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Brief communication

Accelerated aging of the putamen in men but not in women

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Abstract

Age-related structural brain changes have been demonstrated repeatedly but data on the effect of gender on age-related structural brain changes are conflicting. Using high-resolution T1-weighted magnetic resonance imaging and voxel-based morphometry, we examined a population of 133 healthy adults (women, 73; men, 60; age range, 29–80 years) focusing on differential aging between men and women (i.e., interaction of age and gender). Compared to women, men showed accelerated age-related gray matter (GM) loss in the posterior putamen. Our data may constitute the structural substrate for age-related differences in motor function between men and women such as the higher incidence and earlier onset of Parkinson's disease in men.

Keywords: Putamen; Gender; Aging; Voxel-based morphometry

1. Introduction

Age- and gender-related effects on the human brain have been extensively studied *post mortem* and *in vivo*. Beyond doubt, brain mass declines with age. Magnetic resonance imaging (MRI) studies showed that gray matter (GM) of almost all cortical and subcortical areas negatively correlates with age (Good et al., 2001b; Smith et al., 2006; Taki et al., 2004). Yet MRI studies also indicate a remarkable heterogeneity in the regional pattern of age-related GM decline. For example, several studies suggest that the frontal lobe declines more rapidly with age compared to other major lobes (Allen et al., 2005; Cowell et al., 1994; Jernigan et al., 2001).

A number of further MRI studies have demonstrated age- and/or gender-related effects on brain morphology (Coffey et al., 1998; Cowell et al., 1994; Good et al., 2001a,b; Grieve et al., 2005; Gur et al., 1991; Tisserand et al., 2002, 2004; Van Laere and Dierckx, 2001; Xu et al., 2000). However, although significant main effects of gender and/or age were detected in most of these studies, differences in aging between men and women (i.e., an interaction of age and gender) have been reported only in some studies (Coffey et al., 1998; Cowell et al., 1994; Gunning-Dixon et al., 1998; Gur et al., 1991; Raz et al., 1995; Xu et al., 2000). For example, Xu et al. reported significantly more brain atrophy with aging in men than in women in the posterior parts of the right frontal lobe, the middle part of the right temporal lobe, the parietal lobe, the cerebellum and the left basal ganglia (Xu et al., 2000). Another two studies reported that age-related shrinkage of (parts of) the basal ganglia is restricted to men (Gunning-Dixon et al., 1998; Raz et al., 1995). Despite conflicting results on gender differences in age-related brain changes, differences were, if detected, to the disadvantage of men. Yet these studies differ greatly with regard to the techniques applied, the populations examined, and the statistical models used. Addressing this issue, we decided to use voxel-based

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morphometry since this technique is rater-independent and allows the hypothesis-free analysis of GM across the whole brain.

2. Subjects and methods

Images were derived from volunteers who had participated in imaging studies as healthy controls at our department. Before scanning, subjects were interviewed by an experienced neurologist and only included if there was no indication for any neurological or psychiatric disorder. All images were screened by an experienced neuroradiologist and excluded if there were unusual or abnormal findings. We could include the images of 133 subjects (60 men: range, 29–76 years, median, 54 years; 73 women: range, 32–80 years; median, 57 years).

Three-dimensional structural images were acquired on one and the same scanner (Siemens MAGNETOM Symphony; field intensity, 1.5 T; headcoil, standard 2-channel birdcage; sequence, T1 magnetization prepared rapid gradient echo (MP-RAGE); TR, 11.1 ms; TE, 4.3 ms; TI, 800 ms; flip angle, 15°; matrix size, 224 mm × 256 mm; orientation, sagittal; slices, 160; voxel size, 1 mm × 1 mm × 1 mm).

We used SPM2 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Image preprocessing was performed according to the optimized protocol (Ashburner and Friston, 2000; Good et al., 2001b) using study-specific prior probability maps. The resulting GM images were smoothed with a Gaussian kernel of 8 mm full width at half maximum.

As a result of nonlinear spatial normalization, the volumes of certain brain regions may grow, whereas others may shrink. These volume changes can be corrected by an additional step prior to smoothing. This additional step, the modulation, comprises multiplication of voxel values of the segmented images by the Jacobian determinants derived from the normalization matrix. In effect, an analysis of modulated data tests for regional differences in the absolute amount of GM. Since modulation has been recommended especially for the investigation of age-related effects and neurodegeneration (Ashburner and Friston, 2000; Busatto et al., 2003; Good et al., 2001b, 2002; Karas et al., 2003; Senjem et al., 2005), we applied the modulation step.

We analyzed only voxels that were likely to represent GM according to the study-specific probability maps ("priors") for GM, WM and CSF. Therefore, a voxel was only included if it displayed a GM value greater than both the corresponding WM and CSF value. Accounting for the existence of another class apart from the three tissue classes, the background class, we also applied an absolute voxel threshold of a GM value greater than 0.2 (maximum value: 1).

For the analysis of regional effects, we performed a voxel-by-voxel interaction analysis of age with group (i.e., gender) as implemented in SPM2. According to the default setting,

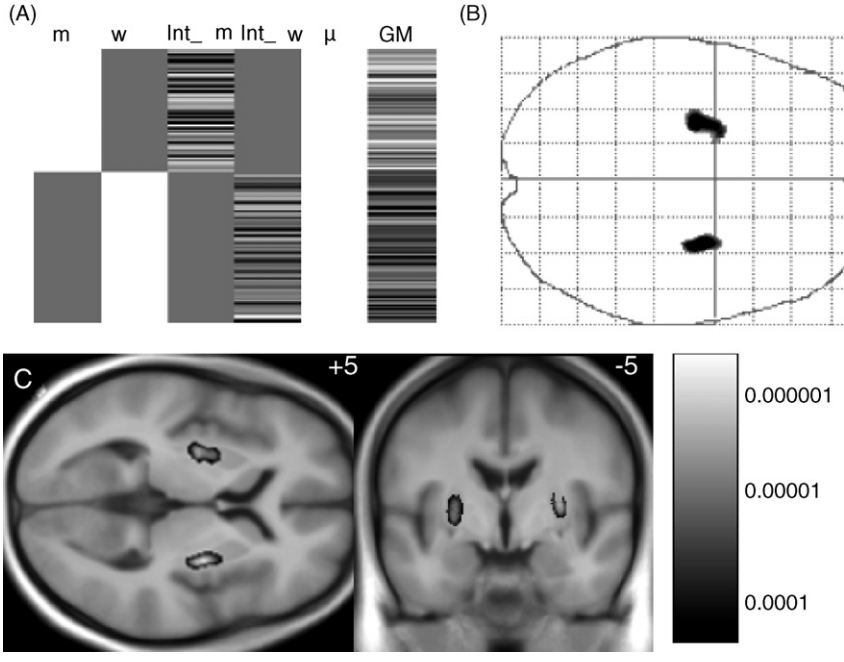

Fig. 1. Interaction of age and gender. The interaction analysis of age and group (i.e., gender) revealed accelerated age-related GM loss bilaterally in the putamen in men compared to women (Montreal Neurological Institute (MNI) coordinates of peak voxels, 30 −5 6 and −26 −10 −5; *Z* values of peak voxels, 4.5 and 4.3; height threshold, $P < 0.05$ corrected with false discovery rate (FDR); extent threshold, >330 voxels corresponding to $P < 0.05$ corrected at the cluster level). (A) Design matrix (Int_m and Int_w, regressors for the interaction of age and gender; GM, global GM volume; m, men; w, women; μ, mean; contrast, 0 0 −1 1). (B) Maximum intensity projection. (C) Projection onto the study-specific averaged T1-image is shown on the left. MNI coordinates are indicated in the right upper corner of each panel. The bar on the right encodes increasing significance.

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age was centered around group means. Since our data were modulated, we had to correct for global volumes (Ashburner and Friston, 2000; Busatto et al., 2003; Good et al., 2001b, 2002; Karas et al., 2003; Senjem et al., 2005) and included the global GM volume as nuisance variable in our model (Fig. 1A).

To correct for multiple comparisons, we set a height threshold (voxel-level) of $P<0.0002$ corresponding to a false discovery rate (FDR) of $P<0.05$ (Genovese et al., 2002). In addition, we applied a spatial extent threshold of 330 voxels corresponding to $P<0.05$ corrected for multiple comparisons at the cluster level (Friston et al., 1996). For clusters showing significant interaction, the absolute GM content (i.e., the sum of all voxel values of the cluster) and the "relative GM content" (i.e., the sum of all voxel values divided by the global GM) were analyzed separately for men and women with standard software (SPSS, version 14.0.1).

3. Results

Analyses of regional GM changes with regard to the main effects of age and gender as well as analyses of global GM volumes revealed results that were largely in the range of previous reports (supplementary material).

The interaction of age and gender revealed accelerated age-related GM loss bilaterally in the posterior putamen in men (Fig. 1) whilst women showed no area of accelerated GM loss. Correlation analysis of the GM content (sum of all voxel values of both clusters within the putamen) with age was significant in men (Pearson correlation coefficient, −0.6; 2-sided P value, <0.001) but not in women (Pearson correlation coefficient, 0.1; 2-sided P value, 0.3). Plotting the "relative GM content" (sum of all voxel values of both clusters within the putamen divided by global GM) against age separately for men and women (Fig. 2) revealed accelerated loss of GM in men as indicated by the negative slope (Pearson correlation coefficient, −0.3; 2-sided P value, 0.02) and relative preservation in women as indicated by the positive slope (Pearson correlation coefficient, 0.3; 2-sided P value, 0.01).

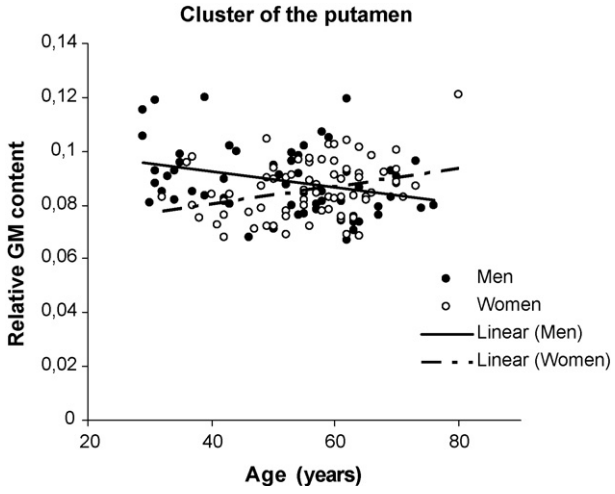

Fig. 2. Relative GM content of the clusters showing an interaction of age and gender. The relative GM content of the significant clusters is plotted against age separately for men and women. In men, the GM content decreases more rapidly than the global GM volume resulting in a negative slope of the regression line (Pearson correlation coefficient, −0.3; 2-sided P value, 0.02). In women, the GM content decreases more slowly than the global GM volume resulting in a positive slope of the regression line (Pearson correlation coefficient, 0.3; 2-sided P value, 0.01).

4. Discussion

Our study aimed to identify brain regions that display gender differences in age-related GM loss. We analyzed cross-sectional data although this implies inherent limitations due to the potential for confounding age and cohort effects which can only be resolved by a longitudinal design. Nonetheless, we found an interaction of age and gender in the sense of accelerated GM loss within the posterior putamen in men compared to women (Fig. 1). Further analyses showed that the posterior putamen undergoes accelerated GM loss (i.e., faster regional GM loss than estimated from global GM loss) in men in contrast to relative preservation in women (Fig. 2).

Addressing the issue of gender differences in age-related brain changes, various morphometry studies have yielded heterogeneous results. A quantitative review of studies on age-related changes in the striatum revealed moderate age-related shrinkage of the striatum (Raz et al., 1995). Based on this finding, a cross-sectional conventional morphometry analysis was performed in 55 healthy adults that, in accordance with our finding, demonstrated age-related shrinkage of the putamen in men but not in women (Raz et al., 1995) although a later longitudinal morphometry study in 53 healthy adults on basal ganglia structures over 5 years yielded only a trend towards an interaction of age and gender (Raz et al., 2003). Another study on differences between men and women with regard to age-related changes in the striatum did not demonstrate an interaction of age and gender either but, in this study, the volume of the whole striatum (caudate, putamen and nucleus accumbens) was measured and only 10 women were included so that the study design may have been inappropriate to demonstrate an interaction of age and gender within the putamen (Koikkalainen et al., 2007). Yet further cross-sectional conventional morphometry studies on populations comparable to ours could not demonstrate an interaction of age and gender within the putamen (Brabec et al., 2003; Brickman et al., 2003; Gunning-Dixon et al., 1998; Xu et al., 2000). Likewise VBM studies have not demonstrated an interaction of age and gender within the putamen so far but the populations of these studies differed remarkably from ours since mainly young adults with a mean age below 30 years (Good et al., 2001b) or older adults exclusively with ages

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above 58 (Lemaitre et al., 2005; Smith et al., 2006) had been studied.

However, our finding of differential aging of the putamen in men and women is compatible with evidence derived from animal studies, behavioral studies in humans and epidemiological studies on Parkinson's disease (PD). In animals, neuroprotective properties of estrogens for the nigrostriatal dopaminergic system have been demonstrated repeatedly (Dluzen, 2000). A study on rhesus monkeys demonstrated age-related slowing of motor function in males but not in females although sexual differences in age-related decrease of the striatum could not be shown in the subgroup of 15 monkeys that underwent neuroimaging (Lacreuse et al., 2005). In humans, behavioral studies found age-related decrease of motor skill acquisition to be less pronounced in women than in men. In a mirror drawing task, women performed better than men and age-related decline in speed was greater in men than in women (Kennedy and Raz, 2005). Moreover, the most common disorder associated with a dysfunction of the putamen, PD, shows differences between men and women according to most but not all studies. In men, PD is more frequent (Baldereschi et al., 2000) and starts earlier (Haaxma et al., 2006). In women, the estrogen status (i.e., parity, age at menopause and fertile life span) correlates with a later onset of PD. Accordingly, striatal degeneration measured with [123I]FP-CIT SPECT was less pronounced in women (Haaxma et al., 2006). Notably, evidence exists that the posterior putamen, the site identified by our interaction analysis, is primarily affected in PD (Jellinger, 2002; Ma et al., 2002).

Conflict of interest

There are neither actual nor potential conflicts of interests for any of the authors of the manuscript. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki 2000.

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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.2007.05.016.

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Accelerated aging of the putamen in men but not in women

– Supplementary material –

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Supplementary introduction

In order to evaluate the plausibility of our data, we also analyzed the main effects of age and gender.

Supplementary methods

Global volumes of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were derived from the first segmentation process. Statistical tests were performed using SPSS software (Statistical Package for the Social Sciences, version 14.0.1, Chicago, Illinois, USA). Total intracranial volume was approximated by the sum of global GM, WM, and CSF. To correct for intracranial volume, fractions of GM (FGM), WM (FWM), and CSF (FCSF) were calculated by dividing the global values by the TIV. For the analysis of gender differences, 2-sided independent t-tests were applied. For the analysis of age-related effects, parametric correlations were used. Moreover, age and gender were fed in an analysis of variances (ANOVA) with global GM volume as dependent variable in order to identify differences in aging between men and women (i.e., the interaction of age and gender) with regard to global GM volumes.

For the voxel-wise analysis of the main effects of age and gender, we applied an analysis of covariance (ANCOVA) model (as implemented in SPM2) for the comparison of 2 groups (i.e., men and women) with age and global GM as covariates in order to identify only regional GM differences that cannot be explained by global effects (supplementary Figure 2E). Therefore, we will refer to these changes as relative gender-related GM differences and decelerated or accelerated age-related GM decrease, respectively.

Supplementary results

The distribution of age is shown in supplementary Figure 1 indicating that younger, middle-aged, and older adults were all represented well in both genders.

Global GM volume decreased significantly with age (P value < 0.001) but we did not find an interaction of age and gender. Compared to women, men displayed higher TIV (1859±132 vs. 1689±166 ml; P value, < 0.001) and higher global GM volumes (676.4±61.7 vs. 618.1±60.5 ml, P value < 0.001). After correcting for the TIV by analyzing FGM, no significant differences were found between men and women (36.4±2.5 vs. 36.7±2.8%; P value, 0.5).

The voxel-wise analysis of age-related effects revealed accelerated GM decrease in frontal, parietal, and occipital cortical areas as well as in the subcortical areas of the medial thalamus, caudate nucleus, and superior insula (supplementary Figure 2A, supplementary Table 1). By contrast, decelerated GM decrease was mainly found in parahippocampal areas, the inferior insula, tectum, and posterior thalamus (supplementary Figure 2B, supplementary Table 1).

Compared to men, women displayed relative GM increase diffusely in frontal, parietal, occipital and lateral temporal cortical areas as well as in the medial thalamus (supplementary Figure 2C, supplementary Table 2). By contrast, men displayed relative GM increase in cerebellar and inferomedial temporal regions as well as in the posterior cingulate (supplementary Figure 2D, supplementary Table 2).

Supplementary discussion

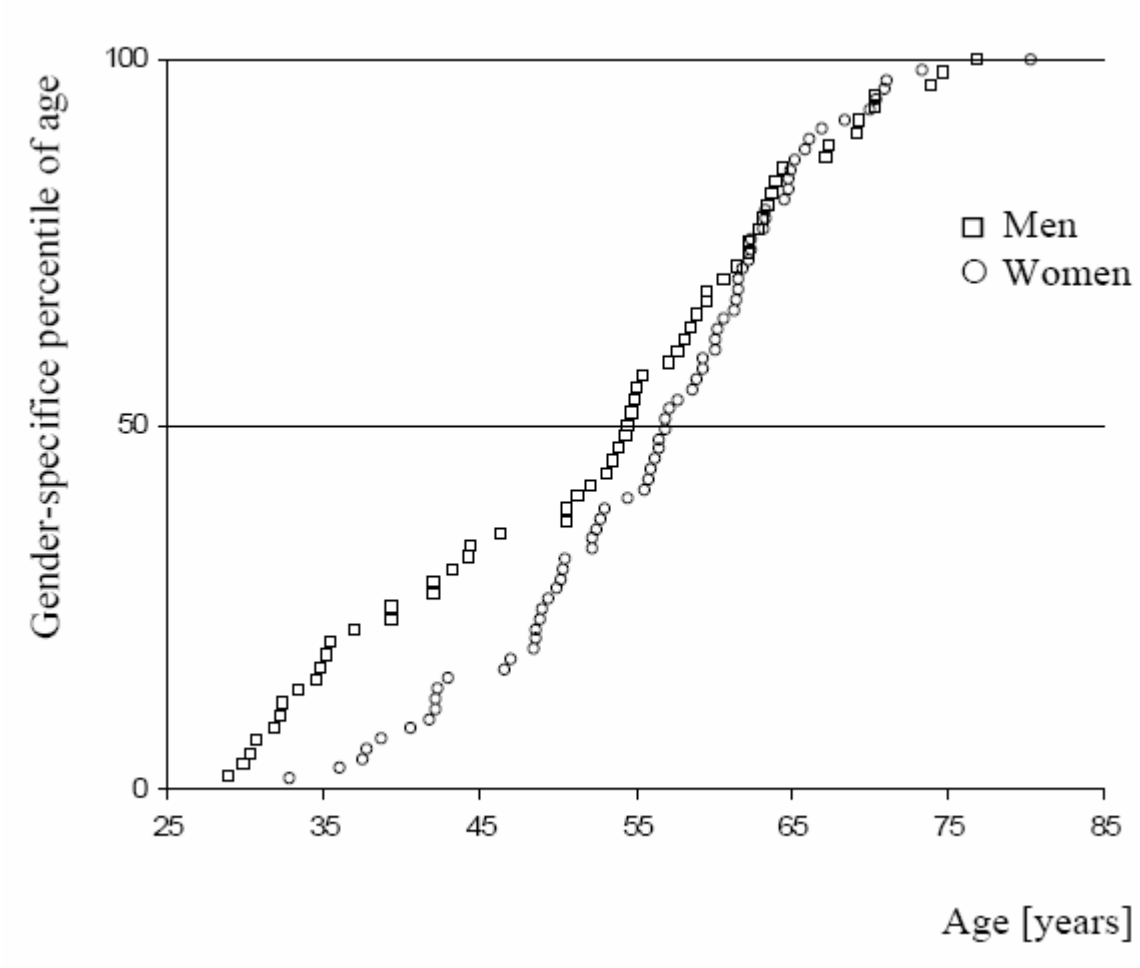
Relating our results on the main effects of age and gender to the results of other morphometry studies is difficult given the marked differences among the studies with regard to the methods applied and the populations examined. Yet our results are largely in the range of previous reports.

Like our study, numerous studies have demonstrated a significant decrease of global GM volume with age (Ge et al., 2002, Good et al., 2001b, Lemaitre et al., 2005, Raz et al., 2005, Resnick et al., 2003, Smith et al., 2006, Taki et al., 2004). In most of these studies, higher TIV and global GM volume in men than in women have been reported. After correcting the global GM volumes for the TIV, some studies reported higher values in men (Good et al., 2001b) whilst others found higher values in women (Lemaitre et al., 2005) or no difference (Riello et al., 2005). Some studies revealed an interaction of age and gender with regard to global GM volumes (Ge et al., 2002, Taki et al., 2004) whilst, in accordance with our results, other studies revealed no such interaction (Lemaitre et al., 2005, Resnick et al., 2003, Riello et al., 2005) or only a trend towards such an interaction (Good et al., 2001b).

With regard to regional changes, relative preservation (i.e., decelerated GM decrease) within hippocampal and parahippocampal structures have not only been demonstrated in our study but also in studies that examined samples of younger subjects with mean ages below 40 years (Good et al., 2001b, Grieve et al., 2005) whilst studies on older populations with mean ages above 60 have not demonstrated a preservation of these regions (Lemaitre et al., 2005, Smith et al., 2006). Both results are compatible with the finding that hippocampal decline accelerates with age (Raz et al., 2004). Furthermore, age-related GM decrease has been shown to be most pronounced around the Sylvian fissure as well as in further frontal and parietal regions (Good et al., 2001b, Lemaitre et al., 2005, Smith et al., 2006, Taki et al., 2004) which, again, largely complies with our data.

Gender differences in human brain anatomy are beyond dispute although the differences shown in numerous studies differ in detail. In accordance with our findings, studies that corrected for differences in global GM volume, demonstrated a diffuse surplus within frontal, parietal, occipital and lateral temporal areas in women (Good et al., 2001a, Luders et al., 2005) whilst men, if at all, displayed a surplus of GM only in medial temporal and cerebellar regions (Good et al., 2001a).

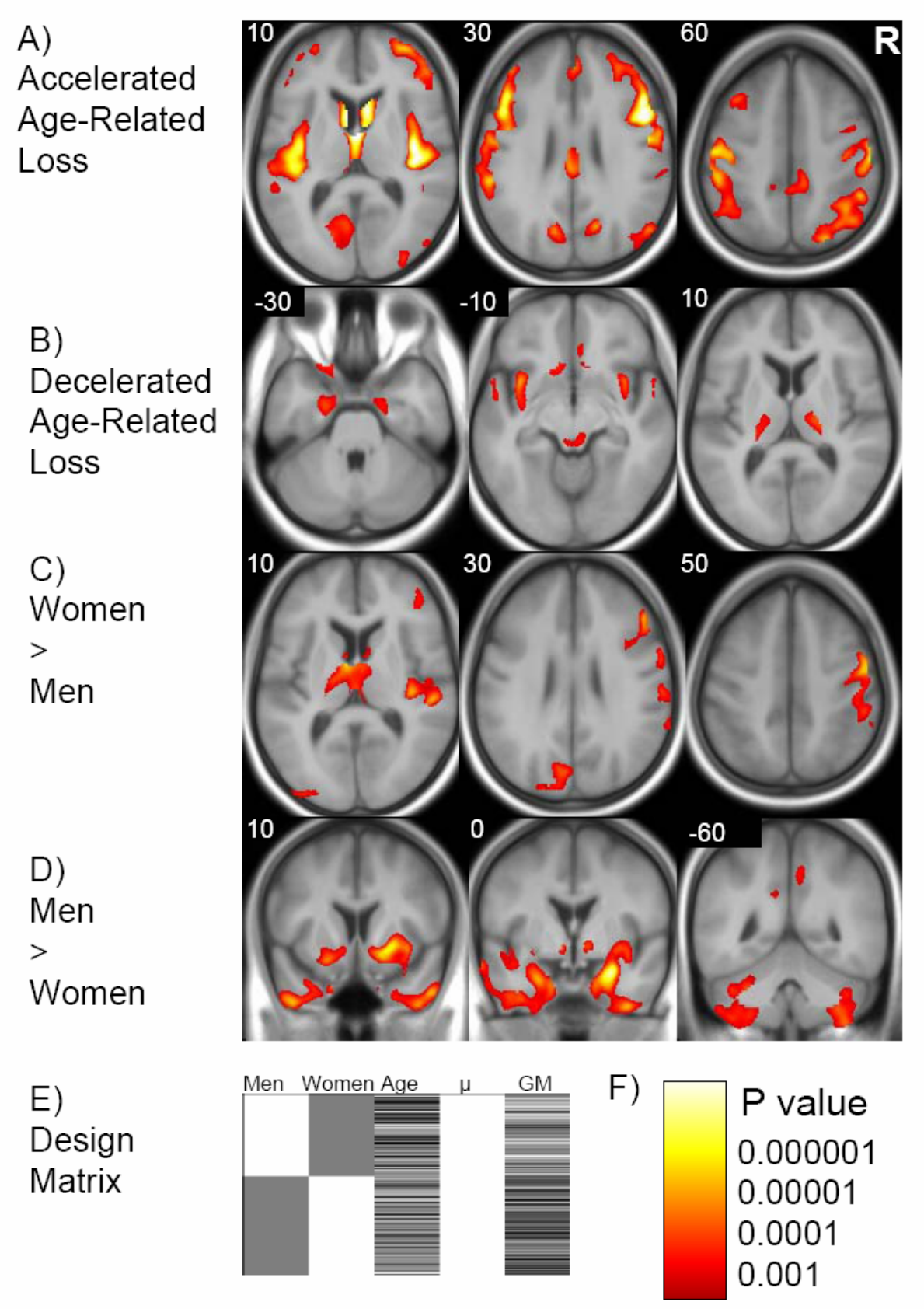
Supplementary figure 1: Distribution of age separately for men and women



Legend of supplementary figure 1

Separately for men and women, age [years] is plotted against the (gender-specific) percentile of age indicating that younger, middle-aged, and older adults were all represented well in both genders.

Supplementary figure 2: **Main effect of age and gender**



Legend of supplementary figure 2

A-D) Main effects of age and gender are projected onto slices of the study-specific averaged T1 image. Montreal Neurological Institute (MNI) coordinates (panels A-C, Z axis; panel D, Y axis) are indicated in the upper left corner of each slice. The right side of the images corresponds to the right hemisphere as indicated with the letter "R" in the upper right corner. Height threshold, $P < 0.05$ corrected (false discovery rate).

A) Accelerated age-related gray-matter loss [contrast: 0 0 -1].

B) Decelerated age-related gray-matter loss [contrast: 0 0 1].

C) Gray-matter increase in women compared to men [contrast: -1 1 0].

D) Gray-matter increase in men compared to women [contrast: 1 -1 0].

E) Design matrix for the analysis of main effects of age and gender.

F) The bar encodes increasing significance form dark red to light yellow as indicated by the uncorrected P values (voxel level).

Supplementary table 1 Age-related relative gray-matter changes

Cluster extent	MNI coordinates x	y	z	Z value	Region
Decelerated age-related gray matter loss					
740	19	-8	-30	3.84	R parahippocampal g., BA35
	24	-13	-23	3.69	R parahippocampal g., BA28
	24	-4	-23	3.54	R uncus, amygdala
1257	37	10	-9	4.84	R inferior insula
	27	21	-4	4.28	R inferior insula
5123	-23	-5	-26	4.98	L uncus, amygdala
	-36	10	-11	5.69	L inferior insula
	-36	2	-7	4.72	L inferior insula
2296	19	-18	7	4.87	R thalamus
	8	-28	-5	4.26	R thalamus/tectum
1110	-19	-14	17	4.96	L thalamus
	-25	-29	8	4.48	L thalamus, pulvinar
	-20	-22	6	4.16	L thalamus
1121	62	0	-3	4.47	R middle temporal g., BA21
	69	-22	4	4.13	R superior temporal g., BA22
	62	-8	-2	4	R superior temporal g., BA21
818	-54	14	-14	5.19	L superior temporal g., BA38
	-54	0	-9	3.91	L middle temporal g., BA21
1567	2	25	-4	4.28	R anterior cingulate, BA24
	-15	17	-13	4.84	L subcallosal g., BA47
1002	11	19	60	3.89	R superior frontal g., BA6
	13	11	63	3.88	R superior frontal g., BA6
	15	-3	71	3.5	R superior frontal g., BA6
Accelerated age-related gray matter loss					
11344	-6	5	14	6.75	L caudate body
	-12	0	21	6.47	L caudate body
	8	13	11	6.35	R caudate head
	0	-18	3	5.43	L/R medial thalamus
28068	50	10	34	7.27	R middle frontal g., BA9
	52	8	43	6.63	R middle frontal g., BA8
	50	25	26	6.59	R middle frontal g., BA46
	58	-16	48	6.01	R Postcentral g., BA3
6626	-46	22	27	6.58	L middle frontal g., BA46
	-48	14	34	6.08	L middle frontal g., BA9
	-45	1	33	5.25	L Inferior frontal g., BA6
21025	-48	-17	37	6.47	L precentral g., BA4
	-57	-39	20	6.36	L superior insula
	-55	-24	42	6.14	L postcentral g., BA3
	-41	-25	9	5.87	L transverse temporal g., BA41
9031	40	-14	13	6.9	R superior insula
	45	-11	-3	6.66	R superior temporal g., BA22
	50	-15	7	6.02	R superior temporal g., BA22
3228	-14	-68	25	4.76	L precuneus, BA31
	-20	-69	8	4.56	L posterior cingulate, BA30
	-5	-71	17	4.46	L precuneus, BA31

BA, Brodmann area; g., gyrus; L, left; MNI, Montreal Neurological Institute; R, right; voxel size, 1x1x1 mm^3. Voxel threshold, $P < 0.05$ corrected with false discovery rate.

Supplementary table 2 Gender-related relative gray-matter differences

Cluster extent	MNI coordinates x	y	z	Z value	Region
Gray-matter increase in women compared to men					
8385	9	-4	16	4.34	R caudate body
	4	-3	7	4.25	R thalamus
	-12	-7	17	5.82	L caudate body
	-15	-36	-5	5.2	L parahippocampal g., BA30
	-6	-3	10	5.14	L thalamus
4384	54	36	18	5.49	R middle frontal g.
	50	29	31	4.92	R middle frontal g., BA9
	54	20	24	4.52	R Inferior frontal g., BA9
3240	-21	62	-5	5.3	L superior frontal g., BA10
	-33	60	-7	4.51	L middle frontal g., BA10
18263	52	-28	12	5.47	R transverse temporal g., BA41
	53	-7	48	5.21	R precentral g., BA4
	54	-29	22	4.94	R inferior parietal lobule, BA40
	39	-21	9	4.88	R insula
4674	-11	-76	36	4.56	L precuneus, BA7
	-8	-84	36	4.48	L precuneus, BA19
	-33	-91	13	3.91	L middle occipital g., BA19
Gray-matter increase in men compared to women					
20603	27	0	-23	6.14	R parahippocampal g., amygdala
	25	11	-5	5.5	R putamen
	42	7	-46	5.19	R middle temporal g., BA38
17627	-38	5	-17	5.82	L superior temporal g., BA38
	-45	12	-43	5.4	L middle temporal g., BA21
	-20	14	-16	5.08	L Inferior frontal g., BA47
7743	37	-47	-58	4.7	R cerebellum, lobules VIIB/VIIIA, crus II
	34	-50	-49	4.27	R cerebellum, lobules VIIB/VIIIA, crus II
	43	-55	-55	4.21	R cerebellum, lobules VIIB/VIIIA, crus II
7788	-32	-44	-55	4.8	L cerebellum, lobules VIIB/VIIIA/VIIIB
	-27	-56	-33	4.53	L cerebellum, lobules VIIB/VIIIA/VIIIB
	-30	-44	-34	4.37	L cerebellum, lobules VIIB/VIIIA/VIIIB
2326	5	-44	29	4.25	R cingulate g., BA31
	9	-51	48	3.6	R precuneus, BA7
	-6	-44	31	4.71	L posterior cingulate g., BA31

BA, Brodmann area; g., gyrus; L, left; MNI, Montreal Neurological Institute; R, right; voxel size, 1x1x1 mm^3.

Voxel threshold, $P < 0.05$ corrected with false discovery rate.

Cerebellar regions are described according to Schmahmann et al. (Schmahmann et al., 1999).

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