

Male brain ages faster: the age and gender dependence of subcortical volumes

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Abstract Effects of gender on grey matter (GM) volume differences in subcortical structures of the human brain have consistently been reported. Recent research evidence suggests that both gender and brain size influences volume distribution in subcortical areas independently. The goal of this study was to determine the effects of the interplay between brain size, gender and age contributing to volume differences of subcortical GM in the human brain. High-resolution T1-weighted images were acquired from 53 healthy males and 50 age-matched healthy females. Total GM volume was determined using voxel-based morphometry. We used model-based subcortical segmentation analysis to measure the volume of subcortical nuclei. Main effects of gender, brain volume and aging on subcortical structures were examined using multivariate analysis of variance. No significant difference was found in total brain volume between the two genders after correcting for total intracranial volume. Our analysis revealed significantly larger hippocampus volume for females. Additionally, GM volumes of the caudate nucleus, putamen and thalamus displayed a significant age-related decrease in males as compared to females. In contrast to this only the thalamic volume

loss proved significant for females. Strikingly, GM volume decreases faster in males than in females emphasizing the interplay between aging and gender on subcortical structures. These findings might have important implications for the interpretation of the effects of unalterable factors (i.e. gender and age) in cross-sectional structural MRI studies. Furthermore, the volume distribution and changes of subcortical structures have been consistently related to several neuropsychiatric disorders (e.g. Parkinson's disease, attention deficit hyperactivity disorder, etc.). Understanding these changes might yield further insight in the course and prognosis of these disorders.

Keywords Subcortical structures · Brain volume · Gender · Aging · MRI

Introduction

Gender differences in behavioral aspects of addiction (Bisagno and Cadet 2014; Fattore et al. 2014), motor control (Kauranen and Vanharanta 1996; Ruff and Parker 1993), emotional memory (Cahill 2003) and several major neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD) (Gershon 2002) and Parkinson's disease (Bourque et al. 2009) have been recently reported. Accordingly, the sexual dimorphism of the human brain anatomy has gained attention with neuroimaging methods being widely used to detect these differences (Cahill 2006; Cosgrove et al. 2007; DeLacoste-Utamsing and Holloway 1982; Goldstein et al. 2001). Whereas males convergingly exhibit larger cerebral volumes (Gur et al. 1991; Sowell et al. 2007) and head sizes (Scahill et al. 2003), females generally have a thicker cortex in several regions of the brain (Luders et al. 2006; Sowell et al. 2007).

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There is much less evidence on the sexual dimorphism of subcortical grey matter (GM) structures including the amygdala, caudate nucleus, accumbens, hippocampus, amygdala, pallidum, putamen and thalamus (Ahsan et al. 2007; Filipek et al. 1994). Considering that the basal ganglia nuclei possess a high density of sex steroid receptors (for reviews, see: (Taber et al. 2001), (Gray and Bingaman 1996)), the effect of gender on the volume of these structures might be crucial. Nevertheless, results are somewhat contradictory with several studies reporting larger volumes of the caudate nuclei (Luders et al. 2009), hippocampus (Murphy et al. 1996) and thalamus in females (Murphy et al. 1996; Takahashi et al. 2011), and some with opposing results (Sullivan et al. 2004; Rijpkema et al. 2012). The amygdala (Cheng et al. 2009), pallidum and the putamen (Rijpkema et al. 2012) have been consistently found to be larger in males.

Research evidence confirms aging to be associated with decrease in whole-brain volume (Courchesne et al. 2000; Gur et al. 1991; Scahill et al. 2003), grey matter volume (Courchesne et al. 2000; Ge et al. 2002a; Good et al. 2001; Guttmann et al. 1998; Pell et al. 2008; Raz et al. 1997; C. D. Smith et al. 2007; Taki et al. 2004), cortical thickness (Sowell et al. 2007), as well as temporal lobe volume (Scahill et al. 2003) and the hippocampal and thalamic volumes (Good et al. 2001). Studies on effects of aging on white matter (WM) volume decrease are inconsistent: some studies did not find a significant effect of aging on WM changes (Good et al. 2001; Taki et al. 2004), while others reported an increase in volume until middle adulthood, followed by a decline (Courchesne et al. 2000; Ge et al. 2002a) and yet others concluded that there was a steady decline with progressing aging (Guttmann et al. 1998; Lemaitre et al. 2005; Taki et al. 2011). Two studies using voxel-based techniques that reported no overall significant effect of aging on WM volume did reveal a decline with age in some areas (Good et al. 2001; Taki et al. 2004). The combined effects of age and gender on the human brain have been assessed suggesting a more profound decline in GM volume in males (Ge et al. 2002a; Raz et al. 1997; Taki et al. 2004). However, research evidence is inconsistent on one hand (Lemaitre et al. 2005) and sparse on the other, especially considering the subcortical GM structures. Most of the studies focusing on subcortical nuclei applied a voxel-based morphometric approach to identify gender differences. The deformable surface model based segmentation approach what we used in the current analysis offers advantages over intensity based procedures especially in regions with low tissue contrast. While age, gender and head size (intracranial volume) are the most commonly included “nuisance” variables when performing neuroimaging analysis, studies vary as to

which of these variables are included and which method is used for correction (Perlaki et al. 2014). These factors might widely account for the great variability in the results.

In the present study an automatized, deformable mesh based segmentation toolkit (FSL-FIRST) was used to extract subcortical structures from the brain. Partial brain volumes were extracted with an intensity-based segmentation toolkit (FSL-SIENAX). Multivariate analysis of covariance and correlation analysis were run to evaluate the following: (1) gender effects on subcortical GM volumes with and without normalization for skull size; (2) interactions between aging and gender affecting volume changes.

Methods and materials

Participants

Fifty-three healthy males (mean age: 31.08 ± 10.03 years) and fifty age-matched healthy females (mean age: 33.00 ± 11.34 years) with no history of any neurological or psychiatric disorder were included in the study (Table 1).

The study was approved by the Ethics Committee of University of Szeged (authority number: 87/2009). All enrolled participants provided their written informed consent.

Image acquisition

Imaging was carried out with a 1.5 T GE Signa Excite MRI scanner. High-resolution T1-weighted images (3D IR-FSPGR: TR/TE/TI: 10.3/4.2/450 ms, flip angle: 15°, ASSET: 2, FOV: 25*25 cm, matrix: 256*256, slice thickness: 1 mm) were acquired.

Image processing

Tools from the FMRIB Software Library (FSL, version 5.0; Oxford Centre for Functional MRI of the Brain (FMRIB), UK; www.fmrib.ox.ac.uk/fsl) were used for data processing.

Comparison of basal ganglia and partial brain volumes

We used FIRST, a model-based segmentation/registration tool for volume comparison of the subcortical structures of males and females (Patenaude et al. 2011). This approach uses deformable surface meshes specific to subcortical structures, namely the amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus. Given the observed intensities in a T1-weighted image, FIRST searches through linear combinations of shape modes of variation for the most probable shape instance based on learned models. We decided not

Table 1 Demographic data on the participant subjects

	Male			Female		
	mean	±SD	range	mean	±SD	range
N	53	–	–	50	–	–
Age (years)	31.08	10.03	21–58	33.00	11.34	21–57
Handedness (left)	6	–	–	7	–	–
Volumes						
Total intracranial (mm ³)	1,192,105.89	85,334.42	972,761.85–1,381,750.59	1,064,220.04	84,530.88	887,409.06–1,296,592.68
Total brain (mm ³)	1,165,217.63	83,151.41	948,950.34–1,342,429.91	1,041,990.31	82,652.01	861,476.12–1,270,109.32
Gray matter (mm ³)	642,377.23	46,905.62	527,133.52–758,544.08	579,578.16	42,978.76	495,802.20–674,384.25
White matter (mm ³)	522,840.39	43,260.20	421,816.82–608,111.83	462,412.14	44,986.73	360,447.47–621,760.47
Cortex (mm ³)	501,307.86	37,441.32	410,306.09–593,261.73	451,801.73	35,256.74	381,160.13–520,349.99

to include the nucleus accumbens due to inappropriate segmentation.

Specific entities of brain volume (total brain volume, total GM, white matter, cortical GM and ventricular cerebrospinal fluid) were compared between the two groups with and without normalization for total intracranial volume. Total intracranial volume as well as grey and white matter volumes were estimated using SIENAX (S. M. Smith et al. 2001; S. M. Smith et al. 2002), an approach included in the FSL (S. M. Smith et al. 2004). SIENAX starts by extracting brain and skull images from the single whole-head input data (S. M. Smith 2002). The brain image is then affine-registered to MNI152 space (Jenkinson et al. 2002; Jenkinson and Smith 2001) using the skull image to determine the registration scaling, primarily to obtain the volumetric scaling factor (*vscale*), which is then used as normalization for head size. Subsequently, tissue-type segmentation with partial volume calculation is carried out (Zhang et al. 2001) in order to calculate the total volume of brain tissue, including separate estimates of grey and white matter partial volumes.

The raw and the normalised volumes of the subcortical structures were compared between the groups. For normalisation, the FIRST output volumes were multiplied by the *vscale* factor, obtaining normalised GM volumes of subcortical structures - as if skull size would have been identical for all participants.

Additionally, left/right volume ratios of subcortical structures were compared between groups. A ratio larger than 1 indicates larger structures on the left, while smaller than 1 larger structures on the right.

Multiple univariate analysis of variance with age as covariant (MANCOVA) was applied for statistical analysis (IBM SPSS Statistics 20). Correlations between volumes of subcortical structures, grey/white matter ratio, partial brain volumes and age were calculated for both groups (IBM SPSS Statistics 20). The results were Bonferroni-corrected (p_{corr}) and $p < 0.05$ was chosen as the significance threshold.

For voxel-based morphometric analysis of the cortical gray matter, please see: Supplementary material.

Results

Gender differences of partial brain volumes and subcortical structures – raw data

MANCOVA (mean age of comparison = 32.02 years) revealed that all subcortical structures (max. $P_{\text{corr}} < 0.002$) and all partial brain volumes (max. $p < 0.002$) without normalization for skull size were significantly larger in the male than in the female group (Fig. 1). The grey/white matter ratio did not reveal a significant difference ($p < 0.077$).

No significant group difference was found between left/right volume ratios of subcortical structures. However, it is noteworthy that volumes of the right caudate nucleus ($p_{\text{corr}} < 0.052$) and the left thalamus ($p_{\text{corr}} < 0.049$) were significantly larger than those of the corresponding contralateral structures in the male group only.

Gender differences of partial brain volumes and subcortical structures – skull size normalised data

After normalization for skull size, MANCOVA (mean age of comparison = 32.02 years) revealed significantly larger subcortical GM volumes for the left ($p_{\text{corr}} < 0.011$) and right hippocampus ($p_{\text{corr}} < 0.010$) in the female group. Strikingly, the total ($p < 0.003$) and the cortical GM were also found to be relatively more extended in the female group as compared to males ($p < 0.009$) (Fig. 2).

In the male group, the volumes of the right caudate nucleus ($p_{\text{corr}} < 0.047$) and the left thalamus ($p_{\text{corr}} < 0.015$) were found to remain significantly larger than the contralateral pair of these structures.

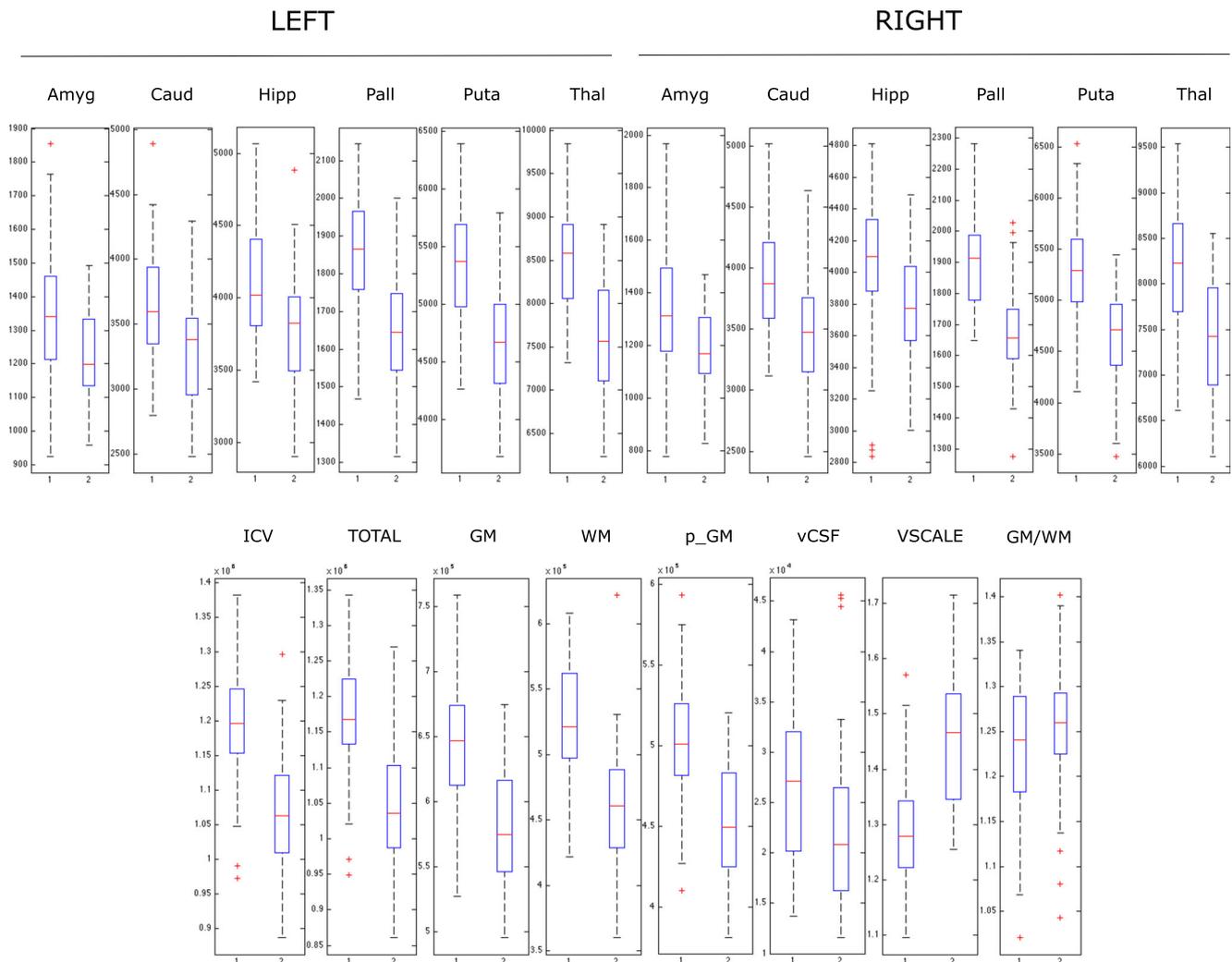


Fig. 1 Gender differences in the raw volumes

Correlation of total, partial and subcortical GM volumes with age – raw data

In the male group, total GM volumes ($R = -0.366$, $p < 0.0071$), cortical GM volumes ($R = -0.332$, $p < 0.015$) and the right thalamus ($R = -0.365$, $p_{\text{corr}} < 0.043$) showed a significant negative correlation with age when corrected for multiple comparisons. As for the volume of the left thalamus a tendency to a significant negative correlation with age ($R = -0.345$, $p_{\text{corr}} < 0.069$) was detected.

In the female group, volumes of total GM ($R = -0.425$, $p < 0.002$), cortical GM ($R = -0.418$, $p < 0.003$), the right hippocampus ($R = -0.411$, $p_{\text{corr}} < 0.018$) as well as the left ($R = -0.373$, $p_{\text{corr}} < 0.045$) and the right thalamus ($R = -0.439$, $p_{\text{corr}} < 0.008$) showed a significant negative correlation with age.

The grey/white matter ratio was found to correlate negatively with age for both males ($R = -0.476$, $p < 0.00032$) and females ($R = -0.397$, $p < 0.004$). However, the age-related

grey/white matter ratio was found to be higher for females ($p < 0.016$).

Interestingly, the left/right volume ratio of the hippocampus exhibited a significant positive correlation with age in the female group only ($R = 0.509$, $p_{\text{corr}} < 0.00094$).

Correlation of total, partial and subcortical GM volumes with age – skull size normalised data

In the male group, total brain volume ($R = -0.507$, $p < 0.00011$), total ($R = -0.685$, $p < 10^{-6}$) and cortical GM ($R = -0.616$, $p < 10^{-6}$), left ($R = -0.393$, $p_{\text{corr}} < 0.021$) and right caudate nucleus volume ($R = -0.376$, $p_{\text{corr}} < 0.033$), left ($R = -0.384$, $p_{\text{corr}} < 0.0274$) and right putamen ($R = -0.408$, $p_{\text{corr}} < 0.014$) as well as left ($R = -0.489$, $p_{\text{corr}} < 0.0012$) and right thalamus volume ($R = -0.508$, $p_{\text{corr}} < 0.0006$) showed a significant negative correlation with age (Figs. 3 and 4).

In the female group a significant negative correlation with age was revealed for total brain volume ($R = -0.373$,

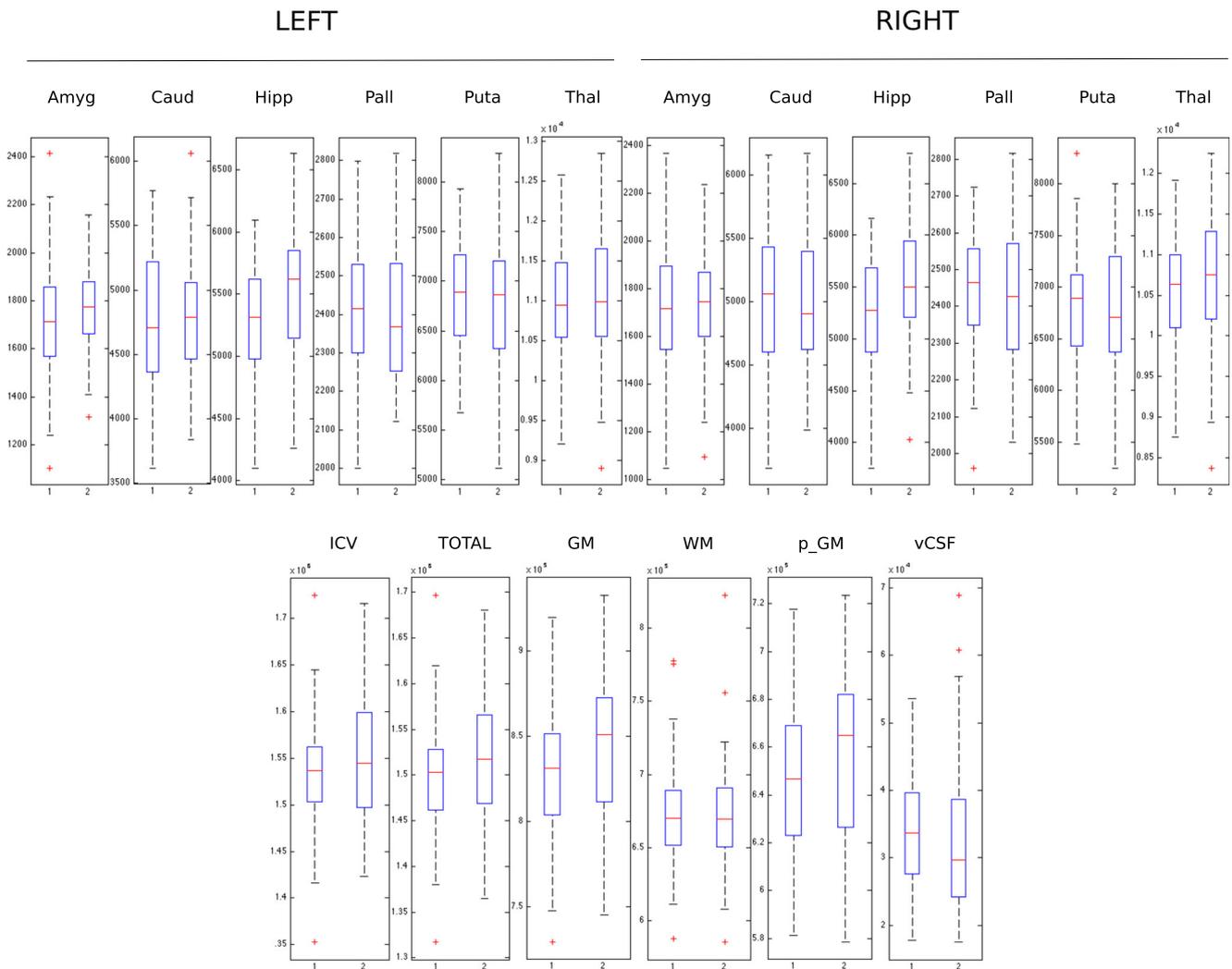


Fig. 2 Gender differences in the normalised volumes

$p < 0.0076$), total ($R = -0.525$, $p < 0.00009$) and cortical GM ($R = -0.516$, $p < 0.00013$), left ($R = -0.399$, $p_{\text{corr}} < 0.024$) and right thalamus ($R = -0.452$, $p_{\text{corr}} < 0.006$) (Figs. 3 and 4).

Interestingly, the decline with age in normalized GM volume occurred at a faster pace in the group of males than for females ($z = 2.21$, $p < 0.0271$) (Fig. 3).

Discussion

In the current study we aimed to identify gender effects on subcortical GM volumes as well as interactions between aging and gender affecting volume changes in the human brain.

To our best knowledge, this study is the first to report the effect of interplay between gender and aging accounting for differences in head size on subcortical structures using a model-based segmentation tool. The main strength of our study consists in the large size of our cohort with homogeneous acquisition and analyses procedures.

In general, male brains were found to be larger than females', with larger grey and white matter as well as subcortical structures. However, most of these differences disappear when skull size is accounted for. As a result of correction for total intracranial volume we found females to have larger cortical and subcortical GM volume. Noteworthy, the volume of the hippocampus was found significantly larger in the female group as compared to males. We also detected a significant effect of hemisphere in the male group only, with larger volumes of the right caudate and the left thalamus as compared to their contralateral structures.

More importantly, we found an age dependent decrease in the the volume of cortical as well as subcortical grey matter. Latter remained significant after correction for skull size in the caudate, putamen and thalamus bilaterally for males and the thalamus bilaterally for females. Within the age-range of 21 to 58 years we found a linear decrease in GM volume with aging. Strikingly, this process proved to occur at a faster pace in males.

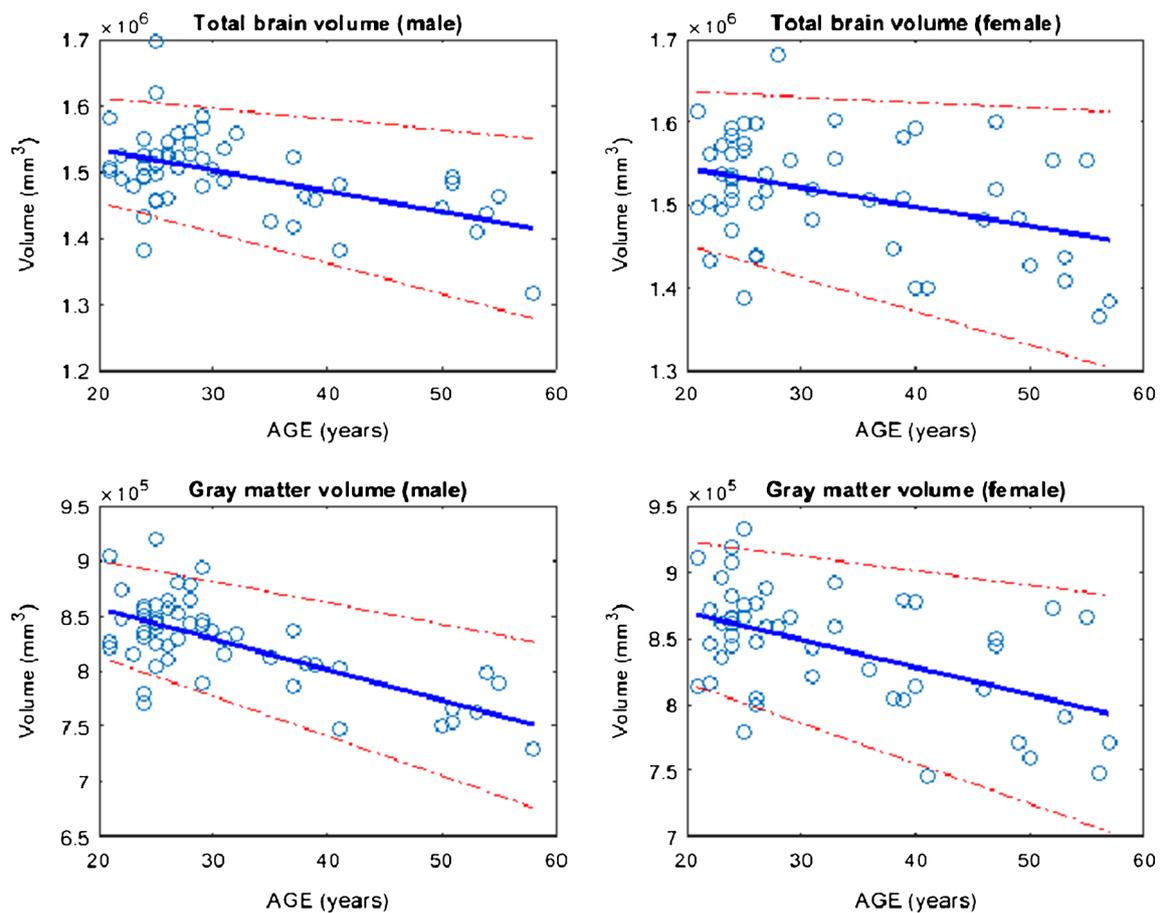


Fig. 3 Age-related decline in the normalized brain volumes in males and females

We propose the use and importance of our current findings to be two-fold: (1) methodological considerations of the investigation of subcortical structures and (2) potential functional implications related to gender and GM decline with age.

(1) While there is converging research evidence for total brain and GM volume to decline with age (Barnes et al. 2010; Courchesne et al. 2000; Ge et al. 2002b; C. D. Smith et al. 2007; Lemaitre et al. 2005; Takahashi et al. 2011), analysis approaches are typically different (Callaert et al. 2014). Volumes of the insular, medial frontal, posterior-parietal, occipital and temporal regions were shown to correlate negatively with age in an elderly population (C. D. Smith et al. 2007). Furthermore, a VBM study revealed that cortical volume loss is not homogeneous (Takahashi et al. 2011).

Research evidence becomes much more sparse when focusing on the subcortical structures. Previous VBM style analyses indicated a decline with age in the caudate and thalamic volumes (Callaert et al. 2014; C. D. Smith et al. 2007). However, the enlargement of the third and fourth ventricles might be a confounding variable in VBM analysis (C. D. Smith et al. 2007). Further studies applied manual tracing of subcortical structures identifying an age-related volume decline in the thalamus (Sullivan et al. 2004), the caudate and the putamen (Abdelahi et al. 2013). However, investigation was limited to

certain structures and the relationship with age was observed for both genders. A recent study found significant brain size effects in the right amygdala and the bilateral caudate nucleus and significant gender effects in the bilateral putamen but no interactions between brain size and gender (Tang et al. 2013).

Our results echoed a previous study reporting an age-related decline in the caudate, putamen and nucleus accumbens and a marginal effect in the thalamus in a similar age-range (35–60 years) (Goodro et al. 2012). However, the authors suggested that normalization to the cranium size accounted for the observed gender effect. Other studies have included gender as a nuisance variable in the general linear model analysis and found a negative correlation between age and the volumes of the hippocampus, amygdala, caudate and putamen (Barnes et al. 2010). Yet, other results were reported using Freesurfer, with a disproportionate degeneration of the subcortical volumes with aging (Li et al. 2014). Our current results regarding the hippocampus are in agreement with previous reports of larger relative hippocampal size in females with the use of FIRST, also confirmed by a VBM style analysis (Kauranen and Vanharanta 1996).

We propose that the inconsistency of findings about gender and age-related differences in subcortical GM volumes might stem from methodological differences and relatively small

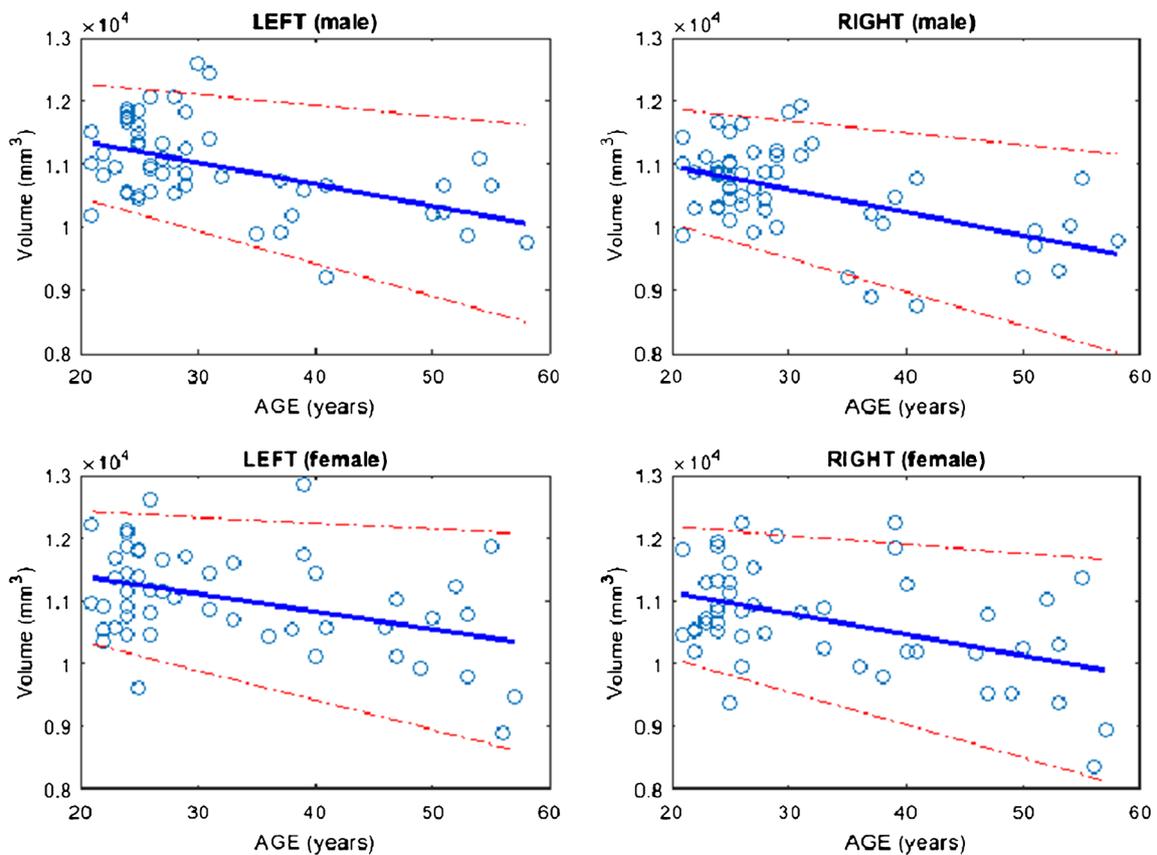


Fig. 4 Age-related decline in the normalized thalamic volumes in males and females

sample sizes. Most of the studies applied a VBM approach to identify gender differences in subcortical nuclei. While VBM is an excellent tool for the investigation of focal grey matter density differences, deformable surface model approaches such as FIRST are directly tuned for the volumetric analysis of the subcortical structures. Furthermore, in MRI studies, age, gender and head size (intracranial volume) are the most commonly included “nuisance” variables, though studies greatly vary as to which of the variables are included and which method is used for correction (Perlaki et al. 2014). Nevertheless, it is important to communicate transformation approach and group intracranial volume considerations when reporting structural findings of subcortical GM since it might carry several implications for interpretation of the results (Schwab et al. 2014).

In contrast with FIRST, the VBM analysis in our study did not detect any effects of age or gender on the subcortical structures (supplementary material). While the VBM approach is based on tissue-type/locally-averaged GM segmentation, FIRST utilises shape and intensity information jointly (Patenaude et al. 2011).

(2) The second aspect involves the underlying cellular, molecular and functional mechanisms of the age and gender related decline of GM volume. Primarily, neuronal and synaptic pruning has been proposed to play a critical role (Webb et al.

2001). However, findings of post-mortem histological studies suggested, that it is rather the size than the number of the individual cells explaining the age-related decline of GM (Terry et al. 1987; Peters et al. 1998). At the molecular level the expression of NoGo-A, a myelin-associated neurite growth inhibitor protein decreases with age (Kumari and Thakur 2014). Recent results also imply the impact of aging on GM/WM diffusion changes, explaining some cognitive variability and even decline (Salminen et al. 2015).

The background of the disproportionate GM volume changes in males and females has not yet been elucidated, but the changes in hormone levels and the consequent sensitivity of the brain to hormonal effects are most certainly involved (Barron and Pike 2012). Above the structural differences, there is increasing evidence for the functional sexual dimorphism of subcortical structures. Amphetamine has been shown to cause a higher level of dopamine release in the male striatum, which correlates with the behavioural effect of the drug (Riccardi et al. 2011; Munro et al. 2006). Hippocampus-related memory functions are differently affected by stress in males and females (Guenzel et al. 2014). Peripartum hormonal changes are known to modulate the hippocampal function (Galea et al. 2014). In addition to gender effects, recent evidence supports the influence of brain hemisphere showing lateralization of structure-function relationships, as well as

more specific relationships between individual structures (e.g., left hippocampus) and functions relevant to particular aptitudes (e.g. vocabulary) (Jung et al. 2014). Our current results revealed a significant effect of hemisphere in the male group only, with larger volumes of the right caudate and the left thalamus as compared to their contralateral structures. It might be hypothesized that this difference relates to handedness, however, we did not find such a relationship. A recent study examining the deep GM of healthy adults by using magnetic susceptibility-weighted imaging did not reveal an association with handedness (Liu et al. 2013).

Considering that the volume of subcortical GM critically impacts the size of neurons, glia cells and number of synapses it entails, we might hypothesize that this also affects the function and performance of these structures. It is clear that deducing motor, cognitive and affective functional activity of subcortical GM solely from their structural characteristics would be inadmissibly simplified. Furthermore, observing changes in volume of subcortical GM influenced by gender and aging might yield better insight and with further investigations, even explain some clinically significant differences in males and females in several neurological and psychiatric conditions, e.g. Alzheimer's dementia (Qian et al. 2014), Parkinson's disorder (Gillies et al. 2014; Geevarghese et al. 2015), headache disorders (Macgregor et al. 2011), multiple sclerosis (Greer and McCombe 2011), major depression and bipolar disorder (MacMaster et al. 2014). Strikingly, some recent findings suggest that the volume of certain subcortical nuclei is even associated with crucial psychiatric conditions such as suicidal behavior (Gifuni et al. 2015). Further investigation of functional and behavioral correlates of accurately identified subcortical structures might have crucial implications for preventive measures and treatment of related disorders.

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