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

E. Luders,[a,c] K.L. Narr,[a] P.M. Thompson,[a] R.P. Woods,[a] D.E. Rex,[a] L. Jancke,[b] H. Steinmetz,[c] and A.W. Toga[a,*]

[a]*Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, 4238 Reed, Los Angeles, CA 90095-1769, USA*
[b]*Department of Neuropsychology, University of Zurich, Switzerland*
[c]*Department of Neurology, Johann-Wolfgang-Goethe University Frankfurt am Main, Germany*

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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

* Corresponding author. Fax: +1 310 206 5518.
E-mail address: toga@loni.ucla.edu (A.W. Toga).
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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.