The Quantitative Differences of Gray Matter Concentration in Healthy Brains due to Gender and Aging

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Helen Nguyen became interested in signal and imaging applications for biomedical technology when she became acquainted with Professor Kruggel's research, and she considers having the opportunity to work with her mentor to be the best part of her undergraduate education. For Helen, the most rewarding parts of her research have been working with computer codes, analyzing MRI data, and interpreting quantitative data to produce meaningful and interesting results. Along with improving her C programming skill, Helen feels that her research has made an important contribution to the field of neurobiology. Helen hopes to attend graduate school, with a focus on bioimaging.

Abstract

Until recently, brain structures could only be quantified *post mortem*. Now, the detailed human brain anatomy can be revealed *in vivo* by combining magnetic resonance imaging (MRI), with automated image analysis tools. In this study, a large MRI database was used to find quantitative differences in brain structures due to gender and changes that occur with healthy aging. High resolution T1-weighted MR images were acquired in 502 healthy subjects (age 16–70, 248 females and 254 males). First, images were corrected for scanner-induced artifacts. Next, the intracranial compartment was extracted and segmented into the major compartments, grey and white matter and cerebrospinal fluid. Each brain was separated into 116 regions-of-interest based on the Anatomical Automatic Labeling template. Grey matter (GM) concentrations in all regions of all subjects were calculated. Finally, gender-related differences and age-related changes were determined using linear regression. Highly significant results were found in 16 regions in which the GM concentration differed up to 4% between males and females. A highly significant loss of GM concentration with age was found in 72 regions at a rate up to 0.4% per year. The results of our study can be used as normative data to assess the amount of pathological changes due to brain diseases (*e.g.*, cerebral infarction) or due to pathological aging (*e.g.*, Alzheimer's disease).

Faculty Mentor

Each human brain is unique, even in its macroscopic structure. Magnetic resonance imaging (MRI) is a non-invasive technique to reveal anatomical structures of organs at a high spatial resolution within minutes. We have analyzed a large database of MR images acquired in a population of healthy normal subjects over a life span of five decades. Thus, we define gender-related differences in brain structure, and changes that occur during adulthood. Helen Nguyen, an undergraduate student in Biomedical Engineering, was fascinated to see how new knowledge in Neurobiology can be distilled by mining large databases. This publication summarizes the results of two years of research in Dr. Kruggel's lab.

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Key Terms

- Age-Related Changes
- Gender-Related Differences
- Human Brain
- Magnetic Resonance Imaging
- Morphometry

Introduction

The brain is the center of the human nervous system that controls thoughts, memory, movement, and speech, and it is considered the most complex organ of the body. Understanding the relationship between the brain's structure and function is a major challenge in the neurosciences. The importance of research in this field is recognized by major funding agencies; the National Academy of Engineering (NAE) listed "reverse-engineering of the human brain" as a "grand challenge for the 21th century" (Atkins, 2011). Recently, the European Union awarded a research consortium $1.35B for building computational models of the human brain (Human Brain Project, 2013).

Today, non-invasive techniques for assessing the brain *in vivo* are widely available. Magnetic resonance imaging (MRI) provides detailed images of brain structures, and, in its functional variant, produces images that capture metabolic correlates of brain functioning. Diligent computer-based processing tools are required to extract quantitative, meaningful information from imaging content that can be related in statistical models to a subject's personal, behavioral or clinical features. Morphometry, the structural analysis of compartments in the human head, yields information about the volume, shape and texture of various brain structures. Results of such quantitative neuro-imaging studies have changed the classical understanding that the brain largely remains unchanged throughout life: not only growth, gender and aging, but also learning processes influence the macroscopic structure of the human brain. A considerable individual variance in brain structures is even found in mono-zygotic, "identical," twins. Given this individual variability, neuro-morphometric studies often face the difficulty of deciding whether any group-related differences are due to features of a given group, or just a sampling artifact.

Thus, large population samples must be studied in order to differentiate clearly between individual features and group-related differences. We analyzed the largest database of MR brain images available to determine the region-specific grey matter concentration in healthy brains, their differences due to gender and changes with aging. Although very large databases can be collected in a multi-center study, the comparability of results between centers and different MR imaging devices has recently been challenged (Kruggel et al., 2010); thus, differences in quantitative measures acquired in the same subject on two different scanners are often larger than any expected disease-related effects. It is a unique feature of the sample studied here that all data were acquired on the same scanner under the same conditions. Thus, results presented here can serve as reference data for future studies because differential effects (*e.g.*, gender-related differences) are assumed to be of similar magnitude in other settings.

This study aims at analyzing age-related changes and gender-related differences in brain structures. Autopsy studies clearly revealed that the brain (as other organs) degenerates in elderly subjects. However, only *in vivo* studies can pinpoint any changes that occur in a healthy subject throughout their life span, starting from early adulthood. This study also provides normative data for the expected brain volume at a given age. A wide range of diseases can affect the human brain during lifetime: traumata, cerebral infarctions, hemorrhages, tumors and metastases, inflammations, and auto-immune processes destroy neuronal structures and impair brain function (Glass, 2010). Often, pre-clinical imaging data are not available. Our results can help estimate the pre-morbid structure of the individual brain and to compare it with the actual status (Kruggel, 2006). Several previous studies with smaller sample sizes have focused on determining changes with age (*e.g.*, Courchesnet et al., 2000; Jernigan et al., 2001, Resnick et al., 2003), and we compare our results to published data.

Researchers have recently recognized a gender-related dimorphism in healthy brains (Schlaepfer et al., 1995; Allen et al., 2002). The functional meaning of these differences is unclear. For age-related degenerative changes the working hypothesis is that a loss of brain structure in a specific region leads to a functional impairment attributed to this region. Any gender-related structural differences can only be functionally interpreted if we make the simplifying assumption that the layout of functional brain networks is independent of gender; however, insufficient information is available at this time to draw such a conclusion.

We would like to emphasize another aspect of our work: fully automated data analysis was used to process the imaging data. In comparison with earlier studies, no manual intervention or correction was necessary. All data sets were processed with the same parameter settings, or settings were derived from the data. The whole processing chain required less than two days of computation time on a computer cluster of 30 nodes. This is an important engineering aspect of our work: we developed robust and reliable analysis methods that do not require tedious interaction or visual control of intermediate processing steps by an expert in neuro-radiology. Such an analysis can be conducted by a technician or, as in this study, by an undergraduate researcher.

In this study, we determined the brain compartment volumes and regional grey matter (neuronal) concentrations in a group of 502 adult healthy subjects. We characterized the sample and outline the image analysis chain. After we extracted the quantitative information from the images, we related these figures with demographic information. We hoped to address the following questions: Are there any significant structural differences between healthy male and female brains? Which brain regions differ across gender? How much are macroscopic brain structures affected by healthy aging? Do atrophy rates differ across brain structures? Is aging a linear process?

Subjects and Methods

We examined a population of 502 healthy adult subjects and acquired high-resolution anatomical images of the head using MR imaging. Image processing methods were used to segment the major compartments—namely, intracranial space (IC), brain (BR), grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF)—from MR images (Figure 1). The GM compartment was further divided into brain regions. Two subgroups (age-matched and gender-matched) were formed to analyze differences in grey matter concentration.

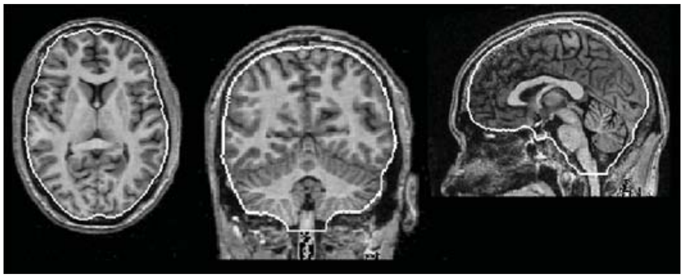

Figure 1

Sample cross-sections from a 3D MR image of a human head. Left: axial slice (perpendicular to the body axis), middle: coronal slice (parallel to the body plane), right: sagittal slice (front-to-back). The white line represents the border between the skull and the brain, and encloses the intra-cranial space. The bright regions inside the skull comprise the white matter (WM) of the human brain, roughly corresponding to the compartment of the brain's fiber connections. The thin grey layer (grey matter, GM) corresponds to the neuronal compartment. The dark regions are fluid-filled (cerebro-spinal fluid, CSF).

Subjects

Enrolled participants came from the Max-Planck Institute of Cognitive Neuroscience in Leipzig, Germany, during 1995–2000. Informed consent was obtained from all participants, and the study was approved by the local ethics committee. High-resolution T1-weighted volumetric MR images were acquired from 502 healthy subjects, aged 16 to 70, with 248 females (mean age 30.0 years) and 254 males (mean age 27.3 years).

Two subgroups were selected based on subjects' age and gender. The gender-related differences were studied in a group of healthy young subjects aged 18 to 32 years (group GEN). This subgroup comprised 290 subjects, with 145 gender-match pairs of young healthy subjects (mean age 24.2±2.7 years). The age-related changes were sampled from a group of healthy subjects aged 18 to 70 years (group AGE). This subgroup included 152 subjects, comprised 76 age-matched male-female pairs. The numbers of pairs were evenly distributed to avoid an over-representation of a particular age group.

Image Acquisition

MR imaging was performed on a Bruker 3 T-Medspec 100 system. T1-weighted images were acquired using a 3D MDEFT protocol (Lee et al., 1995), using a 256x256 matrix, a voxel size of 0.9x0.9 mm, and a slice thickness of 1.5 mm. During the 15-min scanning time, 128 sagittal slices were recorded (Kruggel, 2006).

Image Analysis

All T1-weighted MR images were automatically checked for image quality based on the signal-to-noise and contrast-to-noise ratios, the acuity, and summary estimates of the tissue distribution. Heads in the imaging data sets were aligned with the stereotactic coordinate system and interpolated to an isotropic resolution of 1mm, corresponding to a volume of 200x256x256 mm (Kruggel and von Cramon, 1999). The intracranial compartment (IC) was extracted from the head by removing the outer hulls of the brain. The extracted compartment was corrected for intensity non-uniformity while segmenting it into its three major compartments: GM, WM, and CSF (Figure 1). Note that IC consists of GM, WM and CSF, and the brain compartment (BR) consists of GM and WM. The volume of each compartment (ICV, BRV, GMV, WMV, CSFV) was obtained by summing up the corresponding voxels, which were multiplied by the voxel size. The GM concentration in 116 brain regions-of-interest (ROIs) (Poldrack, 2007) was determined using the Anatomical Automatic Labeling (AAL) template (Tzourio-Mazoyer, 2002), which resides in standardized neuro-anatomical space. To obtain quantitative results for individual regions, we performed a nonlinear transformation from the standardized space to each individual image. This transformation was determined as the inverse of a nonlinear transformation that mapped individual data into the common

Table 1

Gender-related differences of gross compartment volume in group GEN, without and with normalization by the intracranial volume. Column P denotes the significance level of the difference, expressed as p-values.

Compartment or ratio	Female	Male	P
Intracranial volume, ICV	1503.4 ± 110.6 ml	1676.2 ± 121.1 ml	< 0.001
Brain volume, BRV	1241.4 ± 93.9 ml	1377.7 ± 101.9 ml	< 0.001
Grey matter volume, GMV	725.3 ± 52.4 ml	802.0 ± 58.1 ml	< 0.001
White matter volume, WMV	516.0 ± 46.7 ml	631.9 ± 61.9 ml	< 0.001
Fluid compartment, CSFV	262.0 ± 32.2 ml	298.5 ± 34.9 ml	< 0.001
Ratio BRV/ICV	0.8257 ± 0.0169	0.8220 ± 0.0158	< 0.05
Ratio GMV/ICV	0.4828 ± 0.0175	0.4788 ± 0.0195	< 0.05
Ratio WMV/ICV	0.3429 ± 0.0156	0.3431 ± 0.0186	
GMV/WMV	1.4120 ± 0.1014	1.4010 ± 0.1113	

standardized space. A study-specific common reference was developed for this process. As a result, the GM concentration was obtained in all 116 brain ROIs for each of the 502 subjects. The Brain Imaging Analysis (BRIAN) environment (Kruggel and Lohmann, 1996), running on a 30-node PC cluster under the Linux operating system, was used for these image processing steps.

Statistical Analysis

To address the questions stated at the end of the introduction, we compiled the independent variables, gender and age, and the dependent variables, compartment volumes (ICV, CSFV, GMV, WMV) and ROI-wise GM concentration, for all 502 subjects in a table. Two columns were added to designate membership in the gender (GEN) and age (AGE) groups. Gender-related differences and age-related changes were analyzed using linear regression, with and without normalization by the IC volume. From the results of the region-wise analysis, the significance (p-value) of the corresponding regression coefficients was converted into a z-score and multiplied by the sign of the regression coefficient. Z-values were color-mapped and assigned to the corresponding region a reference brain. The statistical analysis was implemented with a software package R (Becker et al., 1988; Chambers and Hastie, 1992)).

Results

Our first question was: are there any significant structural differences between healthy male and female brains? We focus on the group consisting of young, age- and gender-matched subjects, and compare the quantitative measures obtained from the analysis described above.

Gender-Related Differences

The results of average brain compartment volumes, absolute and relative changes of brain volumes per year, and the volume ratios were determined (Table 1). All measured gross volumes were larger in males: the intra-cranial volume (ICV, $\Delta V = +173$ml, 10.3%), the brain volume (BRV, $\Delta V = +136$ml, 9.98%), grey matter volume (GMV, $\Delta V = +73.7$ml, 9.56%), white volume (WMV, $\Delta V = +116$ml, 18.3%), and fluid compartment (CSFV, $\Delta V = +36.5$ml, 18.3%). Differences were highly significant ($p < 0.001$). Because males are typically taller than females, we normalized the intracranial compartments by the intracranial volume to form the ratios in the bottom four rows of Table 1. This normalization almost removed gender-related differences. Thus, gender-related differences in gross compartment volumes are mostly due to a scaling effect, and are related to body height rather than to gender.

tNext, we addressed our second question: Which brain regions differ across gender? We performed a finer-grained analysis of regional differences in the grey matter concentration of the brain across gender. Highly significant gender-related differences were found in 16/116 regions ($p<0.01$). Regions with the most prominent changes are listed in Table 2 and depicted in Figure 2. Notably, males had higher grey matter concentrations than females in both motor cortices, and lower values in language-related cortices on the left side (OR, HESCHL, T1A, T1) and secondary visual cortices (O1, O2) on the left side.

We then focused on the question: how much are macroscopic brain structures affected by healthy aging? First, we

Table 2

Major regions with gender-related differences in grey matter concentration. Males had a higher grey matter concentration in both motor cortices (rows 1–2), while females had a higher concentration in language-related regions and visual cortices on the left brain hemisphere (rows 3–7).

Region	Δ%	P
Motor cortex left	1.01	0.0097
Motor cortex right	1.65	0.0002
Auditory cortex left, OR	-2.48	0.0001
Auditory cortex left, HESCHL	-3.01	0.0001
Superior temporal gyrus left, TI	-1.12	0.0033
Superior temporal gyrus left, TIA	-2.34	0.0002
Visual cortex left, O1	-1.90	0.0022
Visual cortex left, O2	-1.51	0.0005

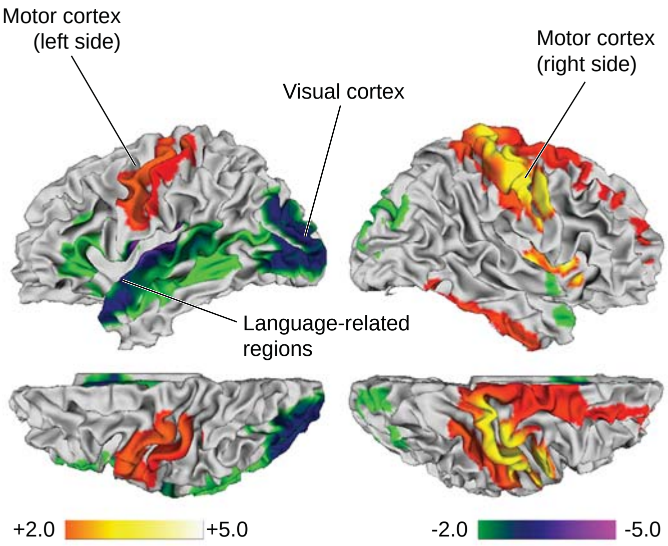

Figure 2

Gender-related differences in GM concentration. Colors correspond to significance of gender-related differences, expressed as z-scores. Thus, males have significantly higher grey matter concentrations in white-yellow regions, while females have higher concentrations in blue-magenta areas.

used the gross compartment volumes obtained in the sample AGE, and studied their dependency on age.

Age-Related Changes

Aging leads to a significant loss of grey, not white matter, compensated for by an increase in fluid-filled compartment (see Table 3). Thus, aging affects predominantly the neurons in the brain (the grey matter), and much less their connections (the white matter). Over a span of 50 years, the average volume change was estimated as: ICV (-91.2ml, -5.8%), BRV (-105ml, -11.2%), GMV (-125.3ml, -15.8%), WMV (-24.4ml, -4.5%), and CSFV (+58.5ml, +24.3%). All compartments had decreasing volumes except for CSF.

Table 3

Age-related changes of gross compartment volumes, expressed as absolute and relative rates per year of age, without and with normalization by the intracranial volume. Column P denotes the significance of the changes.

Compartment or ratio	Absolute change	Relative change in %	P
Intracranial volume, ICV	-1.8245 ml	-0.1155	< 0.05
Brain volume, BRV	-2.0994 ml	-0.2237	< 0.001
Grey matter volume, GMV	-2.5067 ml	-0.3153	< 0.001
White matter volume, WMV	-0.4873 ml	-0.0897	< 1
Fluid compartment, CSFV	1.1696 ml	0.4852	< 0.001
Ratio BRV/ICV	-1.002e-03	-0.1180	< 0.001
Ratio GMV/ICV	-1.095e-03	-0.2168	< 0.001
Ratio WMV/ICV	9.231e-05	0.0269	< 1
Ratio GMV/WMV	-0.48728	0.0867	< 1

Table 4

Examples of regions with age-related changes in the grey matter concentration, expressed as percent per year of age. All regions show a highly significant loss ($p < 0.001$).

Regions	Δ%/year
Motor cortex, left	-0.153
Motor cortex, right	-0.142
Auditory cortex left, OR	-0.302
Auditory cortex left, HESCHL	-0.383
Superior temporal gyrus left, TIA	-0.252
Superior temporal gyrus left, TI	-0.230
Hippocampus, left, HIPPO	-0.084
Parahippocampus, left, PARA_HIPPO	-0.068

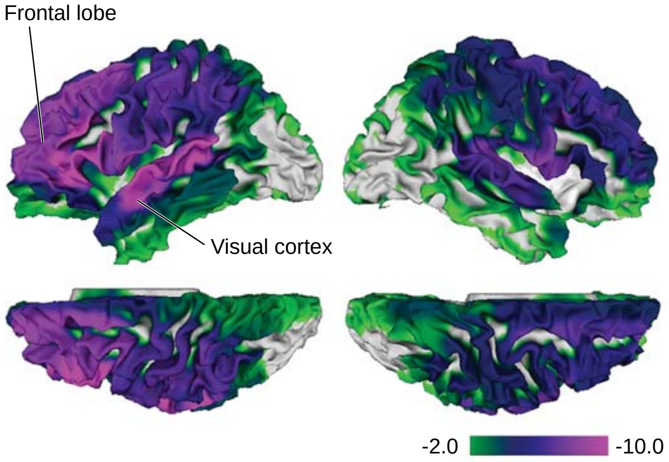

Figure 3

Age-related changes in grey matter concentration. Colors correspond to the significance of the age-related loss, expressed as z-scores. Regions depicted in magenta experienced a considerable loss, while green and white regions remained relatively stable.

Normalization of the compartments by the intracranial volume did not influence age-related changes, which indicates that the age-related atrophy is (largely) independent of brain size (scale).

Finally, we were interested whether all brain areas degenerated at the same rate. Thus, we performed a more fine-grained analysis of regional differences in the grey matter concentration of the brain across age.

A highly significant age-related loss of grey matter was found in 72/116 regions ($p<0.01$) (refer to Table 4 for selected regions). As shown in Figure 3, this loss was stronger on the left than the right side and occurred predominantly in the frontal lobe and motor cortex, language-oriented areas (T1A, T1), and memory-related cortices on the mesial side of the temporal lobe (denoted as hippocampus, HIPPO, and para-hippocampus, PARA_HIPPO, not shown).

Discussion

A large sample of brain datasets, acquired from 502 healthy subjects, was analyzed by quantitative MRI. Differences in brain structures due to gender were found in a subgroup of 290 age-matched young subjects, and the age-related brain atrophy was quantified in a subgroup of 145 subjects aged 18 to 70 years. This is the largest sample population ever studied. While results for the gross compartment volumes can be compared with previous autopsy and MRI-based studies, recent advances in image processing methods allowed us to use the automated, fine-grained region-wide analysis for the first time here.

Previous studies of brain compartments provided similar results, albeit in smaller samples, and limited to the more conventional methods that were available at the time. Schlaepfer *et al.* (1995) measured differences in cortical regions involved in verbal behavior across gender. They concluded that women have higher grey matter percentages than men in the language-related regions. Courchesne *et al.* (2000) compared results of their quantitative MR analysis of healthy brain development and aging of 116 volunteers with values of previous *post mortem* studies. They found that grey matter volume decreased by 13% in subjects from 40 to 80 years of age. Resnick *et al.* (2003) measured volumetric changes in elderly subjects. This study concluded that grey matter loss due to aging occurred predominately in the orbital and inferior frontal, cingulate, insular, and inferior parietal cortices. All these studies are qualitatively and quantitatively in accord with our results.

It is tempting to interpret anatomical differences in brain structures in terms of functional differences. We assumed that the measured grey matter concentration is proportional to the regional neuronal population, albeit as a larger regional volume and/or higher neuronal density. It is commonly accepted that a regional decrease in grey matter concentration (such as found here with age) corresponds to an impairment or loss of function(s) typically addressed to that cortex. Thus, the atrophy in memory-related cortices (HIPPO, PARA_HIPPO) can be related to the well-known reduction in memory performance typically attributed to elderly subjects. Likewise, the reduction in frontal cortices may be related to lower flexibility, creativity and problem-solving capabilities. Interestingly, primary and secondary visual areas appear to remain stable during aging. Note that these areas are similar in extent and amount to those affected by Alzheimer's disease, leading some researchers to hypothesize that Alzheimer's disease is a form of "accelerated aging." Further analyses (not shown here) indicate that there is no "plateau phase" between early adulthood and a mature age before degenerative processes begin. Rather, measurable atrophying processes start in the third decade of life.

In contrast, the functional interpretation of a relative difference in the grey matter concentration between healthy groups of subjects is not unanimous in the literature. The tempting assumption may not be warranted that simply "more is better." The most convincing examples are found with lateralized functions such as handedness and language production, where the corresponding cortices on the dominant side are larger in extent (but not thicker) than the corresponding collateral cortices. It is difficult to estimate how much a difference in the extent of a cortex translates into a difference in grey matter concentration. A more fine-grained analysis that assesses the extent and cortical thickness in this sample is under way. It is also possible that (some) functional networks may be implemented differently in males and females. For our group, a common set of functional data (*e.g.*, from psychometric tests) were not available, so we do not attempt to provide a functional interpretation of the anatomical differences. Because our results are based on a large sample acquired on a single scanner, gender-related differences found in our study may not easily be attributed to a selection artifact or other methodological issues. Thus, we are confident that our anatomical results can be used as a reference to support any gender-related functional differences related to these cortices.

The homogeneity of the population and image database may be considered to be an advantage of this study. All participants stem from a population of white Caucasian ethnicity and were examined on the same scanner and protocol. It is unknown, however, how much results may be generalized for other ethnicities and scanning conditions. While absolute measures may differ, it is expected that relative findings are similar in a different setting. Thus, we are confident the results of our study can be used as normative data to assess the amount of pathological changes due to focal brain diseases (*e.g.*, cerebral infarction) or pathological aging (*e.g.*, Alzheimer's disease).

Besides our neurobiological results, we consider the engineering aspect of this study—the development and testing of the image processing methodology—to be a major outcome. All datasets were automatically processed with the same parameter settings. These tools, therefore, are sufficiently mature and robust to serve similar needs in neurobiology and clinical neuroscience.

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