI/FA = 2730 ms/3.43 ms/1000 ms/7° Matrix: 256 × 256 Scan time: 8 min and 46 s per volume Each volume consisted of 128 sagittal slices (1.33 × 1 × 1 mm)
3	General Electric Signa	One 3D SPGR pulse T1-weighted sequence TR/TE/FA = 24 ms/6.0 ms/35°, number of excitations was 2 Matrix: 256 × 192 Each volume consisted of 1.5 mm coronal slices, no gap, FOV = 24 cm
4, 5, and 8	Siemens Vision	3–4 individual T1-weighted MP-RAGE sequences TR/TE/TI/FA = 9.7 ms/4.0 ms/20 ms/10° Matrix = 256 × 256 Each volume consisted of 128 sagittal slices (1.25 × 1 × 1 mm).
6	General Electric Signa	One 3D SPGR pulse T1-weighted sequence TR/TE/FA = 24 ms/5.0 ms/30° Matrix = 256 × 192 Each volume consisted of 124 contiguous axial slices (1.30 × 0.94 × 0.86 mm), FOV = 22 cm
7	Siemens Avanto	Two 3D MP-RAGE T1-weighted sequences TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8° Matrix: 192 × 192 Scan time: 7 min and 42 s per volume Each volume consisted of 160 sagittal slices (1.25 × 1.25 × 1.20 mm)

FOV, Field of view; FA, flip angle; TR, repetition time; TE, echo time; TI, inversion time; MP-RAGE, magnetization-prepared rapid gradient echo; SPGR, spoiled gradient recalled.

maps are not restricted to the voxel resolution of the original data and are thus capable of detecting submillimeter differences between groups (Fischl and Dale, 2000). This has been validated using MR and histology (Rosas et al., 2002; Kuperberg et al., 2003), and the results are not biased across scanner platforms (Han et al., 2006; Han and Fischl, 2007). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of 15 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl et al., 1999b). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Statistical comparisons of surface maps were generated by computing a general linear model (GLM) of the effects of each variable on thickness at each vertex, which were mapped on the semi-inflated surface of the average brain of the sample (Dale et al., 1999; Fischl et al., 1999a).

Statistics. Effect of sample was regressed out from all variables before statistical analysis. To test main effects of sex and sex × age interactions, GLMs were used, with brain structure (17 levels) as the within-subjects factor, and sex and age as between subjects factors. The analyses were done on uncorrected and ICV-corrected (residuals) volumes. ICV correction controls for sex differences in body size as well as in brain size at the earliest stages of development when ICV is affected by brain growth. In addition, group comparisons were done with corrections for total brain volume (TBV), adjusting the regional volumes for the differences in brain size, since previous studies have used this approach. This will not give a good approximation of age effects on the different structures, so these are not reported. TBV was quantified as the sum of all brain structures, not including CSF/ventricular system. The GLMs were followed by *post hoc* paired-samples *t* tests, and correlated with age for each sex separately. Since Pearson coefficients are not symmetrically distributed around other values than 0, the coefficients from the correlation analyses were *z*-transformed ($Z = \frac{1}{2}\ln[1 + r/(1 - r)]$, where ln is the base-*e* logarithm, $SD = 1/\sqrt{n - 3}$) and compared between women and men by *t* tests. To test for nonlinear relationships, multiple regressions with age and age^2 as simultaneous predictors were run for the ICV-corrected structures for women and men separately. Finally, GLMs were computed to test interactions between sex and age in the AD sample for the 17 volume estimates. *Post hoc* multiple regressions with age, sex, and age × sex were run, with cognitive status [CDR and Mini Mental Status Exam (MMSE) score] as additional predictors to control for possible gender differences in cognitive function.

Results

Subcortical analyses

For the 13 uncorrected hemispheric brain volumes [cerebral cortex, cerebral white matter (WM), hippocampus, amygdala, putamen, caudate, pallidum, accumbens, thalamus, lateral ventricles, inferior lateral ventricles, cerebellum cortex, and cerebellum WM], ANCOVA with hemisphere × sex × structure (13 volumes) with age and sample as covariates established that sex and hemisphere did not interact ($F_{(1,1139)} = 0.001$, $p = 0.973$). Thus, the sum of left and right hemisphere was used in the rest of the analyses. The effect of sex on the volume of the different brain structures are shown in Figure 1. A GLM with 17 uncorrected volumes, sex, and age was run. Significant effects of sex ($F_{(1,998)} = 290.99$, $p < 10^{-56}$) and age ($F_{(75,998)} = 4.65$, $p < 10^{-29}$) were found, in addition to structure × sex ($F_{(8.28,8263.38)} = 8.60$, $p < 10^{-11}$), structure × age ($F_{(621.00,8263.38)} = 8.58$, $p = 0.000$), and structure × sex × age ($F_{(563.04,8263.38)} = 1.30$, $p < 10^{-5}$) interactions. However, sex and age did not interact significantly ($F_{(68,998)} = 1.214$, $p = 0.119$). *Post hoc t* tests for each structure are presented in Table 3. Men had significantly larger volume than women for all structures. The largest differences were found for cerebral WM and cortex, cerebellum cortex, amygdala, and thalamus, in addition to TBV.

Correlations between age and structure, split by sex, are presented in Table 4. The difference in coefficient strength was assessed by *t* tests of Fisher's *z*-transformed coefficients. Only for CSF did the age correlations differ significantly between the sexes (0.31 vs 0.49 for women and men, respectively). Scatter plots are

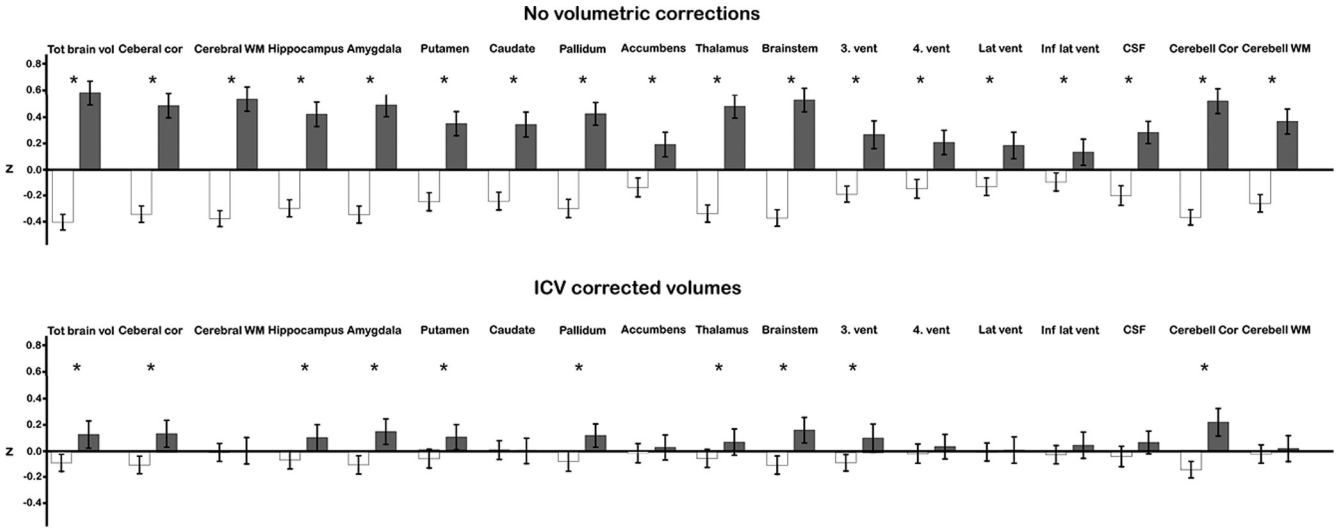

Figure 1. Volumetric differences between women and men. The bars illustrate the mean volume for women (red) and men (blue) separately for each of the brain volumes tested. The 95% confidence intervals are indicated. In the upper row, volumes are corrected for the effects of sample by means of regression analyses, and the standardized residuals are shown. In the middle row, the volumes are corrected for ICV in addition to sample, and in the final row they are corrected for total brain volume and sample. Men had significantly larger uncorrected volumes for all structures, and for several ICV-corrected structures, although the differences were much smaller in the latter cases. *$p < 0.05$.

Table 3. Volume differences between women and men

	Corrected for sample		Corrected for sample and ICV		Corrected for sample and TBV	
Structure	Difference (*z*)	*t* (*p*)	Difference (*z*)	*t* (*p*)	Difference (*z*)	*t* (*p*)
3rd ventricle	−0.455	-7.761 ($<10^{-13}$)	−0.189	−3.154 (<0.01)	−0.703	-12.458 ($<10^{-32}$)
4th ventricle	−0.354	-5.978 ($<10^{-08}$)	−0.054	−0.893 ($>0.05^{n.s.}$)	−0.271	-4.540 ($<10^{-06}$)
Accumbens	−0.327	-5.506 ($<10^{-07}$)	−0.043	−0.722 ($>0.05^{n.s.}$)	0.131	2.190 (<0.05)
Amygdala	−0.838	-15.283 ($<10^{-47}$)	−0.253	-4.247 ($<10^{-03}$)	−0.083	−1.377 ($>0.05^{n.s.}$)
Brainstem	−0.902	-16.731 ($<10^{-55}$)	−0.268	-4.490 ($<10^{-04}$)	−0.294	-4.948 ($<10^{-6}$)
Caudate	−0.586	-10.164 ($<10^{-22}$)	0.007	0.121 ($>0.05^{n.s.}$)	−0.034	−0.561 ($>0.05^{n.s.}$)
Cerebellum cortex	−0.889	-16.432 ($<10^{-53}$)	−0.363	-6.143 ($<10^{-07}$)	−0.169	−2.824 (<0.005)
Cerebellum WM	−0.626	-10.938 ($<10^{-25}$)	−0.041	−0.682 ($>0.05^{n.s.}$)	−0.014	−0.225 ($>0.05^{n.s.}$)
Cerebral cortex	−0.830	-15.114 ($<10^{-46}$)	−0.238	-3.988 ($<10^{-03}$)	0.159	2.658 (<0.01)
Cerebral WM	−0.914	-17.009 ($<10^{-57}$)	−0.013	−0.222 ($>0.05^{n.s.}$)	−0.093	−1.556 ($>0.05^{n.s.}$)
CSF	−0.483	-8.264 ($<10^{-15}$)	−0.107	−1.781 ($>0.05^{n.s.}$)	−0.472	-8.067 ($<10^{-14}$)
Hippocampus	−0.719	-12.785 ($<10^{-34}$)	−0.169	−2.821 (<0.005)	0.125	2.088 (<0.05)
Inferior lateral ventricle	−0.228	-3.808 ($<10^{-02}$)	−0.072	−1.194 ($>0.05^{n.s.}$)	−0.565	-9.785 ($<10^{-21}$)
Lateral ventricle	−0.315	-5.306 ($<10^{-06}$)	−0.016	−0.259 ($>0.05^{n.s.}$)	−0.559	-9.665 ($<10^{-20}$)
Pallidum	−0.724	-12.872 ($<10^{-34}$)	−0.197	−3.292 (<0.005)	−0.123	−2.046 (<0.05)
Putamen	−0.597	-10.386 ($<10^{-23}$)	−0.166	−2.765 (<0.01)	0.040	0.666 ($>0.05^{n.s.}$)
Thalamus	−0.820	-14.904 ($<10^{-45}$)	−0.124	−2.065 (<0.05)	0.055	0.922 ($>0.05^{n.s.}$)
Total brain volume	−0.988	-18.798 ($<10^{-68}$)	−0.216	−3.615 (<0.001)	NA	NA

t test of mean differences in volume are presented for the various brain structures included in the present paper. Results are shown for analyses done on the residuals after the effect of sample is regressed out, when the effects of sample and ICV are regressed out, and finally when the effects of sample and total brain volume are regressed out. Negative difference score and *t* value indicate larger volume for men and positive indicate larger for women. Men had significantly larger uncorrected volumes for all structures and significantly larger ICV-corrected volumes for 10 structures. n.s., Not significant; NA, not applicable.

presented in Figures 2 (cerebrum cortex and WM), 3 (subcortical structures), and 4 (CSF compartments). To test whether the lack of sex × age interactions was caused by reduced sensitivity due to merging of different subsamples, the GLM was rerun in each of the seven samples separately. For sample 2 ($F_{(28,128)} = 2.33$, $p < 0.001$) and sample 7 ($F_{(36,159)} = 1.96$, $p < 0.05$), significant age × sex interactions were found, while this was not seen in the other five samples (p ranging from 0.21 to 1.00). In sample 2, CSF correlated significantly differently with age between the sexes ($r = 0.25$ vs 0.51 in women and men, respectively, $z = 1.98$, $p < 0.05$). In sample 7, cerebellum cortex correlated significantly differently ($r = -0.45$ vs -0.63 in women and men, respectively, $z = 2.03$, $p < 0.05$).

The analyses were repeated with ICV-corrected volumes. Main effects of sex ($F_{(1,998)} = 14.22$, $p < 0.001$) and age ($F_{(75,998)} = 6.59$, $p < 10^{-47}$) were confirmed. In addition, significant structure × sex ($F_{(8.20,8187.37)} = 3.82$, $p < 0.001$), structure × age ($F_{(615.28,8187.37)} = 7.97$, $p < 0.000$), and structure × sex × age ($F_{(557.86,8187.37)} = 1.33$, $p < 10^{-6}$) interactions were found. Age and sex did not interact ($F_{(68,998)} = 0.90$, $p = 0.71$). *t* tests showed significantly larger volumes for the third ventricle, amygdala, brainstem, cerebellum cortex, cerebral cortex, hippocampus, pallidum, putamen, and thalamus, in addition to TBV, for men (Table 3). Significant differences in age correlations were observed only for CSF (0.36 vs 0.59 for women and men, respectively) and pallidum (−0.49 vs −0.58) (Table 4). The GLM was rerun in each of the seven samples separately, with no significant age × sex interactions (p values from 0.22 to 0.85). The ANOVA for the total sample was repeated for the participants over 60 years of age, to test whether age × sex interactions could be found in this age span. There were still no significant age × sex interaction ($F_{(25,247)} = 0.65$, $p = 0.90$). The residual

Table 4. Age correlations for women and men

	Corrected for sample			Corrected for sample and ICV		
Structure	Women	Men	Diff (*z*)	Women	Men	Diff (*z*)
3rd ventricle	0.55	0.61	1.50	0.59	0.63	1.05
4th ventricle	0.11	0.08	0.50	0.15	0.10	0.84
Accumbens	−0.62	−0.61	0.27	−0.60	−0.61	0.26
Amygdala	−0.58	−0.51	1.65	−0.55	−0.52	0.70
Brainstem	−0.19	−0.15	0.68	−0.10	−0.12	0.34
Caudate	−0.32	−0.33	0.19	−0.26	−0.35	1.65
Cerebellum cortex	−0.53	−0.53	0.00	−0.48	−0.53	1.11
Cerebellum WM	−0.38	−0.33	0.95	−0.33	−0.34	0.19
Cerebral cortex	−0.69	−0.66	0.91	−0.67	−0.69	0.62
Cerebral WM	−0.34	−0.25	1.64	−0.31	−0.30	0.18
CSF	0.31	0.46	**2.93**	0.36	0.50	**2.86**
Hippocampus	−0.53	−0.49	0.90	−0.50	−0.49	0.22
Inferior lateral ventricle	0.51	0.58	1.65	0.53	0.60	1.71
Lateral ventricle	0.58	0.59	0.25	0.63	0.62	0.27
Pallidum	−0.54	−0.56	0.48	−0.49	−0.58	*2.09*
Putamen	−0.71	−0.68	0.96	−0.68	−0.68	0.00
Thalamus	−0.60	−0.57	0.76	−0.62	−0.61	0.27
Total brain volume	−0.62	−0.55	1.77	−0.67	−0.66	0.30

Pearson correlations between age and the various neuroanatomical structures are presented for women and men separately. *t* test of Fisher's *z*-transformed coefficients were done, and the *z*-scores for the pairwise contrasts as well as the significance levels are presented. Results are shown for analyses done on the residuals after the effect of sample is regressed out, and when the effects of sample and ICV are regressed out. The only difference was found for CSF, where the correlations for men were significantly higher than for women. Bold indicates $p < 0.01$ for the difference between the coefficients; italic indicates $p < 0.05$ for the difference between the coefficients. Diff, Difference.

variance for each variable was calculated for each sex separately. An ANOVA showed that the residual variance was highly and positively related to age ($F_{(75,998)} = 135.91$, $p < 0.0001$), but no age × sex interaction was seen ($F_{(68,998)} = 1.22$, $p = 0.12$).

GLM with TBV-corrected volumes confirmed main effects of sex ($F_{(1,998)} = 53.344$, $p < 10^{-12}$). *t* tests showed significantly larger TBV-corrected volumes for women for cerebral cortex and accumbens area, while larger volumes for men were found for the ventricular system (third ventricle, fourth ventricle, lateral and inferior lateral ventricles, and CSF), brainstem, cerebellum cortex, and pallidum (Table 3).

Effects of introducing a quadratic term were investigated for the ICV-corrected volumes (Table 5). A nonlinear fit yielded significantly more explained variance for both women and men for most structures. For pallidum, age^2 did not increase amount of explained variance for either of the groups. For cerebral cortex, adding age^2 as a predictor increased the amount of explained variance from 45 to 48% ($p < 10^{-6}$) in women, while the amount of explained variance did not increase significantly for men. The effect of age on cortical volume in women was decreasing with advancing age. For amygdala and cerebellum cortex, increasing effect of age in higher age was seen for men only. Generally, however, the amount of variance explained by age was very similar for men and women, as is illustrated in Figure 5. CSF and pallidum seemed to be more related to age in men than in women, and when the nonlinear component was added, cerebral white matter also seemed to be more related to age in the sample of men than in the sample of women.

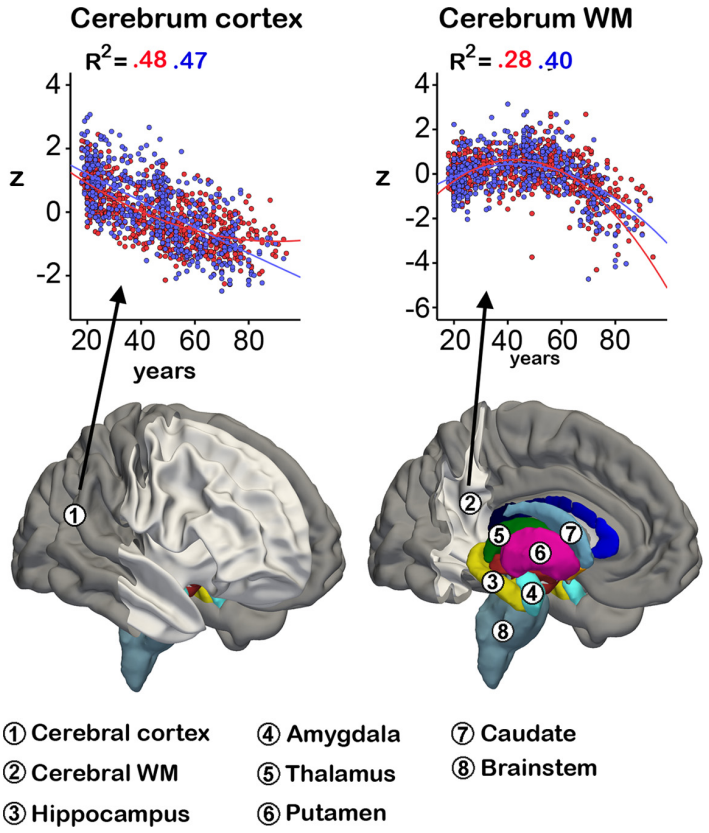

Figure 2. Scatter plots of age effects on cerebrum. The scatter plots show the individual data points and the aging pattern for women (red) and men (blue) for cerebral cortex and white matter after ICV corrections of the volumes (the *y*-axes denote *z*-scores of the residuals). The numbers above each plot are the R^2 for women (red) and men (blue), respectively, including the contributions from both linear and nonlinear terms. In addition, the three-dimensional renderings of several of the structures included in the present paper are shown above the plots, based on the average brain of ~70 participants below 40 years.

Cortical analyses

GLMs were run to test for sex differences in cortical thickness and effects of aging (see Fig. 6). When age was regressed out, only minute and scattered effects of sex were seen, going in both directions (yellow-red: women thicker, blue-green: men thicker). When a

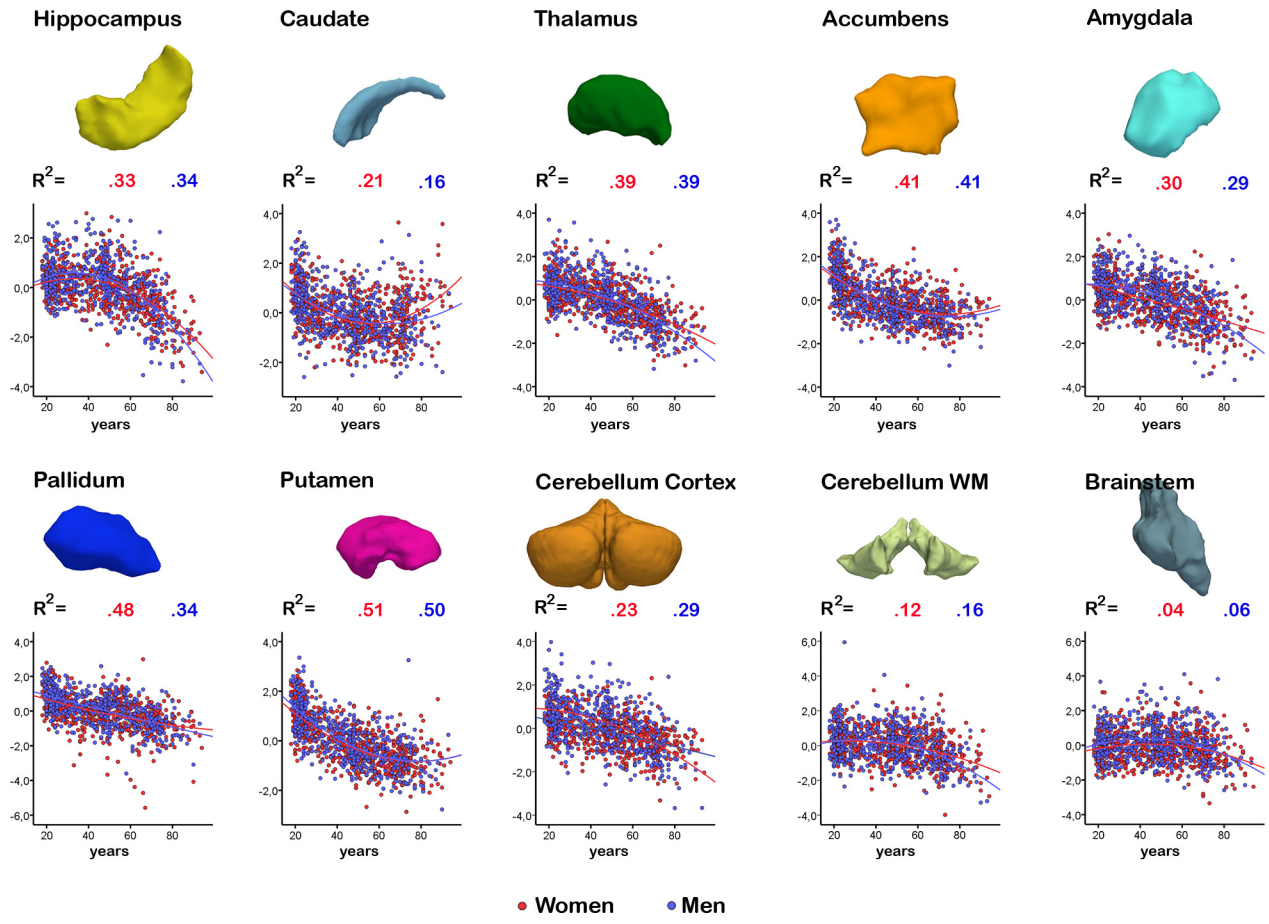

Figure 3. Scatter plots of age effects on subcortical structures. The scatter plots show the individual data points and the aging pattern for women (red) and men (blue) for selected subcortical structures after ICV corrections of the volumes (the *y*-axes denote *z*-scores of the residuals). The numbers above each plot are the R^2 for women (red) and men (blue), respectively, including the contributions from both the linear and the nonlinear terms. Above the plots, the three-dimensional renderings of the structures are shown, based on the average brains of ~70 participants below 40 years. Note that these are rescaled for the figure, and so their size cannot be visually compared. The age effects did not differ between women and men.

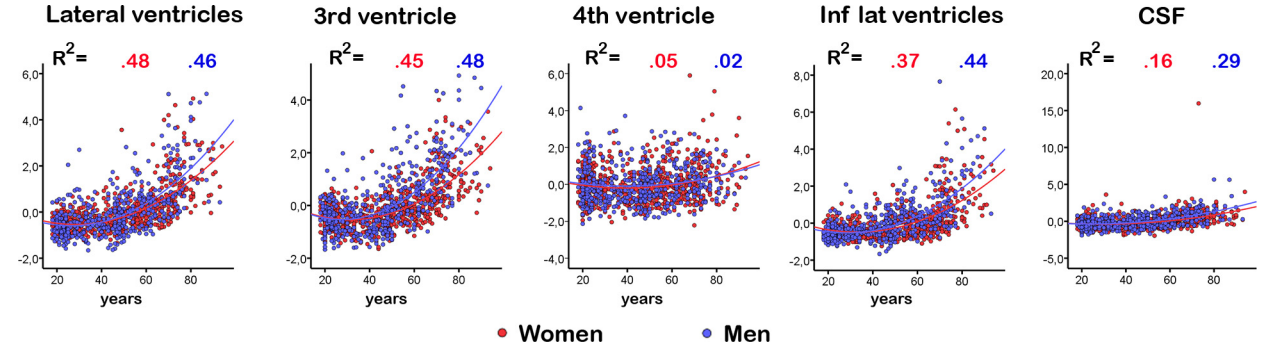

Figure 4. Scatter plots of aging patterns on CSF compartments. The scatter plots show the individual data points and the aging pattern for women (red) and men (blue) for the measured CSF compartments after ICV corrections of the volumes (the *y*-axes denote *z*-scores of the residuals). The numbers above each plot are the R^2 for women (red) and men (blue), respectively, including the contributions from both the linear and the nonlinear terms. CSF differed in age slope between women and men.

commonly used criterion for correction for multiple comparisons were used [false discovery rate (FDR) < 0.05], no effects survived. The same was found when comparing the effects of age between women and men. Some scattered areas of steeper age slope in women than men (yellow-red) were seen, but did not survive correction for FDR. To test whether lack of effects could be due to merging of data from different samples, sex × age interactions were tested for each of the seven samples independently. No effects survived the FDR < 0.05 criterion for any of the samples.

Alzheimer's disease

ANCOVA with sex, age, and 17 uncorrected neuroanatomical volumes, and MMSE and CDR as covariates, yielded an effect of sex ($F_{(1,47)} = 35.54$, $p = 10^{-6}$, men larger), but no age × sex interaction ($F_{(17,47)} = 1.58$, $p = 0.11$). For ICV-corrected volumes, trends were observed for sex ($F_{(1,47)} = 3.90$, $p = 0.054$), age ($F_{(28,47)} = 1.53$, $p = 0.10$), and sex × age ($F_{(17,47)} = 1.73$, $p = 0.07$). Finally, analysis of TBV-corrected volumes yielded no significant results (all p values > 0.59). *Post hoc* multiple regression

Table 5. R^2 from multiple regressions with age and age^2 as predictors

	Corrected for sample and ICV	
Structure	Women	Men
3rd ventricle	**0.45**	**0.48**
4th ventricle	**0.05**	**0.02**
Accumbens	**0.41**	**0.41**
Amygdala	0.30	**0.29**
Brainstem	**0.04**	**0.06**
Caudate	**0.21**	**0.16**
Cerebellum cortex	0.23	**0.29**
Cerebellum WM	**0.12**	**0.16**
Cerebral cortex	**0.48**	0.47
Cerebral WM	**0.28**	**0.40**
CSF	**0.16**	**0.29**
Hippocampus	**0.33**	**0.34**
Inferior lateral ventricle	**0.37**	**0.44**
Lateral ventricle	**0.48**	**0.46**
Pallidum	0.24	0.34
Putamen	**0.51**	**0.50**
Thalamus	**0.39**	**0.39**
Total brain volume	**0.46**	**0.50**

All structures were significantly related to age for both women and men. Bold indicates that the contribution from age^2 significantly ($p < 0.05$) increased the amount of explained variance.

analyses were run, with each of the 17 structures as dependent variables in turn, and CDR, MMSE, age, sex, and age × sex interaction as predictors. No sex × age interactions were significant.

Discussion

The results from the present large-scale multisample study indicate that sex exerts minute and unstable effects on age differences in brain morphometry, both in healthy aging and in AD. Sex did not influence the age slopes of regional cortical thickness, while there was a small effect of sex on the age slope of CSF and pallidum in healthy controls when corrected for ICV. Sex and age interacted in predicting brain morphometry uncorrected for ICV in two subsamples, but the effects were not replicable across other subsamples. This fits with the inconsistency of effects seen in previous research. Some find larger age slopes for men for at least some structures (Cowell et al., 1994; Murphy et al., 1996; Coffey et al., 1998; Resnick et al., 2000; Xu et al., 2000; Good et al., 2001; Pruessner et al., 2001; Gur et al., 2002a; Raz et al., 2004b; Riello et al., 2005; Chung et al., 2006; Sowell et al., 2007; Nunnemann et al., 2009), while others do not observe differences (Salat et al., 2004; Lemaître et al., 2005; Sowell et al., 2007; Greenberg et al., 2008). The large number of analyses conducted across multiple samples and brain regions increased the susceptibility to type I errors. This may have contributed to the between-samples inconsistency seen for the uncorrected volumes, i.e., the significant age × sex interactions found for samples 2 and 7. While the effect in sample 2 would have survived a Bonferroni correction with a factor of almost 50, the effect in sample 7 would not survive any correction for multiple comparisons, even though the *n* was as high as 260.

The sex differences in age slope for CSF could indicate nonspecific sex effects on global atrophic processes. However, the age slopes for ICV-corrected total brain volumes were almost identical between the sexes (−0.67 vs −0.66 for females and males, respectively), which may speak against this interpretation. Further, as noted above, the CSF measure captures only a proportion of the total CSF, is less well validated than the other CSF measures, and should be interpreted with caution. It should also be stressed that the present data are cross-sectional, and thus can only address the issue of age differences, not aging per se. However, it interesting that a longitudinal study did not find different rates of volumetric change for women and men over 4 years (Resnick et al., 2003).

With its 1143 healthy adults and 96 AD patients, the present study is among the largest MR studies to date. Of the 44 MR studies testing effects of sex on brain morphometry reported in the present paper, the median *n* was 116, while the median *n* for the 29 who tested for sex differences in aging was 140. Coupled with the use of validated, automated segmentation techniques, covering the entire brain, the present results could provide a firm basis for conclusion. Still, the most unique aspect of the present data is that separate analyses could be done in eight different samples, confirming the conclusions from the total sample.

As argued in the introduction, the discrepant results in previous literature can be caused by one or more of four different factors: (1) sample characteristics, (2) scan quality, (3) segmentation approach, or the (4) statistical procedures used. (1–2) To examine the influence of sample characteristics and scan quality, seven healthy subsamples were used, from six different scanners, four different research groups, and three different countries. If differences in sample characteristics and/or scan quality are responsible for the discrepancies in previous literature, it is likely that this would have been reflected across the subsamples included in the present study. Some inconsistencies across samples were found, but different age slopes for men and women were generally not seen. Differences in sample characteristics/scan quality may have contributed to the observed inconsistencies in previous literature, but did not appear to have a major impact on the results in the present study. (3) Further, the normalization procedure for head size had small but notable effects on the sex × age interactions. The significance of the interaction term changed for some samples when the volumes were ICV corrected, indicating that different procedures can explain some of the discrepancies in previous literature. (4) Finally, it is possible that the segmentation procedure used may affect the degree to which sex differences are observed. It is interesting to note that the present results are in accordance with findings from the first surface-based study that mapped sex differences in thickness across the brain surface, in which age × sex interactions were largely not found (Sowell et al., 2007). Surface-based methods are likely to improve anatomical correspondence between the participants, which may enhance sensitivity to group differences. Further, the cortical analysis used in the present study is not restricted to anatomically defined areas. This stands in contrast to many volumetric studies, and increases the likelihood of detecting unexpected group differences. Finally, the methods applied in the present paper have been validated using both histological and manual methods (Fischl et al., 2002, 2004; Rosas et al., 2002; Kuperberg et al., 2003), and have been shown to be sensitive to various morphometric effects, e.g., of schizophrenia (Kuperberg et al., 2003; Nesvåg et al., 2008), mild cognitive impairment and AD (Du et al., 2007; Fjell et al., 2008), and prenatal opiate exposure (Walhovd et al., 2007). Further, the present results show high correlations between brain volumes and age, and replicated the established finding of larger raw volumes in men.

Effects of sex on cortical thickness and brain volumes

Sex differences in cortical thickness were not found. Sowell et al. (2007) found thicker cortex in women than men in posterior temporal and inferior parietal regions, independently of differences in brain or body size. They studied a relatively large sample (176 participants), and *p* values of the three regions that differed

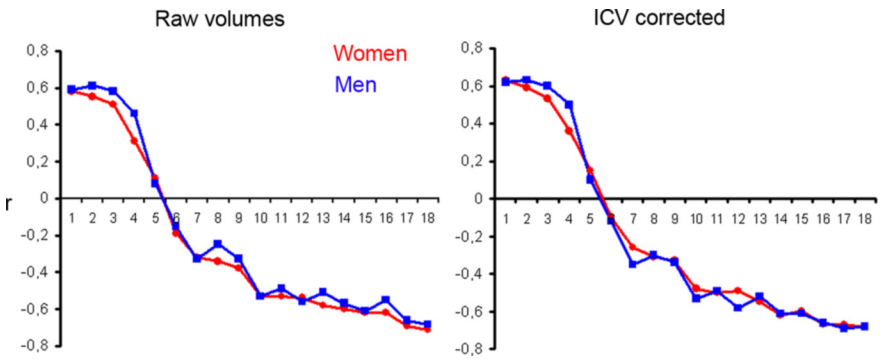

Figure 5. Correlations with age in women and men. The lines illustrate the Pearson correlations between volume and age for women (red) and men (blue). The values are sorted by the coefficient strength for the raw volumes in women. With the exception of CSF, where men showed higher correlations, none differed significantly between women and men. 1, Lateral ventricles; 2, third ventricle; 3, inferior lateral ventricles; 4, CSF; 5, fourth ventricle; 6, brainstem; 7, cerebral WM; 8, cerebellum WM; 9, cerebellum cortex; 10, cerebellum cortex; 11, hippocampus; 12, pallidum; 13, amygdala; 14, thalamus; 15, accumbens; 16, TBV; 17, cerebral cortex; 18, putamen.

were just below 0.05 (0.017–0.048). Thus, it seems that sex differences in cortical thickness, even when observed, are statistically small or nonexistent, and that very large samples are necessary to detect them in a reliable way. Since the cortical surface is larger in men, it is likely that cortical volume measures, especially when no corrections for head or brain size are applied, will distinguish more between the sexes than thickness. Group comparisons of volumetry confirmed previous findings of larger brains in men, especially for brainstem, cerebral WM, and cerebral cortex (Courchesne et al., 2000; Goldstein et al., 2001; Ge et al., 2002; Lüders et al., 2002; Raz et al., 2004b; Allen et al., 2005; Luders et al., 2005; Kruggel, 2006; Smith et al., 2007). The effects of sex on ICV-corrected volumes were much smaller, even though men had larger residual volumes of third ventricle, brainstem, cerebellum cortex, thalamus, putamen, pallidum, hippocampus, amygdala, and the cerebral cortex, in addition to TBV. Except for cerebellum cortex (3% explained variance), sex explained between 0.3% and 1.7% of the variance in the structures that were significantly different. This supports previous studies showing larger ICV-corrected brain volumes for men (Resnick et al., 2000, 2003; Kruggel, 2006; Chen et al., 2007), but that the differences are small, and only apply to some structures (Blatter et al., 1995; Courchesne et al., 2000; Ge et al., 2002; Gur et al., 2002b; Eberling et al., 2003; Smith et al., 2007; Ikram et al., 2008). Further, as noted by Raz et al. (2004b), corrections for ICV may not be appropriate in testing sex differences in morphometry, as it includes some of the brain variance shared with ICV since the early months of life. The present study also replicated earlier findings that in women's brains the cerebral cortex and the hippocampus occupy a larger part of the TBV than in men's (Filipek et al., 1994; Gur et al., 1999; Goldstein et al., 2001; Lüders et al., 2002; Luders et al., 2005, 2006; Riello et al., 2005; Im et al., 2006; Kruggel, 2006; Chen et al., 2007; Sowell et al., 2007). Men had larger relative volume of brainstem, cerebellum cortex, and pallidum, in addition to all parts of the ventricular system. However, with exception of CSF compartments, all differences were small. Sex explained ~0.6% of the variance in cortical and ~0.4% of the variance in hippocampal TBV-corrected volume. Thus, although these effects were statistically significant due to the very large sample, it is unlikely that they have any cognitive implications.

Conclusion

Previous studies of effects of sex on brain and aging have yielded inconsistent results. In the present cross-sectional study, we aimed to overcome several sources of discrepancy by basing the analyses on a very large pool of participants from seven different samples. The main finding was that most brain structures were not differentially affected by aging in men and women who were healthy or had Alzheimer's disease. The few observed differences were small and unstable across subsamples. Thus, from the present data, it seems unlikely that men and women differ in the rates of age-related volume loss.

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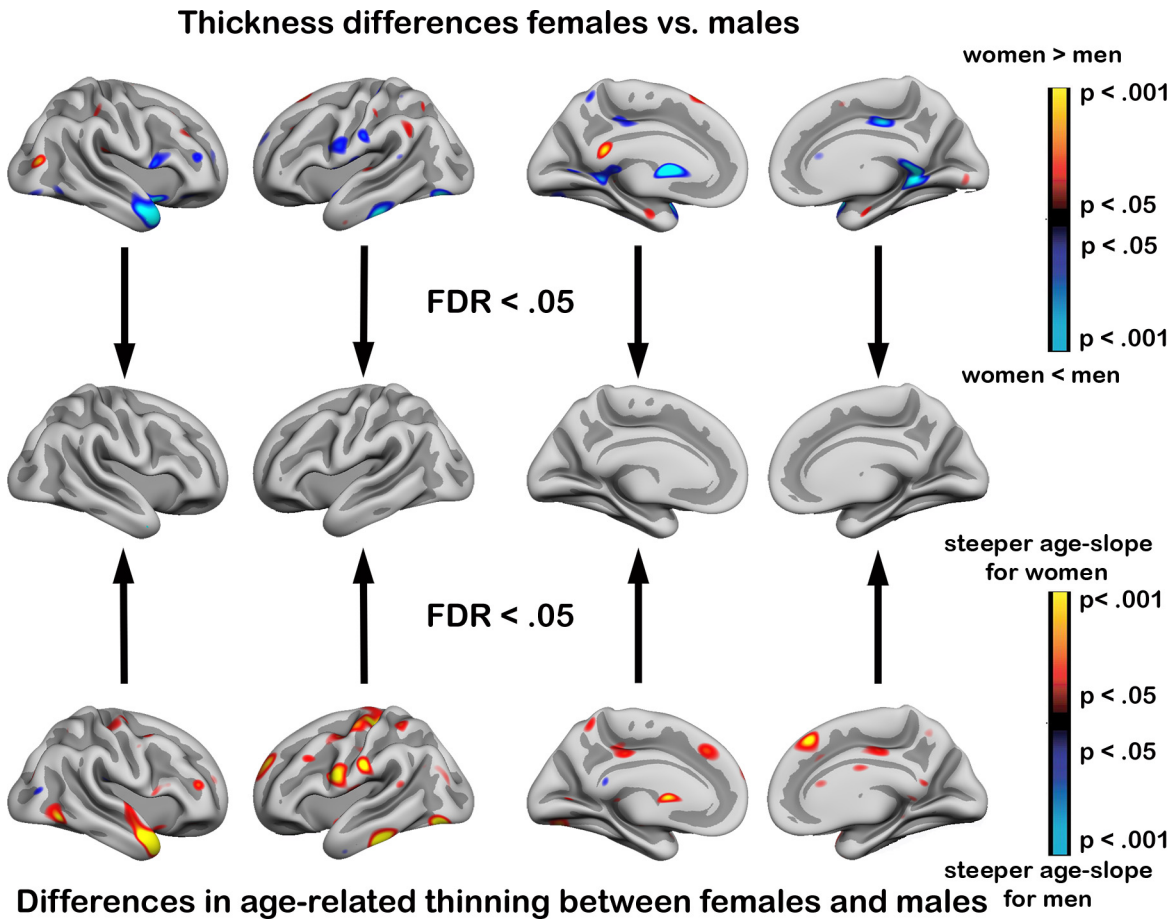

Figure 6. Testing of effects of sex on cortical thickness. The figure shows that no effects of sex on cortical thickness were found when conventional procedures for multiple comparisons (FDR < 0.05) were used. Further, there were no significant differences in the age slopes of cortical thickness between women and men when the same threshold was used (FDR < 0.05). Top panel, The effects of sex on cortical thickness are shown as color-coded *p*-value maps, and projected onto a semi-inflated template brain. Blue-green indicates thinner cortex for men than women, while red-yellow indicates that women have thicker cortex ($p < 0.05$, uncorrected). The analyses were corrected for the effects of age and subsample. The middle panel illustrates that all effects vanish if a conventionally used procedure for correction for multiple comparisons is used (FDR < 0.05). Bottom panel, Red-yellow areas indicate that women have more age-related reduction in cortical thickness than men, while blue-green areas indicate the opposite. The analyses are corrected for the effect of subsample. When the results were thresholded at FDR < 0.05, all effects vanished.

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