Brain size and grey matter volume in the healthy human brain

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Magnetic resonance imaging was used to evaluate the influence of sex and brain size on compartmental brain volumes (grey matter, white matter, CSF) in a large and well-matched sample of neurologically normal women ($n = 50$) and men ($n = 50$). As expected, we found a significant sex difference for the absolute volumes of total brain, grey matter, white matter and CSF, with greater volumes for men. Relating these compartmental volume measures to brain volume resulting in proportional volume measures revealed a higher proportion of grey matter in women. No significant sex differences were found for white matter and CSF proportions. However, when the influence of sex was partialized out by regression analyses, brain volume explained 40–81% of the variance of the absolute grey matter, white matter and CSF volumes. Performing these regression analyses for the proportional volume measures revealed that brain volume explained ~16% of the variance in grey matter proportion. Sex or the interaction between sex and brain volume revealed no additional predicitve values. Interestingly, the correlation between brain volume and grey matter proportion was negative, with larger brains exhibiting relatively smaller proportions of grey matter. Thus, sex is not the main variable explaining the variability in grey matter volume. Rather, we suggest that brain size is the main variable determining the proportion of grey matter. *NeuroReport* 13:2371–2374 © 2002 Lippincott Williams & Wilkins.

Key words: Brain size; Brain volume; Cerebrospinal fluid; Grey matter; Sex difference; White matter

INTRODUCTION

It is still a matter of dispute whether the often reported sex differences in cognitive abilities (e.g. verbal and spatial cognition) are related to underlying biological factors (genetic, hormonal, or maturation) affecting both brain structure and function. Sexual dimorphisms in humans have been described using autopsy material and *in vivo* imaging techniques. The most consistent of these differences is brain size (brain weight or brain volume), with men exhibiting ~8–10% larger brains than women (for a summary see [1]). This dimorphism cannot be explained by the 10–15% smaller body size of women, because brain and body sizes are more or less unrelated [1]. Thus, this sexual dimorphism may indeed indicate a sex-specific difference in brain organization. In addition to this gross sex difference, several studies have found larger regional brain volumes related to brain size favoring women with respect to the planum temporale [2,3], the whole temporal cortex [4], the hippocampus [5,6] the caudate nucleus [6], the anterior cingulate [7], the dorsolateral prefrontal cortex [4], the right inferior parietal lobe [8], or the proportional grey matter volume [9]. In addition, Witelson *et al.* [10] reported greater cell packing density and number of neurons for women in the vicinity of the planum temporale. Finally, several papers have reported relatively larger corpus callosum (CC) areas for women, suggesting more or larger interhemispheric axons crossing the midline [11–14]. On the other hand, men showed larger volumes relative to brain size for the amygdala [5], the hypothalamus [15–17], the paracingulate gyrus [7], and the white matter [9]. Although these latter findings might indicate additional sexual brain dimorphisms, it is worth noting that they have not been consistently replicated across laboratories. For example, the often-cited sex difference in the size of the total CC area or the size or form of the posterior CC has not been replicated in other studies examining larger samples [18,19]. Also, the aforementioned sex difference of the size and asymmetry pattern of the planum temporale was not confirmed by others [20]. Inconsistent findings have also been reported for the amygdala and the hippocampus. Thus, one may conclude that, with the exception of brain size, other possible sexual brain dimorphisms in the human brain have not been established beyond doubt.

The reasons for these inconsistencies may be related to a number of methodological problems limiting the conclusions of previous work. A major source of inconsistency is certainly the fact that sex and brain size effects are confounded because women on average exhibit smaller brains than men. In order to study true sex influences on brain volume measures, it is necessary to control for brain

size influences, or if one is interested in studying brain size influences, one has to control for sex influences. Thus, the present study was designed to re-evaluate sex differences for grey matter, white matter and CSF volumes by statistically controlling brain size. We also planned to study brain size influences on the compartmental volumes independent of sex. Following our recent findings [19,21] our hypothesis was that brain size is the major source explaining interindividual volume differences and not sex.

MATERIALS AND METHODS

Subjects: The study group consisted of 100 young, healthy and right-handed Caucasian volunteers, mostly comprising university students of different faculties. Handedness was determined by referring to hand preference. The sample was matched according to sex (50 women, 50 men) and age (women: 24.2 ± 4.2 years; men: 25.1 ± 4.5 years). Subjects gave informed consent according to institutional guidelines (Ethics Committee of the University of Magdeburg).

MRI acquisition and image analysis: Images were obtained on a 1.5 T GE Signa LX MR scanner by using a strongly T1-weighted gradient echo puls sequence (MP-RAGE, magnetization-prepared, rapid acquisition gradient echo) with the following parameters: TR = 24 ms, TE = 8 ms, 15° flip angle, FOV 250 × 250 mm^2, matrix size = 256 × 256, 124 sagittal slices with 1.5 mm thickness. Image analysis was performed on a PC workstation using MATLAB 5.3 (Mathworks Inc., Natiek, MA, USA; http://www.mathworks.com/products/matlab) and SPM99 software (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm/).

Quantification of the different volume measures: Grey matter, white matter and CSF were segmented by applying the segmentation procedure provided by SPM99. First, the brains were linearily normalized into the standard space defined by the Montreal Neurological Institute (MNI) that approximates the space defined in the atlas of Talairach and Tournoux [22]. After this initial step, the segmentation algorithm assigned each voxel to grey matter, white matter, or CSF.

This separation procedure takes into account not only the intensity of each voxel, but also operates by comparing each brain voxel with voxels from probability maps specifying the likelihood that each voxel belongs to a certain compartment class [23,24]. The final classification of voxels to a particular compartment class is determined iteratively in dependence of mean and variance of the developing compartment cluster, whereby the present segmentation procedure is supplemented by a correction for image intensity non-uniformity. Finally, the segmented partitions are written and graphically presented.

Subsequent statistical analysis was performed on a PC workstation using SPSS 10.0 (SPSS Inc. 1989–99; http://www.spss.com). In order to calculate the volumes of the separate intracranial compartments, we determined the number of voxels belonging to the grey matter, white matter or CSF partitions. Each volume count was then multiplied with the voxel dimensions (0.97 × 0.97 × 1.5 mm). Every single voxel in the compartmental images contains a certain probability value, ranging from zero to one, identifying the likelihood that this voxel belongs to a particular compartment. Hence we also multiplied the number of voxels with the probability values of each voxel. Were these probabilities ignored, the compartmental volumes may have been over estimated, because we cannot exclude the fact that a single voxel may be assigned to more than just one compartment. After determining the volumes of grey matter, white matter and CSF, brain volume was calculated by summing the compartmental volumes. As well as the absolute volume measures, we also calculated proportional volumes by relating these compartmental volumes to brain volume. *t*-tests were used to compare all volume measures between males and females. In addition hierarchical regression analyses were used to study the influence of sex, brain volume and the interaction between sex and brain volume on the various volume measures.

RESULTS

Findings concerning the absolute and proportional volumes are summarized in Table 1. As expected, comparing the volumes of both sexes revealed larger volumes for men. With reference to the proportional compartmental volumes, women showed a significantly higher proportion of grey matter than men. Descriptively, men show slightly higher proportions of white matters and CSF which, however, did not exceed conventional statistical thresholds.

In a further step, we performed hierarchical regression analyses in order to examine the relationships between the volume measures. For this, the volume measures were logarithmically transformed to accord with statistical prerequisites of allometric analysis [25]. In these analyses we used sex (coded as a dummy variable), $\log_{10}$ brain volume and the interaction between these predictors as independent variables. The interaction term (sex × $\log_{10}$ brain volume)

Table 1 Means (± s.d.) and ranges of absolute volumes and proportional volumes (absolute compartmental volume related to total brain volume in %)

	Men		Women		T	*p*
	Mean ± s.d.	Range	Mean ± s.d.	Range		
Brain volume (dm^3)	1.51 ± 0.4	1.25–1.88	1.32 ± 0.10	1.12–1.60	7.97	0.001
Grey matter (dm^3)	0.82 ± 0.06	0.71–0.98	0.74 ± 0.06	0.61–0.86	7.30	0.001
White matter (dm^3)	0.42 ± 0.06	0.26–0.60	0.36 ± 0.04	0.29–0.49	5.74	0.001
CSF (dm^3)	0.27 ± 0.05	0.16–0.39	0.23 ± 0.03	0.14–0.33	5.71	0.001
Grey matter (%)	54.41 ± 1.98	49.40–58.49	55.71 ± 1.90	52.12–59.62	−3.31	0.001
White matter (%)	27.73 ± 2.00	23.92–32.75	27.14 ± 1.97	23.37–32.09	1.50	0.129
CSF (%)	17.85 ± 2.10	12.62–21.45	17.15 ± 2.02	11.70–22.33	1.68	0.094

Table 2. Correlation coefficents obtained for log_{10} absolute and proportional measures correlated with log_{10} total brain volume

	Log_{10} absolute measures	Log_{10} proportional measures	Log_{10} absolute measures (sex partialized out)	Log_{10} proportional measures (sex partialized out)
Log_{10} Grey matter	0.94^{***}	-0.50^{***}	0.91^{***}	0.37^{***}
Log_{10} White matter	0.83^{***}	0.24^{**}	0.76^{***}	-0.17
Log_{10} CSF	0.75^{***}	-0.25	0.63^{***}	0.18

$^{***}p < 0.001$ level (2-tailed);
$^{**}p < 0.01$.

was used to test group differences in the slopes of these regressions by significance testing of the increment in multiple r^2 value afforded by the addition of the interaction term [26]. These analyses revealed that log_{10} grey matter, log_{10} white matter, and log_{10} CSF volumes white matter volumes were strongly linearily and positively related to log_{10} brain volume with no additional predictive value of sex (sex and the interaction between sex and total brain volume; Table 2). As can be seen in Table 2, correlations between compartmental volumes and total brain volume remain high and significant even when the influence of sex was partialized out. On the other hand, when brain volume was partialized out there was no remaining sex influence (all correlations between sex and the volume measures were no larger than $r = 0.05$). Thus, the variance of the absolute compartmental volumes were explained to a high degree only by the variance of brain volume with no between-sex difference in the slopes of the regression line.

In a second step, tests were conducted to determine whether the proportional compartmental volumes were related to log_{10} brain volume. This analysis revealed that only the proportional log_{10} grey matter was negatively correlated with log_{10} brain volume ($r = -0.37$), with sex and the interaction term revealing no predictive value. Thus, with increasing brain size there was a decrease in the grey matter proportion (Fig. 1). White matter and CSF were moderatly related with log_{10} brain volume, but when sex effects were statistically eliminated there remained no brain size effects (Table 2).

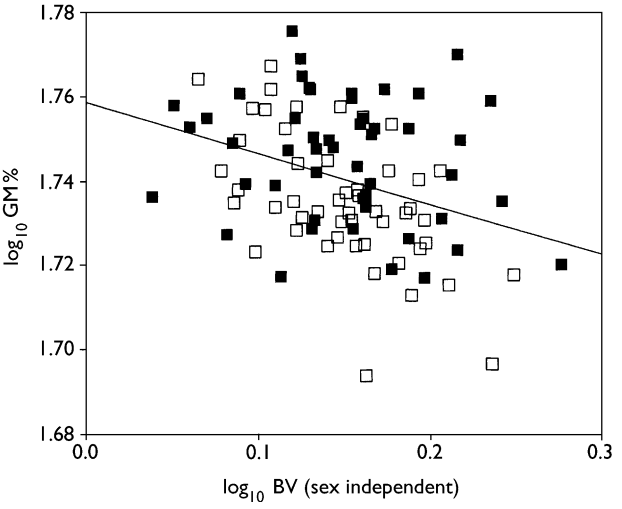

Fig. 1. Relationship between log_{10} brain volume (BV) (sex influences partialized out) and proportional log_{10} grey matter (GM). Filled squares indicate female and unfilled squares male brains.

DISCUSSION

As expected, we found larger volumes of whole brain, grey matter and white matter and CSF for men. More interestingly, we also replicated the recent findings of Gur *et al.* [9], showing a higher proportion of grey matter in females. The relatively larger grey matter volumes in women than men might be the result of sex-specific biological influences which finally influence sex-specific cognition. However, the published studies on sex differences in grey matter are far from conclusive. The reasons for these diverging findings are currently unknown and may be related to differences in sample size, composition of examined brains, methods to quantify the compartmental volumes, or lack of neuropsychological control (e.g. handedness).

A crucial confounding variable in many neuroanatomical studies on sex differences is brain size, because men show ~8–10% larger brains than women. However, that does not mean that all men have a large brain and all women have small brains. In recent studies we found that ~15–20% of women have brains of comparable size to men; likewise 15–20% of men had brain sizes similar to those of women [17,19,21]. Therefore, we argue that brain size might be a crucial variable determining compartmental volume relations more or less independent from sex. This argument basically follows the Ringo hypothesis [27], which was originally developed to model assumed changes in interhemispheric communication in relation to varying brain size. Ringo *et al.* argued that as brain size is scaled up there must be a fall in interhemispheric connectivity, due to the increasing time constraints of transcallosal conduction delay. Consequently, functionally related neuronal elements would cluster in one hemisphere, so that increasing brain size would be the driving force in the phylogeny of hemispheric specialization. With regard to callosal connectivity, the morphometric data of recently published studies of our group provide empirical support of this conjecture [19,21]. With regard to the present data, one may speculate that with decreasing brain size less intra- and interhemispheric communication via white matter tracts is necessary while the number of processing units (e.g. neurons) is more important to subserve information processing. With larger brains there are larger distances between neuronal processing units, which requires more intra- and interhemispheric fibre tracts at the expense of the number of neuronal processing units. In fact, we found strong negative correlations between brain volume and the proportional grey matter volume, the latter decreasing with increasing brain

size. This negative relationship prevails even when the influence of sex was partialized out. Thus, brain volume (but not sex) is the main variable determining proportion of grey matter.

When brain size is the main factor influencing the proportional size of grey matter one has to study the factors influencing brain size. Among those factors which are known to influence, or discussed as possibly influencing, brain size are sex hormones [28], genetic influences independent from sex determining the size of body organs including brain size, nutritional status with undernutrition causing smaller brain sizes [29] and finally use-dependent influences like lifelong intensive training in specific cognitive or motor skills. These specific factors might influence the different compartmental volumes in different ways for which the exact mechanisms and outcomes are not fully understood until now. However, once again brain size independent from sex has been shown to play a major role in determining specific anatomical pecularities. Thus, future studies should concentrate on the examination of factors influencing brain size in both sexes, as was shown in a recent paper by Rademacher *et al.* [32].

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