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Mapping cortical gray matter in the young adult brain: Effects of gender

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Using magnetic resonance imaging and well-validated computational cortical pattern matching methods in a large and well-matched sample of healthy subjects, we analyzed the effects of gender on regional gray matter (GM) concentration across the cortex. To clarify discrepancies in previous reports, we also examined sexual dimorphisms for whole-brain tissue volumes with and without controlling for brain size differences. In addition, we generated spatially detailed maps of average GM distributions and variability across the entire cortex given that these descriptors are not well characterized in the normative literature. After brain size correction, we detected numerous cortical regions showing significantly increased GM concentration in females compared to males, but no regionally increased GM concentration in males. Permutation testing confirmed the statistical significance of these findings. Locally increased concentration of cortical GM in females corroborates findings of larger global GM volumes in females after correcting for individual brain sizes. Larger global volumes of GM, white matter and CSF, however, are observed in males when individual brain volumes are not taken into account. Our results show that gender is a major contributor to regional and global GM differences between individuals, although the nature of these effects depend on whether brain size is taken into account.

Keywords: Gray matter; Sex; Cortex; Mapping; MRI

Introduction

Although numerous sexually dimorphic characteristics have been identified in the human brain, observations of larger total brain volumes (TBV) in men compared to women are most replicated. Post mortem data further suggest that neuronal number and density are modulated by gender (Pakkenberg and Gundersen, 1997; Rabinowicz et al., 1999; Witelson et al., 1995). Similarly, neuroimaging studies show sexual dimorphisms in the major cranial tissue compartments, although results lack consistency. For example, global gray matter (GM) and white matter (WM) volumes are reported as larger in males (Blatter et al., 1995; Luders et al., 2002), but when GM is computed as a percentage of TBV, females show larger GM ratios irrespective of TBV corrections (Gur et al., 1999). Other studies show larger GM percentages in males (Good et al., 2001a), or fail to detect significant gender effects in GM and WM percentages (Nopoulos et al., 2000; Schlaepfer et al., 1995).

Gender differences in regional (as oppose to global) GM distributions have also been examined where traditional region-of-interest studies are complemented by voxelwise comparisons using methods like voxel-based morphometry (VBM). For example, region-of-interest analyses have revealed increased GM percentages in the dorsolateral prefrontal cortex and superior temporal gyrus in females (Schlaepfer et al., 1995). Furthermore, increased GM volumes in cingulate cortices in females and paracingulate cortices in males were observed after transforming images into standardized stereotaxic space to control for TBV (Paus et al., 1996). Studies employing VBM have revealed GM volume increases in females in parietal, temporal, inferior frontal and cingulate cortices and GM concentration increases across the cortex and surrounding the parahippocampal, cingulate and calcarine sulci. In contrast, males showed GM volume increases in mesial/lateral temporal and cerebellar regions, but no significant increases in GM concentration (Good et al., 2001a).

Taken together, previous analyses of global and regional tissue volumes clearly indicate gender differences, albeit findings lack consistency. These inconsistencies may stem from differences in measurement methods (e.g., measurement of GM volume versus GM concentration; whole-brain versus region-of-interest analyses using contiguous brain slices or a single brain slice only). Another major contributor to discrepancies in findings is the failure of some studies to take brain size differences between men and women into account. Moreover, even when brain size is taken into account, the

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different strategies used to correct for individual brain volumes may lead to different results.

The present study was designed to address these issues. We set out to complement analyses of global tissue volumes (GM, WM and CSF) with examinations of regional GM in the same set of data. Furthermore, identical procedures to correct for individual brain volumes were applied for global and regional analyses and achieved through a 12-parameter linear transformation into the standard co-ordinate system of the template of the International Consortium for Brain Mapping (ICBM-305) (Mazziotta et al., 1995). Analyses in a scaled standard space – a method frequently used in VBM studies – might be a better approach to control for individual brain size than including TBV as covariate in (log)linear statistical models if the relationship between TBV and tissue compartment lacks linearity. In order to compare our findings with others in the literature, gender effects on global GM, WM and CSF volumes were additionally examined in raw scanner space without controlling for individual differences in TBV.

Regional GM, hereafter referred to as GM concentration, was defined as the number of GM voxels relative to the total number of voxels within spheres of 15 mm on the cortical surface. Cortical-pattern matching methods were used to map regional GM concentration differences across the cortex (Ashburner et al., 2003; Thompson et al., 2000). This methodological approach was chosen to isolate local GM changes, given that traditional region-of-interest studies cannot characterize group-related differences elsewhere in the cortex, while in VBM studies, data from corresponding cortical regions cannot always be accurately mapped across subjects (Good et al., 2001a). In contrast, cortical pattern matching allows the highly accurate alignment of surface anatomy using manually delineated features in each subject such that local measures of GM can be compared at thousands of homologous cortical surface locations across the entire cortical surface. Finally, we set out to generate spatially detailed maps of (a) average GM distributions and (b) GM variability across the entire cortex in ICBM-305 space given that these descriptors are not well characterized in the normative literature.

Materials and methods

Subjects

We analyzed the brains of 60 right-handed healthy subjects selected from a database of high-resolution anatomical MR images acquired at the Center for Neuroscientific Innovation and Technology (ZENIT), Magdeburg. Male and female subjects were matched in terms of numbers (30 women, 30 men) and age (women: 24.32 ± 4.35 years; men: 25.45 ± 4.72 years). Young adults with a relatively narrow age range were recruited so as to minimize the influences of age and possible interactions of age with gender, which have been demonstrated to influence tissue measures in previous studies (Courchesne et al., 2000; De Bellis et al., 2001; Jernigan et al., 2001; Good et al., 2001b; Sowell et al., 2003). Handedness was determined by referring to self-reports of hand preference. Subjects were volunteers and included university students from different fields who were recruited via notice board and/or Internet advertisements. All subjects gave informed consent according to institutional guidelines (Ethics Committee of the University of Magdeburg).

MRI Acquisition

Images were obtained on a 1.5-T MRI system (General Electric, Waukesha, WI, USA) using a T1-weighted spoiled gradient echo pulse sequence with the following parameters: TR = 24 ms, TE = 8 ms, 30° flip angle, FOV = 250 × 250 mm^2, matrix size = 256 × 256 × 124, voxel size = 0.98 × 0.98 × 1.5 mm.

Image preprocessing

Image volumes passed through a number of preprocessing steps using several manual and automated procedures implemented in the Laboratory of Neuro Imaging (LONI) Pipeline Processing Environment (Rex et al., 2003). First, a spherical mesh of the cortical surface was created automatically for each brain using signal intensity information. Each of these individual meshes was continuously deformed to fit a threshold intensity value which best differentiates extra-cortical CSF from underlying cortical GM (Shattuck et al., 2001). The mesh surfaces were then mapped back onto each image volume and 3D masks of brain tissue only were created. Any small errors identified in the masks were corrected manually. Using these modified brain masks, all extra-cerebral tissues (including extra-cranial CSF) were removed from the image volumes. The skull-stripped images were then transformed into ICBM-305 stereotaxic space using an automatic 12-parameter linear transformation (Woods et al., 1998). Each image volume was segmented into different tissue types by classifying voxels based on their signal intensity values after applying radiofrequency (RF) bias field corrections to eliminate intensity drifts due to magnetic field inhomogeneities (Shattuck et al., 2001). In a parallel data processing stream we created 3D cortical surface models based on the normalized skull-stripped image volumes from each subject (MacDonald et al., 1994) after a different RF correction was applied (Sled et al., 1998).[1] These preprocessing steps are summarized and illustrated in Fig. 1.

As a result of the linear transformation procedure, cortical surface models correspond globally in size, orientation and parameter space coordinates. The same parameter space coordinates in each cortical surface model, however, do not yet index the same anatomy across all subjects. In order to match equivalent cortical regions between subjects, the cortical surface models from each individual were used to identify and manually outline 16 cortical surface sulci in each hemisphere by one rater (E.L.) blind to group status (Sowell et al., 2002a,b). The outlined sulci included the Sylvian fissure, central, post- and precentral sulcus, inferior and superior temporal sulcus (main body and ascending branch), inferior and middle frontal sulcus, intraparietal sulcus, transverse occipital sulcus, occipital-temporal sulcus, olfactory and collateral sulcus, as well as the primary and secondary intermediate sulcus that constitute the posterior borders of the supramarginal and angular gyrus, respectively. Detailed anatomic protocols for delineating

[1] As opposed to using the same RF approach for surface extractions and in tissue classifications, previous analyses in our lab revealed more accurate results applying RF corrections based on different parameters. Of note, the RF correction used in the data processing stream resulting in classified tissues was developed by the same group of researchers who developed the tool for classifying tissue. Likewise, the RF correction used prior to the cortex extraction was developed by the same group of researchers who developed the tool for cortex extraction. This approach insures that the data is in the proper state for the best possible results.

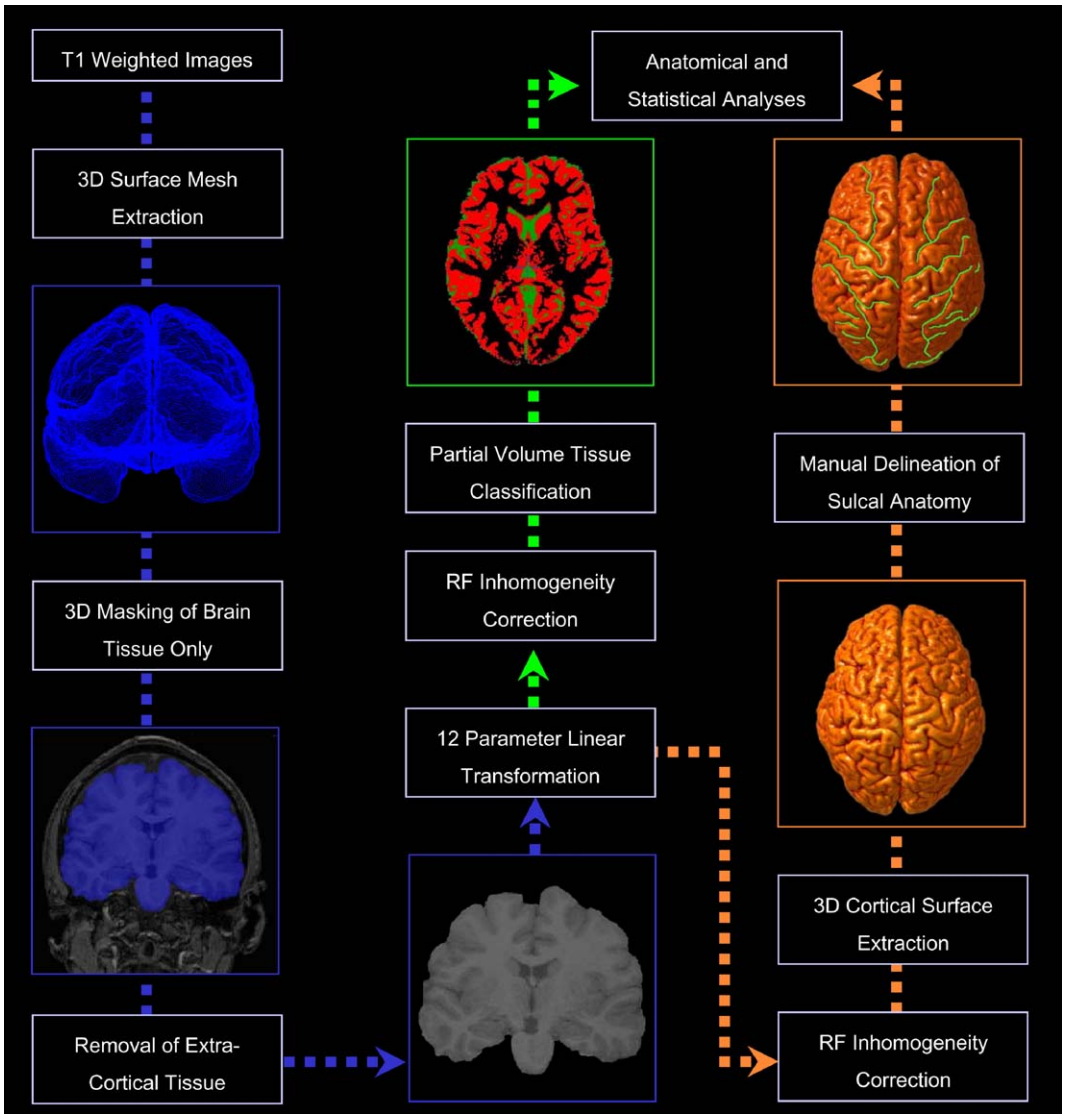

Fig. 1. Summary of image preprocessing steps.

cortical anatomy are available at www.loni.ucla.edu/~esowell/new_sulcvar.html and have been previously validated (Blanton et al., 2001; Narr et al., 2001; Sowell et al., 2002a). Since it is not possible to compute intraclass correlations for 3D curves (as these are not simple scalar measures), inter-rater reliability of manual outlining was measured by mapping the 3D root mean square (r.m.s.) difference in millimeters between 100 equidistant points from each sulcal landmark in six test brains that were traced by one rater (E.L.) and compared to a gold standard arrived at by a consensus of raters. Intra-rater reliability was computed by comparing the 3D r.m.s. distance between equidistant surface points from each sulcal landmark traced six times in one test brain by the same rater (E.L.). 3D r.m.s. distance was <2 mm, and on average <1 mm, for all landmarks within the rater and relative to the gold standard.

Anatomical analyses

Cortical matching procedures

Surface points making up each sulcal outline were made spatially uniform, and homologous sulcal surface points were matched between subjects in 3D (Thompson et al., 2004). The manually derived sulcal landmarks are then used as anchors to drive the surrounding cortical surface anatomy of each individual into correspondence. During the surface-warping procedures, the algorithm computes a 3D vector deformation field that records the amount of x, y and z coordinate shift (or deformation) associating the same cortical surface locations in each subject with reference to the average anatomical pattern of the entire study group (Thompson et al., 2004).

Regional analyses of cortical gray matter

The deformation fields obtained from the cortical pattern matching methods provide a spatial correspondence between equivalent 3D cortical surface locations in each subject that also correspond to point locations in the tissue classified scalp-edited image volumes. Local measurements of GM may thus be obtained from homologous cortical locations in each individual. To quantify the concentration of cortical GM, a sphere with a radius of 15 mm was centered at each of the 65,536 cortical surface points that were matched in each subject. Local GM concentration was defined as

the number of GM voxels relative to the total number of voxels within the sphere. GM concentration measures thus represent values ranging from 0.0 (no GM voxels within the sphere) to 1.0 (all GM voxels) and provide a local estimate of GM volume within the cortical mantle in each individual. Although GM concentration is often also referred to as density, to avoid confusion with the cell packing density measured cytoarchitectonically, in this study we use the term "concentration" (Ashburner and Friston, 2000).

Statistical analyses

Global tissue volumes

To examine whether males and females differed with respect to overall brain tissue volumes, we compared the volumes of the three different types as estimated by counting the number of voxels classified as GM, WM or CSF from scalp-edited image volumes in ICBM-305 space. However, gender effects on TBV and global GM, WM and CSF volumes were additionally examined in raw scanner space without controlling for individual differences in brain volume in order to compare our findings with others in the literature. TBV was determined in liters as the sum of GM, WM and intracranial CSF volumes. Both cerebellum and brainstem, as located above the last slice of the cerebellum, were included in our measurements of tissue volumes and TBV. The statistical analyses were performed on a PC workstation using SPSS 10.0 (http://www.spss.com) and SYSTAT 9.0 (http://www.systat.com/). Bonferroni-corrected repeated measures analyses of variance (ANOVAs) were used to compare volume differences of TBV, GM, WM and CSF in ICBM-305 and raw scanner space between males and females (which were followed by univariate analyses when appropriate). Prior to these analyses, we inspected the distribution of the data to ensure the dependent measures did not deviate from normality.

Regional tissue volumes

The means and standard deviations for GM concentration values obtained from each cortical surface point were calculated to provide maps of average GM concentration and inter-subject variability across the entire cortical surface in standard ICBM-305 space for the whole sample and within groups defined by gender. Independent sample Student's t tests were then performed at each 3D cortical surface location to asses the effect of gender on cortical GM. Uncorrected two-tailed probability values from these t tests were mapped directly onto the average cortical surface model of the entire sample. That is, we generated detailed and spatially accurate statistical maps of local GM differences between men and women in standard ICBM-305 space indicating statistically significant differences of $P < 0.05$.

However, given that t tests were made at thousands of cortical surface points and adjacent data points are highly correlated, permutation testing was employed to serve as a safeguard against type I error. For permutation testing, subjects were randomly assigned to either male or female groups 100,000 times, and a new statistical test was performed at each cortical surface point for each random assignment. The number of significant results from these randomizations was then compared to the number of significant results in the true assignment[2] to produce a corrected overall significance value for the uncorrected statistical maps.

Table 1
Means and standard deviations (SD) of raw volume measures and re-scaled volume measures in liters

	Raw volumes: mean (SD)		Re-scaled volumes: mean (SD)	
	Males	Females	Males	Females
Total brain volume (TBV)	1.40 (0.11)*	1.22 (0.09)	1.79 (0.01)	1.79 (0.02)
Gray matter (GM)	0.72 (0.05)*	0.64 (0.05)	0.92 (0.04)	0.95 (0.03)*
White matter (WM)	0.55 (0.06)*	0.47 (0.05)	0.71 (0.03)*	0.68 (0.03)
Cerebrospinalfluid (CSF)	0.13 (0.02)*	0.11 (0.02)	0.16 (0.03)	0.16 (0.02)

* Indicates the significantly larger volume.

Results

Global tissue volumes

Table 1 shows the means and standard deviations of TBV and tissue volumes obtained in raw scanner space (left column) and ICBM-305 space[3] (right column). The repeated measurement ANOVAs resulted in a significant omnibus effect: $F(1,58) = 40.945$, $P \leq 0.0001$.

Follow-up tests revealed larger raw volumes in males compared to females: TBV ($F(1,58) = 47.195$, $P = 0.0001$), GM volume ($F(1,58) = 36.019$, $P = 0.0001$), WM volume ($F(1,58) = 39.062$, $P = 0.0001$) and CSF volume ($F(1,58) = 9.522$, $P = 0.003$). In contrast, comparing volumes in ICBM-305 space, hereafter referred to as re-scaled volumes, we revealed larger re-scaled GM volumes in females ($F(1,58) = 12.444$, $P = 0.001$) and larger WM volumes in males ($F(1,58) = 10.231$, $P = 0.002$), while the re-scaled total brain volumes and CSF volumes did not show any significant gender effects ($F(1,58) = 2.246$, $P = 0.139$ and $F(1,58) = 0.053$, $P = 0.819$, respectively).

Regional concentration of cortical gray matter

Averages of cortical gray matter

Fig. 2 shows the average GM concentration distributions in standard 305 stereotaxic space for the whole sample. The lowest concentrations bilaterally are in superior regions of the pre- and postcentral gyrus as well as surrounding the occipital poles. The highest GM concentrations seem to be located at the apex where the temporal lobes separate from frontal lobes and on the inferior surface of the temporal lobes. As illustrated, cortical GM appears to be equally distributed between the surfaces of the two hemispheres, with the exception of the temporal and superior-

[2] The number of significant results in the true assignment was determined by calculating the surface area (number of surface points) of significant effects in the real statistical maps. In contrast to calculating the surface area by applying a threshold of $P = 0.05$ (which was the threshold chosen to color-code the significance maps), we decided to run the permutation for a stricter threshold of $P = 0.01$.

[3] Brain volumes acquired in ICBM-305 space are somewhat larger in comparison to other post mortem and in vivo measures as found in the literature because the ICBM-305 template is an average of 305 individual brains, resulting in blurred edges and therefore slightly increased template dimensions.

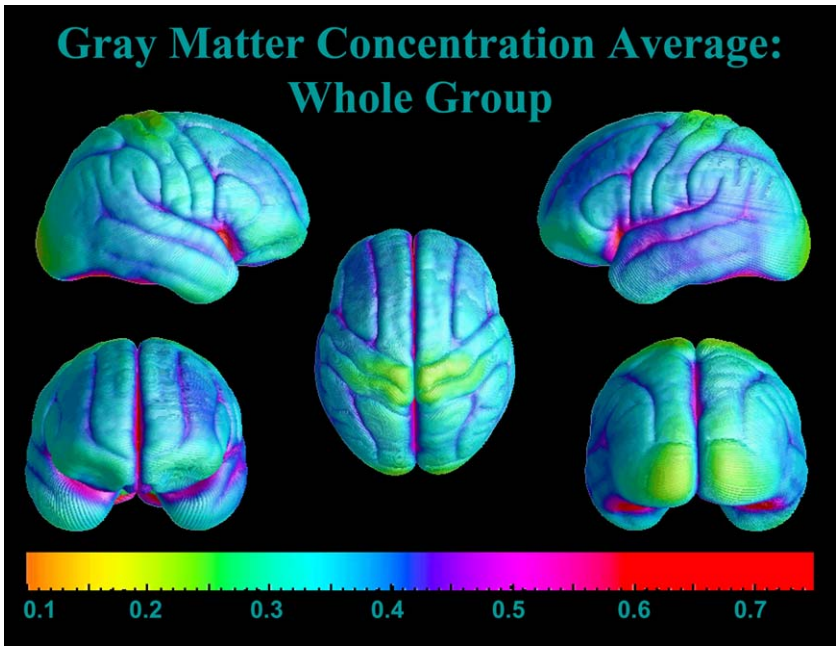

Fig. 2. 3D average cortical GM concentration mapped for the whole sample ($N = 60$) in 305 space. The color bar encodes the proportion of GM voxels relative to the total number of voxels within a sphere using a radius of 15 mm obtained from homologous surface points in each individual. Smaller values indicate lower GM concentrations, while larger values indicate higher GM concentrations.

frontal lobes, which show higher cortical GM concentration in the left hemisphere compared to the right. The local distributions of average GM concentration were similar in males and females (not shown).

Variability of cortical gray matter

Mapping the variability of GM concentration also revealed similar results in males and females. Fig. 3 shows the variability of GM concentration in standard 305 stereotaxic space for the whole sample. The largest standard deviations, and thus the highest variability of cortical GM, are evident bilaterally in inferior regions near the occipital pole extending into the inferior surface of the posterior temporal lobe (illustrated in pink and red). Variability is also more pronounced in the inferior frontal gyrus, or more specifically, in the regions of the pars orbitalis and triangularis (left and right) and also in the pars opercularis (right). Some areas of the frontal and parietal lobe (e.g., around post- and precentral sulcus), located superior and proximal to the midline, as well as the

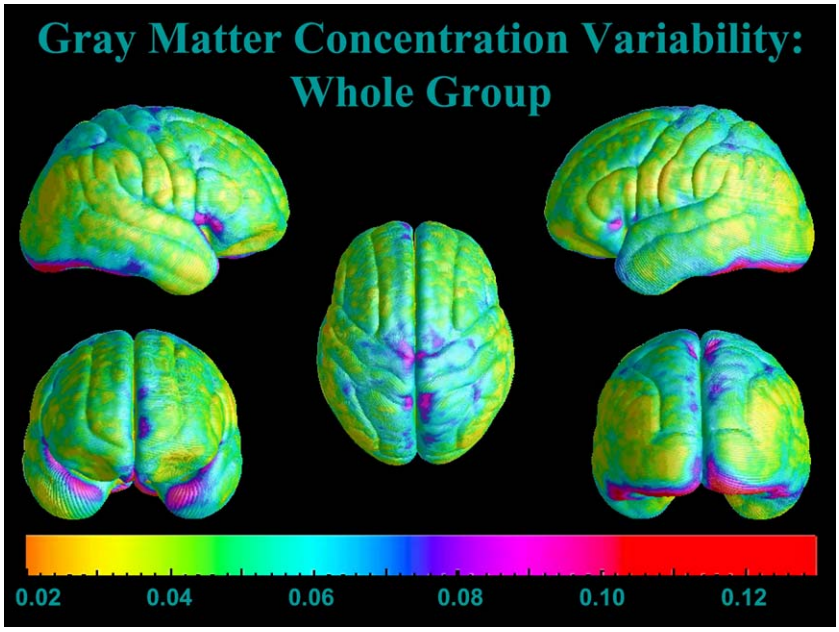

Fig. 3. 3D variability maps of cortical GM concentration. The color bar encodes the standard deviation of GM concentration values ($N = 60$). Smaller values indicate less variation of cortical GM (yellow, green and light blue regions), while larger values indicate more variability (dark blue regions) or the highest variability (pink and red regions).

anterior–superior surfaces of both temporal lobes are also found to be more variable in both hemispheres.

Regional effects of gender on cortical gray matter

Statistical analyses of differences in cortical GM concentration revealed several regions of significantly increased GM in women compared to men, after inter-individual differences in brain size had been removed by transforming images into standard 305 stereotaxic space (Fig. 4). Importantly, no significant local increases in GM concentration were observed in males. Brain regions demonstrating significant GM concentration increases in females are spread over the whole brain surface and can be detected in all four lobes in each hemisphere. Permutation tests were significant for the comparison of GM between males and females ($P = 0.002$) indicating that the observed gender effects do not occur by chance.

The most significant and largest clusters of GM increases can be seen bilaterally in the pre- and postcentral gyrus on the superior brain surface proximal to the midline, but also further inferior along the precentral gyri and postcentral sulci extending into the supramarginal gyri. Significant increases in GM concentration can also be identified surrounding the temporal and occipital poles, bilaterally expanding into posterior regions of the inferior temporal gyrus in the right temporal lobe. While increased GM in the right hemisphere is also represented in the angular gyrus surrounding the ascending branch of the superior temporal sulcus, GM differences in the left hemisphere are highly significant (a) in a distinct region situated posteriorly in the superior temporal gyrus, (b) in the inferior frontal gyrus comprising the pars orbitalis, triangularis and opercularis and (c) along the border between temporal and occipital lobe. Additional smaller regions of higher GM concentration in women are spread over the whole cortex (most prominent in anterior areas of the left and right frontal lobes).

Discussion

Global tissue volumes

Statistical analyses of major cranial tissue component measures in raw scanner space yielded significant gender differences with males having larger volumes of GM, WM and CSF than females which agrees with earlier findings (Blatter et al., 1995; Good et al., 2001a; Luders et al., 2002). Furthermore, as consistent with previous findings, we detected significantly larger TBVs in males than in females. Importantly, sex is genotype, and genes influence brain size accounting for larger male and smaller female brains on average. Thus the question occurs whether brain size corrections are really necessary to accurately establish the effects of gender on cranial compartments. Interestingly, in the present study, approximately 63% of individual brain volumes (male and female) fell between the minimum TBV of males and the maximum TBV of females. That is, even though men have larger brains than women on average, there exist small male brains and large female brains that approach or exceed the average brain dimensions of the opposite sex. Given that brain size overlaps substantially between the sexes, it appears to be necessary to control for individual brain volumes in order to study sex influences on tissue volume measures at the regional level.

Comparing tissue volumes in re-scaled brains revealed larger GM in females and larger WM in males, contrasting with previous analyses that detected higher GM percentages in males (Good et

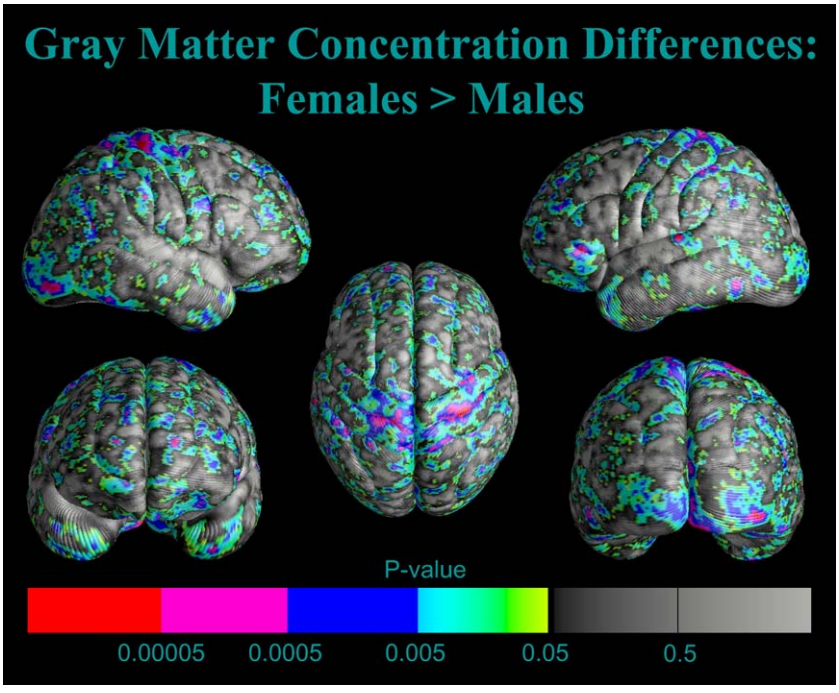

Fig. 4. Uncorrected statistical maps showing increased cortical GM concentration in women compared to men in standard 305 stereotaxic space. The color bar encodes the P value associated with the t tests of GM concentration performed at each cortical surface point. All colored cortical regions indicate statistically significant differences. All gray-shaded regions are not significantly different between males and females (the lighter the gray the more similar the GM concentration). Permutation testing assessing significance of statistical maps revealed a highly significant corrected P value of 0.002 indicating that the observed gender effects do not occur by chance.

al., 2001a) or failed to detect significant gender effects on percentages of overall tissue volumes (Nopoulos et al., 2000; Schlaepfer et al., 1995). These conflicting results may be due to different methods for obtaining tissue measurements and/or controlling for TBV. That notwithstanding, other MRI studies support our results and show that women have a higher percentage of GM, whereas men have a higher percentage or proportion of WM (Goldstein et al., 2001; Gur et al., 1999).

Regional concentration of cortical gray matter

The distribution of GM appears to be rather heterogeneous, with different cortical regions reflecting different proportions of GM. Interestingly, similar reports exist from classic post mortem studies showing that cortical thickness varies across the cortex (von Economo, 1929). Average GM concentrations might reflect the underlying cytoarchitecture related to the organization of pyramidal and granular layers. However, given that the postcentral gyrus and occipital pole contain granular cortices while the precentral gyrus contains agranular cortex, cytoarchitectural boundaries may not map exactly with the patterns of average cortical GM concentration. Thus, it is possible that other factors, such as the density of cortical neurons, may influence the signal intensity values associated with cortical GM in imaging data. Patterns of GM concentration and variability appear to be equally distributed between hemispheres (although higher cortical GM concentrations may exist in the left temporal and superior frontal lobe compared to the right).

While the spatial distribution and variability profiles of cortical GM concentration do not appear to differ between men and women, we observed pronounced gender differences in local GM concentrations. After inter-individual differences in brain size had been removed by transforming images into ICBM-305 stereotaxic space, numerous cortical regions showed increased GM concentration in females compared to males. Interestingly, we did not detect any region showing significantly increased GM concentration in males. It is possible that GM proportion measures may be influenced if the sulcal space is widened such that group differences may represent characteristics intrinsic to the sulci rather than differences associated with cortical gray matter. However, since a sphere with a fixed radius of 15 mm was used to measure GM proportions at each cortical surface location, proportion measures are smoothed thus increasing signal to noise. Moreover, male and female groups were matched for age and represent a young and healthy cohort. There does not appear to be any evidence to suggest that sulcal widening is different between males and females. Gender differences in sulcal depth, if present, were normalized through the transformation into the ICBM-305 stereotaxic space. More precisely, because the curvature penalty during the surface extraction is applied in a standard space, it yields sulcal fissures at a depth which is the same regardless of the original geometry and scale of the cortex.

Our results of locally increased concentration of cortical GM in females corroborate our findings of larger global GM volumes in re-scaled brains in females and are consistent with previous findings of larger overall cortical volumes relative to cerebrum size in women compared to men (Goldstein et al., 2001). Cerebral regions reflecting increased GM in females also agree with reports of higher GM percentages or proportions in the dorsolateral prefrontal cortex, superior temporal gyrus and right parietal lobe (Nopoulos et al., 2000; Schlaepfer et al., 1995) even though these previous findings were generated from region-of-interest analyses of cerebral lobes or selected brain slices. Our results are also consistent with the VBM findings of Good et al. (2001a), perhaps because our methodological approach has many similarities to VBM. Specifically, spatial registration, tissue classification and smoothing of MR data are included in both image analysis preprocessing streams, although the present method compares the proportion of GM between groups in spheres of 15 mm on the cortical surface rather than in voxelwise contrasting of image intensities throughout the whole brain. Furthermore, the term GM concentration in VBM reflects the proportion of GM to other tissue types within a region after spatial normalization similar to the present approach. While earlier VBM results reflected local increases of GM volumes (in terms of true volumetric differences) in both females and males, local GM concentration was increased only in females as consistent with our findings. In further agreement with Good et al. (2001a) we detected increased GM concentration in females in parietal, posterior temporal and frontal brain regions, although some deviations occurred in hemisphere and cluster size. For example, unlike Good et al. (2001a) who detected increased GM in the left angular gyrus, in the right orbital gyrus and inferior frontal gyri bilaterally, we observed GM increases predominantly in the right angular gyrus, left orbital gyrus and left inferior frontal gyrus, although small clusters of higher GM concentration were also detected in the opposite hemisphere. Increases in GM concentration in subcortical regions (Good et al., 2001a; Paus et al., 1996) would have remained undetected in our investigation, given that GM concentration measurements were restricted to the cortex.

Interestingly, we detected the most significant and largest clusters of GM increases in females in the post- and precentral gyrus on the superior brain surface proximal to midline, and surrounding temporal and occipital poles. Similarly, previous studies reported increased relative volumes in precentral and superior frontal gyri (Goldstein et al., 2001) and spatially diffuse increases in GM concentration within frontal and parietal regions in females (Good et al., 2001a). One might argue that some of the highly distinct and significant gender differences in cortical GM concentration in some of the most extreme parts of the brains (pre- and postcentral gyrus, occipital pole) could occur as a potential confound: as men tend to have larger heads and brains than women, the outer limits of their brains are farther away from the center of the coil and therefore might be located in less homogenous parts of the field. As a result, the intensity of the signal might be less in these locations leading to regionally decreased GM measurements in male brains. Although our findings of lower GM concentration in the pre- and postcentral gyrus as well as in the occipital pole might seem to stand in agreement with this assumption, the frontal pole, for example, does not show such an extremely low GM concentration (as can be clearly seen in Fig. 2). Furthermore, our average maps of GM concentration are similar to postmortem estimations of cortical thickness (von Economo, 1929), which cannot be influenced by intensity inhomogeneities. Finally, a 1.5-T whole body scanner was used for the acquisition of the data. Therefore, field inhomogeneities are minor and would be restored by the explicit correction for RF inhomogeneity, so that is extremely unlikely that inhomogeneities account for the observed gender differences. The finding that some regional gender differences appear to correspond to cortical areas with lower average GM concentration, however, may warrant further examination in future studies.

If GM concentration is associated with microstructural factors (e.g., cell packing density, myelination, etc.), gender effects on regional GM may have functional significance. Histopathological data have shown regionally increased neuronal densities in the posterior temporal cortex in females (Witelson et al., 1995), which seems to agree with our findings of increased GM concentration in the left posterior superior temporal gyrus. Importantly, the superior temporal gyrus constitutes part of the Wernicke area, which is a language-associated cortical region. It is possible that the observed gender effect on GM concentration in this region might be related to the improved language skills previously reported in females (Halpern, 1992; Kimura, 1999). Interestingly, we detected another cluster of higher GM concentrations in women adjacent to and partly overlapping with a cortical region in the left inferior frontal gyrus also known to be involved in language processing (Broca's area). Thus, it is possible that there is a direct or indirect relationship between the regional GM concentration at a particular cortical location and the functional organization and outcome mediated by this region. Therefore, our results of gender-specific regional GM concentration could have implications for sex differences in cognition and behavior. Further studies assessing relationships between cerebral micro- and macrostructure as well as cognitive functioning are necessary before regional sexually dimorphic concentrations of cortical GM can be reliably related to gender-specific abilities and/or behavioral differences between men and women. Gender differences in the regional GM concentration might develop as a result of differential environmental and social influences. Interestingly, use-dependent influences like lifelong intensive training in specific cognitive or motor skills have been suggested to modulate regional GM volumes (Draganski et al., 2004; Gaser and Schlaug, 2003). In addition, genetic influences as well as the effects of sex steroids on brain development are very likely to affect regional tissue composition (Geschwind and Galaburda, 1985; Goldstein et al., 2001; Thompson et al., 2001; Toga and Thompson, 2005).

Summary

The present analysis shows that gender is a major contributor to regional and global GM differences between individuals. Gender-specific amounts of GM in particular regions of the cortex may have functional significance and are possibly related to gender differences in cognition and behavior. However, further studies are clearly necessary to systematically evaluate to what extent such a relationship exists.

Acknowledgments

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