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NeuroImage 30 (2006) 1 – 11

MRI-based volumetry of head compartments: Normative values of healthy adults

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Received 22 December 2004; revised 22 August 2005; accepted 20 September 2005
Available online 11 November 2005

The size of head compartments (head and brain volume, intracranial volume, gray and white matter volume, cerebrospinal fluid volume) and their ratios were determined on the basis of magnetic resonance images of the head acquired in a reference population of 502 healthy subjects. Age-matched subgroups were selected to reveal gender-related differences and changes with age. Normative data are provided in the form of simple equations that allow transforming measured compartment volumes into *z* scores, offering the possibility to relate individual data to a larger population.

Keywords: Magnetic resonance imaging (MRI); Morphometry; Normal development; Normative values

Introduction

Compartments of the human head may be recorded by magnetic resonance imaging (MRI) within a few minutes. A computer-based analysis of these imaging data allows a quantitative characterization of structures, tissues and their changes with time. The resulting extensive parameter sets may be used in further statistical studies, e.g., to classify brains, to draw conclusions about structural differences in subject groups (i.e., by gender, structural abnormalities) and to track individual changes with time (aging, CNS diseases, therapeutical interventions).

In this study, we determined the volume of several head compartments, namely, the head (HDV), the intracranial compartment (ICV), brain (BRV), gray and white matter (GMV, WMV) and the cerebrospinal fluid (CSFV) and several brain compartments, the left and right cerebral hemisphere (LHV, RHV), the left and right cerebellar hemisphere (LCV, RCV) and the brain stem (BSV) in a reference population of 502 healthy subjects. From this population, age-matched subgroups were selected to analyze gender-related differences and changes with age. The key idea is to provide normative data, i.e., similar to the CDC growth curves (Kuczmarski et al., 2000). Given age and gender, individual compartment volumes may be transformed by simple equations into *z* scores, offering the possibility to relate individual data to a larger population.

Data on the size of head compartments have been provided by numerous studies using different technology. First, autopsy studies have been carried out systematically for more than 100 years now (Blinkov and Glezer, 1968; Chrzanowska and Beben, 1973; Debakan and Sadowsky, 1978; Hwang et al., 1995; Miller et al., 1980; Peters et al., 2000; Svennerholm et al., 1997). Because real volumes and weights are measured, data from autopsy studies may be considered as the "gold standard". However, inherent technical and logistical problems affect the measurements (e.g., the type of illness, intervals between death and brain removal, weighing in the fresh or fixed condition).

Human brain morphometry advanced dramatically by the invention of the modern neuroimaging methods. Following some initial studies using cranial computed tomography (CCT) (Abbott et al., 2000; Hahn et al., 1984; Schwartz et al., 1985), MRI quickly became the method of choice for data collection because MRI allows discriminating between several tissue types (Caviness et al., 1995, 1999; Kennedy et al., 2003). Several studies focused on the determination of brain compartments and their gender differences (Allen et al., 2002, 2003; Blatter et al., 1995; Filipek et al., 1989, 1994; Sato et al., 2003; Schlaepfer et al., 1995) and changes of compartment volumes with age (Blatter et al., 1995; Courchesne et al., 2000; Ge et al., 2002; Giedd et al., 1996; Harris et al., 1994; Jernigan et al., 2001; Pfefferbaum et al., 1994; Resnick et al., 2003) and tried to find MRI-detectable discriminators of healthy and pathological aging in neurodegenerative diseases (Edland et al., 2002; Jenkins et al., 2000; Wolf et al., 2003, 2004). Often these studies include a small sample size or a few parameters only. Notably, image analysis procedures have matured over the past few years, offering now a fully automatic, bias-free measurement of compartment volumes.

In addition, we also provide normative data for several compartment ratios, e.g., the ratio brain volume/intracranial volume (BRV/ICV). Skull growth occurs along the suture lines and is determined by brain expansion, which takes place during the

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doi:10.1016/j.neuroimage.2005.09.063

normal growth of the brain. Thus, in normal adults, a close relationship between the brain size and the intracranial volume is expected (Falkner, 1977). This relationship is used to estimate the premorbid brain size in degenerative brain diseases (Drachman, 2002; Edland et al., 2002; Jenkins et al., 2000; Wolf et al., 2003) or brain degeneration due to diffuse or focal brain damage.

In the following, we describe the population engaged in this study, the data acquisition and analysis, provide normative data for compartment volumes and discuss our results in relation to the previous studies mentioned above.

Subjects and methods

Subjects

The institute maintains a database of subjects enrolled for functional MRI experiments. Before admission, a brief history and physical inspection is taken by a physician. Subjects are included in this database if they comply with the informed consent for conducting general fMRI experiments, pass the examination and do not exhibit pathological features (e.g., unilateral ventricular enlargements, subarachnoidal cysts) in their MRI tomograms.

Normative data were determined for the whole database (group ALL) of 502 healthy subjects, between 16 and 70 years, including 254 males (mean age 27.3 ± 10.2 years) and 248 females (mean age 30.0 ± 9.6 years). The gender difference in age was not significant (P value = 0.05195).

Volumetric differences associated with gender were evaluated in young healthy subjects aged between 18 and 32 years (group GEN). This subgroup of the database consists of male/female pairs with an within-pair age difference of less than 1 year. Group GEN included 290 subjects, 145 males (age: 24.1 ± 2.6 years) and 145 females (age: 24.3 ± 2.9 years). The age difference was insignificant (P = 0.565).

Changes of compartment volumes with age were studied in a group AGE of 152 healthy subjects, between 18 and 70 years, including 76 males (mean age 35.1 ± 13.4 years) and 76 females (mean age 36.1 ± 14.1 years) matched by age (P = 0.650). The selection procedure was similar to the one described above with two exceptions. First, to avoid an over-representation of young subjects in the group AGE, the number of selected male/female pairs was limited to three pairs per year. Second, due to a relative lack of elderly subjects in the database, the within-pair age difference for subjects older than 35 years was allowed to range up to 2.5 years.

The same database and its subgroups were already used for a study on brain asymmetry (Kovalev et al., 2003).

Image acquisition

Magnetic resonance imaging was performed on a Bruker 3 T Medspec 100 system, equipped with a bird cage quadrature coil. T1-weighted images were acquired using a 3D MDEFT protocol (Lee et al., 1995): FOV 220 × 220 × 192 mm, matrix 256 × 256, 128 sagittal slices, voxel size 0.9 × 0.9 mm, 1.5 mm slice thickness, scanning time 15 min. PD-weighted images were acquired using a 3D FLASH protocol with the same resolution parameters.

Image data processing

T_1-weighted volumetric MR images were aligned with the stereotactical coordinate system (Kruggel and von Cramon, 1999) and interpolated to an isotropical voxel size of 1 mm using a fourth-order b-spline method. Data were corrected for intensity inhomogeneities by a fuzzy segmentation approach using 3 classes (Pham and Prince, 1999), yielding an intensity-corrected T_1-weighted image (I_{b1c}), and a set of 3 probability images. Here, each voxel contained a probability for belonging to the intensity class 0 (I_{c0}: background (BG) and cerebrospinal fluid (CSF)), 1

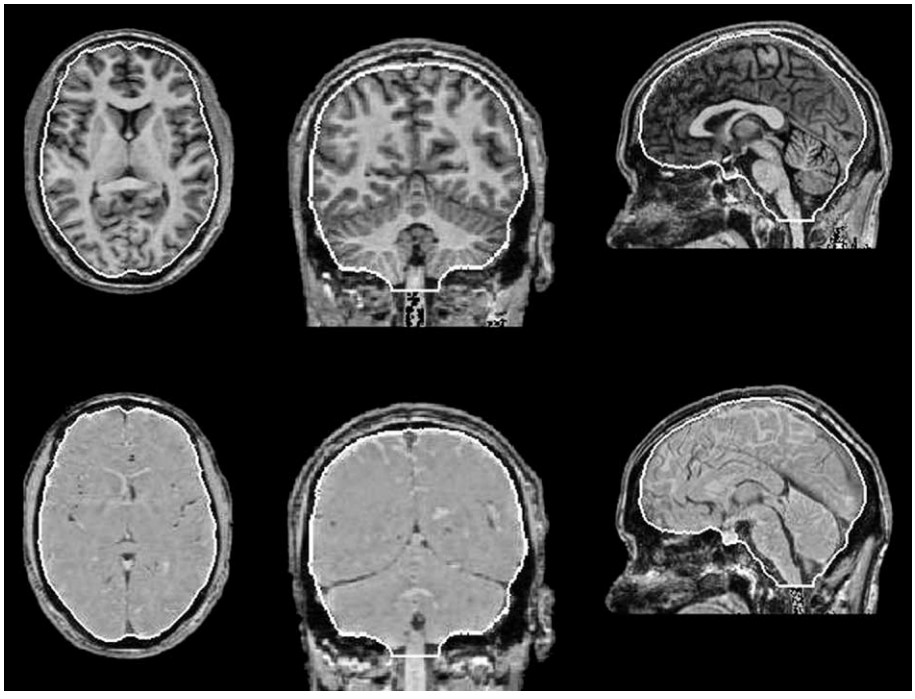

Fig. 1. Border of the ICV mask overlaid on the T_1-weighted image (top row) resp. PD-weighted image (bottom row) for an example dataset.

(I_{c1}: gray matter (GM), facial muscles, connective tissue) or 2 (I_{c2}: white matter (WM), fat).

A mask of the intracranial volume was generated for each dataset by a registration approach (Hentschel and Kruggel, 2004). A non-linear registration between a T_1-weighted dataset of a reference and a study subject yields a deformation field (Christensen, 1996; Wollny and Kruggel, 2001). This deformation field contains the inter-subject structural differences and is applied to a reference PD-weighted dataset in order to obtain an artificial study PD-weighted dataset. Then, an ICV mask for the study subject is segmented from the artificial PD-weighted dataset. The bottom-most slice was set 10 mm below the base of the cerebellum, as suggested by Lemieux et al. (1999). An evaluation of this procedure in a group of 12 dual-weighted datasets using a "leave-one-out" strategy demonstrated an expected error for the IC volume of less than 1.5% (Hentschel and Kruggel, 2004). An example segmentation is shown in Fig. 1.

A mask of the head volume was segmented for each dataset using the T_1-weighted dataset. Following an intensity-based classification into background and foreground, the biggest connected foreground component was selected. Holes in this component were filled, and the resulting mask was cut at the same slice as the ICV mask.

The compartment volumes of the gray matter, white matter and cerebrospinal fluid were determined by summation of the probability values in images I_{c0}–I_{c2} within the ICV mask.

Denote all voxels of class I_{c2} within the ICV mask as the WM segmentation of the brain. To separate the cerebrum from the brain stem and cerebellum, the brain stem was cut at a horizontal plane 15 mm below the posterior commissure. A morphological opening using a small spherical kernel (1.5 mm) was applied to remove remaining bridges. The cerebrum was selected as the largest connected component. The cerebellum and brain stem were separated as follows: in the mid-sagittal plane, a line is placed through the 4th ventricle. This line is enlarged laterally to form a band of 10 mm width. To both sides of this band, cut planes through the cerebellar peduncles were attached. The angle between the cut planes and the band was optimized to minimize the size of the cut. Cerebral and cerebellar hemispheres were separated by the mid-sagittal plane. In all 5 white matter compartments, adjacent gray matter and CSF were reattached by morphological dilation conditional to the ICV mask to yield 5 compartment masks (see Fig. 2).

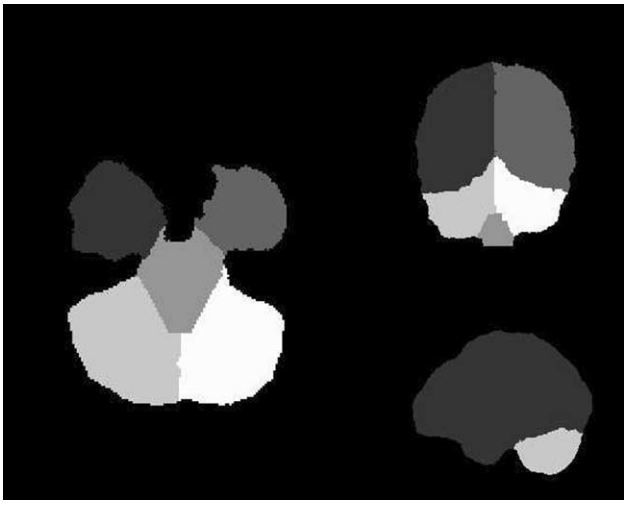

Fig. 2. Compartment masks of the cerebral hemispheres (LHV, RHV), the cerebellar hemispheres (LCV, RCV) and the brain stem (BSV) for an example dataset.

Table 1
Gender-related differences (mean ± standard error) in group GEN

	Female	Male	*P*
HDV	2777.0 ± 206.8	3076.7 ± 225.2	***
ICV	1494.9 ± 96.3	1616.3 ± 91.1	***
BRV	1304.4 ± 87.5	1417.3 ± 86.2	***
GMV	668.0 ± 46.7	714.3 ± 47.5	***
WMV	636.4 ± 69.9	703.0 ± 69.0	***
CSFV	176.3 ± 28.2	183.6 ± 29.7	*
LHV	575.4 ± 38.9	627.3 ± 39.0	***
RHV	575.5 ± 40.8	625.8 ± 39.3	***
LCV	66.7 ± 7.4	74.2 ± 8.2	***
RCV	64.7 ± 8.7	69.9 ± 9.9	***
BSV	27.9 ± 5.3	30.6 ± 6.9	***
ICV/HDV	0.539 ± 0.029	0.527 ± 0.031	***
BRV/ICV	0.873 ± 0.017	0.877 ± 0.018	*
GMV/ICV	0.448 ± 0.027	0.442 ± 0.025	*
WMV/ICV	0.425 ± 0.030	0.434 ± 0.028	***
CSFV/ICV	0.118 ± 0.017	0.114 ± 0.017	*
GMV/WMV	1.062 ± 0.135	1.025 ± 0.116	**
LHV/ICV	0.384 ± 0.009	0.386 ± 0.010	.
RHV/ICV	0.384 ± 0.010	0.385 ± 0.020	–
LCV/ICV	0.045 ± 0.004	0.046 ± 0.004	*
RCV/ICV	0.043 ± 0.005	0.043 ± 0.005	–
BSV/ICV	0.019 ± 0.003	0.019 ± 0.004	–

All volume data (except ratios) are normally distributed (Shapiro–Wilks test) and given in milliliters. Refer to the text for abbreviations. Codes for *P* values are: 0 "***" 0.001 "**" 0.01 "*" 0.05 "." 0.1 "–" 1 ".".

The compartment volumes of the cerebral hemispheres (LHV, RHV), the cerebellar hemispheres (LCV, RCV) and the brain stem (BSV) were determined by summation of the probability values in images I_{c1}–I_{c2} within the compartment masks.

Table 2
Absolute and relative age-related changes per year of compartment volumes [ml] and compartment ratios in group AGE

	Absolute change	% Relative change	*P*
HDV	2.374	0.088	.
ICV	−0.734	−0.048	–
BRV	−2.268	−0.164	***
GMV	−1.562	−0.230	***
WMV	−0.706	−0.101	.
CSFV	1.542	−1.117	***
LHV	−0.859	−0.145	***
RHV	−0.741	−0.124	**
LCV	−0.225	−0.292	***
RCV	−0.239	−0.298	***
BSV	−0.066	−0.212	–
ICV/HDV	−6.542e−4	−0.115	***
BRV/ICV	−1.084e−3	−0.120	***
GMV/ICV	−8.447e−3	−0.189	***
WMV/ICV	−2.403e−4	−0.053	–
CSFV/ICV	1.087e−3	1.204	***
GMV/WMV	−1.380e−3	−0.139	.
LHV/ICV	−3.978e−4	−0.102	***
RHV/ICV	−3.190e−4	−0.082	***
LCV/ICV	−1.257e−4	−0.249	***
RCV/ICV	−1.381e−4	−0.264	***
BSV/ICV	−3.434e−5	−0.170	.

Refer to the text for abbreviations. Codes for *P* values are: 0 "***" 0.001 "**" 0.01 "*" 0.05 "." 0.1 "–" 1 ".".

The analysis software was implemented in the C++ programming language using the BRIAN environment (Kruggel and Lohmann, 1996). Processing took place on a conventional PC (Intel P4 3.4 GHz CPU, 1 GB main memory, Linux 2.6 operating system). The computation time was about 30 min per dataset. User interaction is not required. The software package R (Becker et al., 1988; Chambers and Hastie, 1992) for Linux workstations was used for statistical analysis and charting.

Results

Gender-related differences

All measured compartments were larger in males (see Table 1): the head volume (HDV, ΔV = +299 ml, 10.7%), the intracranial volume (ICV, ΔV = +121 ml, 7.8%), the brain volume (BRV, ΔV = +112.6 ml, 8.0%), the gray matter volume (GMV, ΔV = +45.1 ml, 6.1%) and the white matter volume (WMV, ΔV = +67.4 ml, 10.1%). The relative amount of gray matter is slightly higher in female brains which is also reflected in the lower ratio GMV/WMV in males (−3.53%). Similar volume differences were found for the cerebral hemispheres (LHV, ΔV = +51.9 ml, 8.3%; RHV, ΔV = +50.3 ml, 8.4%), the cerebellar hemispheres (LCV, ΔV = +7.5 ml, 10.6%; RCV, ΔV = +5.2 ml, 7.8%) and the brain stem (BSV, ΔV = +2.7 ml, 9.2%). In males, the left cerebral hemisphere is slightly larger than the right ΔV = +1.5 ml (P = 0.017), while, in females, this difference is insignificant.

The ratio BRV/ICV is slightly higher in females (+0.44%). Normalization of compartments GMV, WMV, BRV and CSFV by ICV reduces but does not remove gender-related differences. So for, any of these parameters' gender-specific normal values should

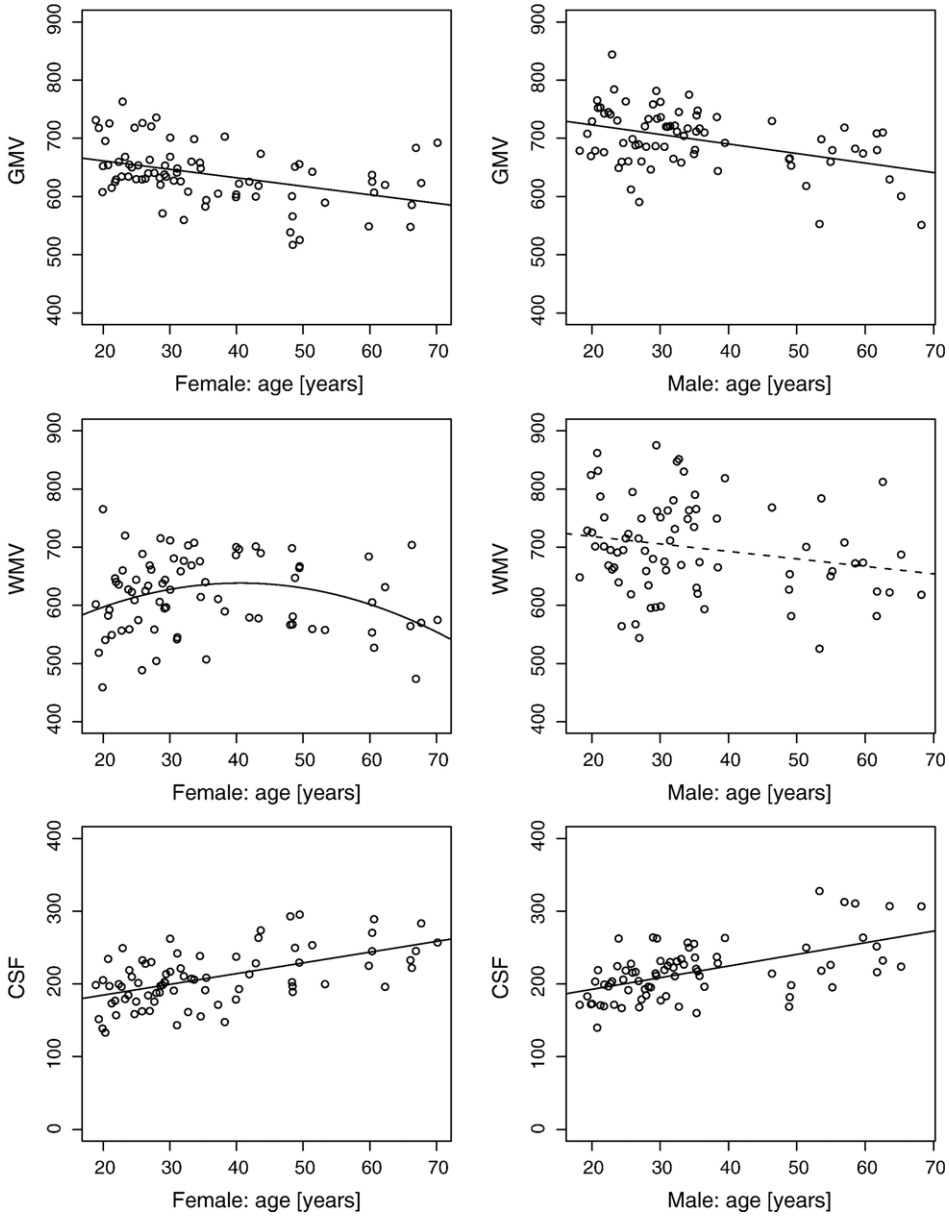

Fig. 3. Dependency of the compartment volumes GMV (top), WMV (middle) and CSFV (below) in group AGE for females (left) and males (right). The trend in the white matter loss of male brains is indicated by a dashed line.

be used. Similar gender-related differences are noticeable for normalized compartments LHV/ICV, RHV/ICV, LCV/ICV, RCV/ICV and BSV/ICV, but statistically insignificant, except for LCV/ICV (see Table 1).

Age-related changes

Changes of compartments volumes with age were examined in a gender-matched group of 152 subjects (group AGE) with an age range between 18 and 70 years.

A small increase in head volume (see Table 2) with age was found that is not significant in group AGE, but in group ALL, most likely paralleling the increasing body weight with age. The intracranial volume does not depend on age (see Table 2) in group AGE, but a slight negative trend was found in group ALL ($P = 0.057$).

Using linear regression models, there is a highly significant loss of gray matter with age (GMV, about 11.5%/50 years) but less for the white matter volume. As a consequence, there is also a notable age-dependent decrease in the brain volume (BRV) and the ratio BRV/ICV. Note that only 69% of absolute change in BRV is explained by gray matter loss, the remaining 31% is due to a loss of white matter. In females, this loss is best described by a quadratic model (in terms of adjusted R^2). In males, a linear model fits best to the data that, however, is statistically insignificant. Similar modeling results were found for the ratio WMV/ICV, in this group and the larger group ALL.

The decrease in brain volume (−113 ml, −8.2%/50 years) leads to a highly significant increase in CSF volume (+75 ml/50 years). The difference is explained by the statistically insignificant reduction of ICV with age. Normalization of compartments

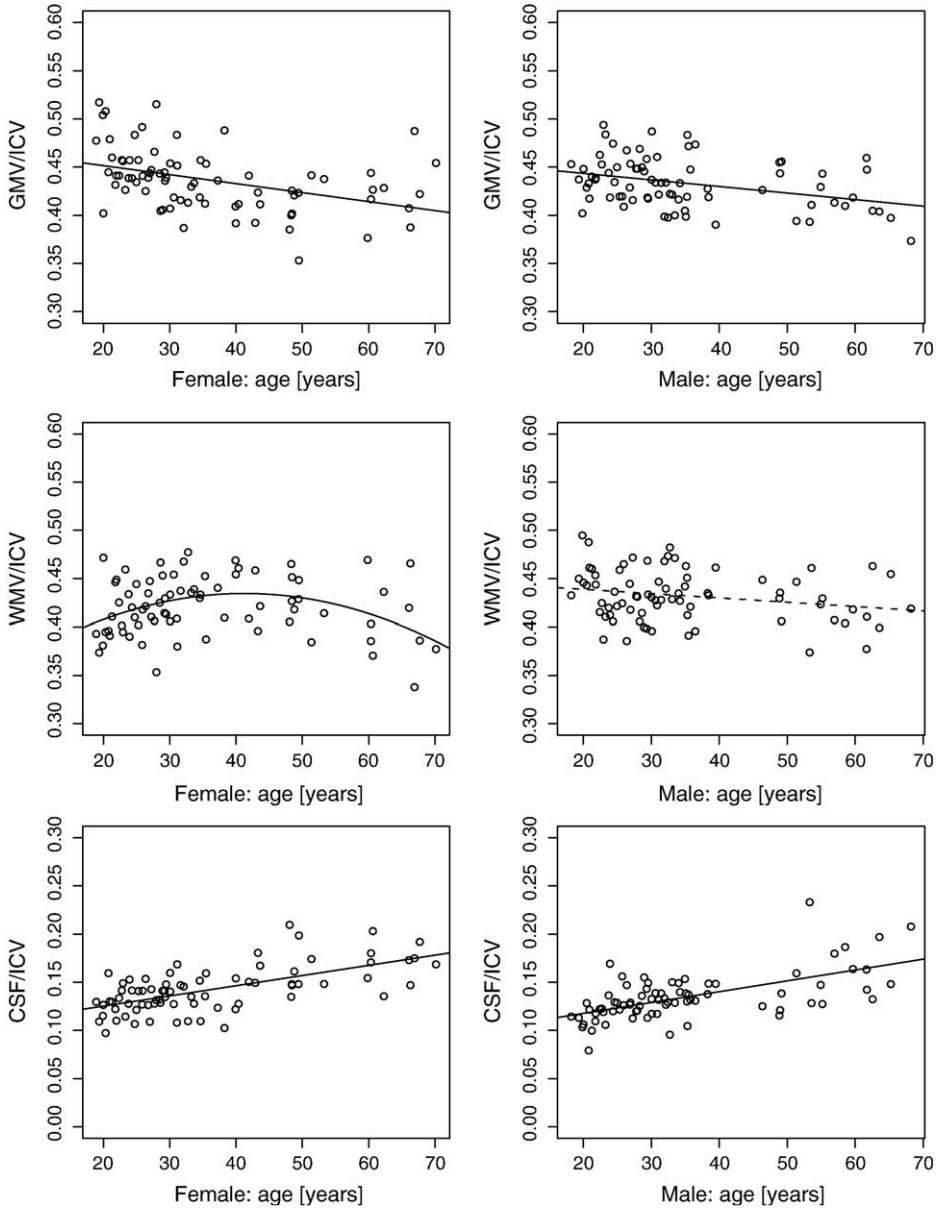

Fig. 4. Dependency of the ratios GMV/ICV (top), WMV/ICV (middle) and CSFV/ICV (below) in group AGE for females (left) and males (right). The trend in the white matter loss of male brains is indicated by a dashed line.

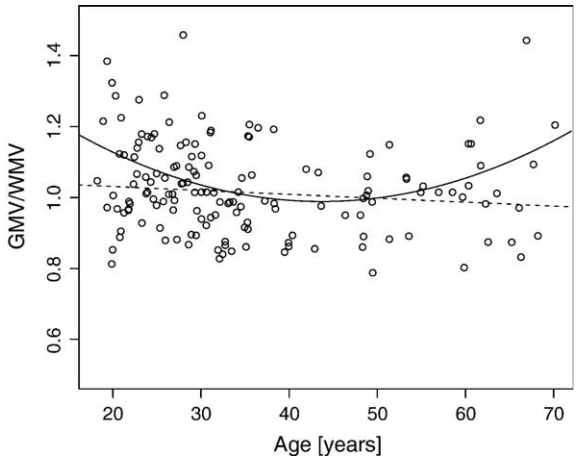

Fig. 5. Dependency of the ratio GMV/WMV in group AGE for females (solid) and males (dashed).

GMV, WMV, BRV and CSFV by ICV reduces but does not remove age-related changes (see Figs. 3 and 4).

A linear regression of the intracranial volume explained by factors age and brain volume models 94% of the variance (adjusted R^2) and thus supports the hypothesis that skull growth is driven by brain growth. This model also supports the use of the ICV for estimating the premorbid brain size. Interestingly, the regression coefficient for factor brain volume is 1.047, suggesting the idea that larger brains are more convoluted (Bartley et al., 1997). This interpretation is further illustrated when splitting the factor brain volume into gray and white matter volumes: a higher regression coefficient for factor WMV (1.06) than GMV (1.02) may indicate that in bigger brains relatively more connections are required. Modeling the head volume by factors age and brain volume explains only 59% of the variance. Thus, other developmental factors contribute to the size of the head.

The ratio GMV/WMV is about −4% smaller in men and decreases with age for females and males at a similar rate. Note that the brain stem and the cerebellum show a higher atrophy rate than the cerebral hemispheres (Fig. 5).

Normal values and ratios

In order to derive normal values, we employed group ALL consisting of 502 subjects (age 16–70 years, 252 males, 248 females). As discussed above, it is useful to normalize compartment data and to correct for age- and gender-related effects. Thus, we computed the ratios ICV/HDV, BRV/ICV, GMV/ICV, WMV/ICV, CSFV/ICV and GMV/WMV as well as LHV/ICV, RHV/ICV, LCV/ICV, RCV/ICV and BSV/ICV and determined gender-specific regression models explaining a given ratio by the factor age. However, these ratios corrected for age- and gender-related effects generally do not follow a normal distribution because ratios (except GMV/WMV) are bound within an interval and a transition to a pathological value typically occurs only in one tail of a distribution. This is best exemplified for the ratio BRV/ICV (see Fig. 6): the mean (0.9) is very close to the upper bound of 1, and a long tail is expected for low ratios (i.e., in the case of a brain atrophy).

In order to obtain z scores for these ratios, we followed a procedure employed for human growth curves (Kuczmarski et al., 2000). First, we performed a Box–Cox transformation: $x' = x\,q - 1/q$. All transformed data x' follow a normal distribution (Shapiro–Wilks test). Finally, x' were converted into z scores by subtracting the mean m and dividing by the standard deviations. Regression coefficients and transformation parameters are compiled in Table 3.

Of course, ratios x' are not independent of each other: GMV/ICV and WMV/ICV add up to form BRV/ICV, BRV/ICV and CSFV/ICV (ideally) sum up to 1. The clinically most useful ratios are ICV/HDV (relating the intracranial compartment to the head), BRV/ICV (relating the brain volume to the intracranial compartment),and GMV/ICV, WMV/ICV (relating the gray (white) matter volume to the intracranial compartment).

In summary, the procedure to obtain z scores for a given dataset is to apply the image processing chain discussed above to compute the compartment volumes. The corresponding ratios are corrected for age and gender using the regression parameters from Table 3, Box–Cox-transformed using parameter q and converted into z scores using the mean m and the standard deviation s. From the z-transformed ratios, outliers and potentially pathological values are easily detected.

Example use in two cases

The use of this method is further illustrated by two example cases that were selected for didactical purposes. A male (EX1, 20 years) and a female volunteer (EX2, 60 years) were both examined

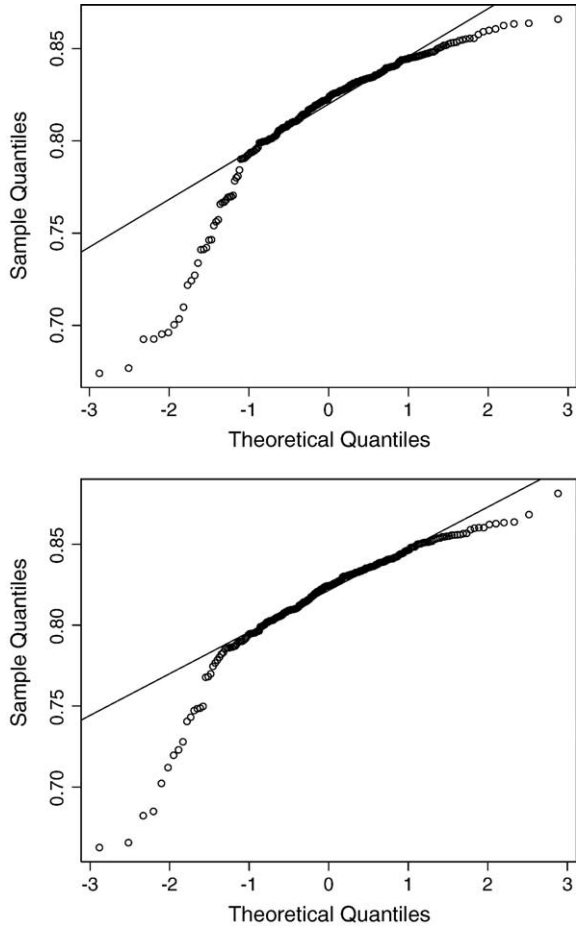

Fig. 6. QQ-plots of the untransformed ratio BRV/ICV (top figure: females, below: males). A long tail for low values indicates a non-normal distribution.

Table 3
Regression coefficients, Box–Cox transformation power q, mean m and standard deviation s used in the z transformation for females (top) and males (below) of group ALL

	Equation	q	m	s	5%	95%
ICV/HDV	0.5679 − 7.624e−4 age	−0.592	−7.068e−1	7.587e−2	0.5073	0.6007
BRV/ICV	0.9060 − 1.150e−3 age	9.589	−6.574e−2	6.843e−3	0.8686	0.9253
GMV/ICV	0.4475 − 1.007e−3 age	−0.833	−1.040e+0	1.069e−1	0.4338	0.5226
WMV/ICV	0.4022 + 3.308e−3 age −4.345e−5 age^2	1.446	−4.928e−1	2.074e−2	0.3748	0.4689
CSFV/ICV	0.0845 + 1.150e−3 age	0.116	−2.109e+0	1.438e−1	0.0639	0.1208
GMV/WMV	1.4619 − 2.165e−2*age + 2.477e−4 age^2	−0.605	1.009e−1	1.136e−1	0.9288	1.3535
LHV/ICV	0.3945 − 4.626e−4 age	7.816	−1.279e−1	1.625e−5	0.3810	0.4101
RHV/ICV	0.3966 − 4.505e−4 age	4.566	−2.158e−1	3.547e−4	0.3800	0.4110
LCV/ICV	0.4972 − 1.070e−4 age	1.334	−7.367e−1	1.609e−3	0.0388	0.0542
RCV/ICV	0.0506 − 1.035e−4 age	1.432	−6.902e−1	1.516e−3	0.0355	0.0544
BSV/ICV	0.0181 − 8.588e−6 age	−1.764	−6.488e+2	1.721e+2	0.0148	0.0252
ICV/HDV	0.5591 − 5.728e−4 age	0.538	−5.241e−1	3.992e−2	0.4913	0.5884
BRV/ICV	0.9071 − 1.028e−3 age	9.464	−6.506e−2	7.418e−3	0.8719	0.9293
GMV/ICV	0.4415 − 9.124e−4 age	0.849	−5.615e−1	2.809e−2	0.4255	0.5068
WMV/ICV	0.4627	−1.271	−1.510e+0	1.897e−1	0.3880	0.4860
CSFV/ICV	0.0834 + 1.028e−3 age	0.145	−2.059e+0	1.438e−1	0.0609	0.1168
GMV/WMV	0.9541 − 1.899e−3 age	0.662	7.609e−2	1.142e−1	0.8837	1.2714
LHV/ICV	0.3925 − 4.158e−4 age	6.346	−1.571e−1	7.316e−5	0.3779	0.4126
RHV/ICV	0.3922 − 2.523e−4 age	7.479	−1.336e−1	2.254e−5	0.3723	0.4059
LCV/ICV	0.0531 − 1.617e−4 age	0.384	−1.788e+0	3.046e−2	0.0424	0.0571
RCV/ICV	0.0522 − 1.353e−4 age	1.174	−8.284e−1	3.241e−3	0.0379	0.0545
BSV/ICV	0.0191 − 1.076e−5 age	−1.483	−2.531e+2	6.365e+1	0.0144	0.0254

The 5- and 95-percentile values of the age-corrected ratios are tabulated in the last two columns. All data are dimensionless, except for the regression coefficients [year^{-}1].

according to the guidelines detailed above. High-resolution MRI datasets of the head were acquired in both subjects (see Fig. 7).

Compartment volumes HDV, BRV, GMV, WMV, ICV, LHV, RHV, LCV, RCV and BSV were determined by applying the image processing chain explained above (see Table 4, top). As seen from the results, EX2 has a normal ICV, while the ICV of EX1 is slightly above normal. However, BRV is rather large in EX1 and small in EX2. Conversely, CSFV is rather small in EX1 and large in EX2.

Ratios ICV/HDV (the intracranial part of the head), BRV/ICV (the relative amount of brain tissue within the intracranial volume), GMV/ICV, WMV/ICV, CSFV/ICV (the relative amount of the compartments within the intracranial space) and the ratio of gray to white matter (GMV/WMV) were computed (see Table 4, below). For a better interpretation, ratios were corrected for age and gender using the regression parameters from Table 3. Finally, corrected ratios x were converted into z scores z by using: $z = (x^q - m * q - 1) / (q - s)$ and the corresponding values for q; m; s from Table 3. Results are compiled in Table 4 below.

Now, EX1 has a z-transformed ratio BRV/ICV of +2.64 (corresponding to an unusual high brain volume inside the cranium) and, consecutively, a low $z\{\text{CSFV/ICV}\}$ of −2.72. This constellation is best explained by a relatively large white matter compartment ($z\{\text{WMV/ICV}\} = +1.78$). In contrast, EX2 has a low z-transformed ratio BRV/ICV of −1.77 and, correspondingly, a high $z\{\text{CSFV/ICV}\}$ of 1.76. The reason is a loss of white matter ($z\{\text{WMV/ICV}\} = -1.65$, $z\{\text{GMV/WMV}\} = 1.08$) in the transition zone to a brain atrophy.

Results and discussion

Our results for the compartment volumes compare well with data published by Blatter et al. (1995) (see Table 5), except for the intracranial volume that is 5% larger in our sample of young adults. However, their reported CSF volumes appear quite low (only 7% of the ICV), while our results (11%) are consistent with other reports [10.8% (Alfano et al., 1998), 14% (Courchesne et al., 2000), 14.4% (Lemieux et al., 2003)] based on similar young sample groups. The brain volume determined for our group of young adults is well in line with autopsy data (Chrzanowska and Beben, 1973; Debakan and Sadowsky, 1978) and MRI-based results (Blatter et al., 1995; Filipek et al., 1994) (see Table 6).

In addition, the gender difference in brain size of 8.0% (or 113 ml) is well established in the literature (Blatter et al., 1995; Debakan and Sadowsky, 1978; Filipek et al., 1994; Peters et al., 1998), while the relative amount of brain volume to intracranial volume is almost gender-independent. We confirm previous findings (Allen et al., 2003; Filipek et al., 1994; Peters et al., 1998) that the relative amount of gray matter is slightly higher in female brains, while the relative amount of white matter is slightly higher in male brains. Our data also support the hypothesis that there is less white matter in females compared to males, most likely as a consequence of the higher symmetry of female brains (Kovalev et al., 2003).

The independence of ICV on age is consistent with previous reports based on autopsy data (Davis and Wright, 1977) and MRI data (Blatter et al., 1995; Courchesne et al., 2000; Edland et al., 2002; Jenkins et al., 2000). However, a slight negative trend found in group ALL amounts to −42 ml/50 years and was found with similar magnitude in other studies (Blatter et al., 1995; Miller et al., 1980). Röthig (1974) as well as Miller et al. (1980) discussed this finding in terms of a secular effect that affects the whole population rather than an individual member. This effect parallels the increase in mean body height (that is correlated with brain weight and thus with ICV) during

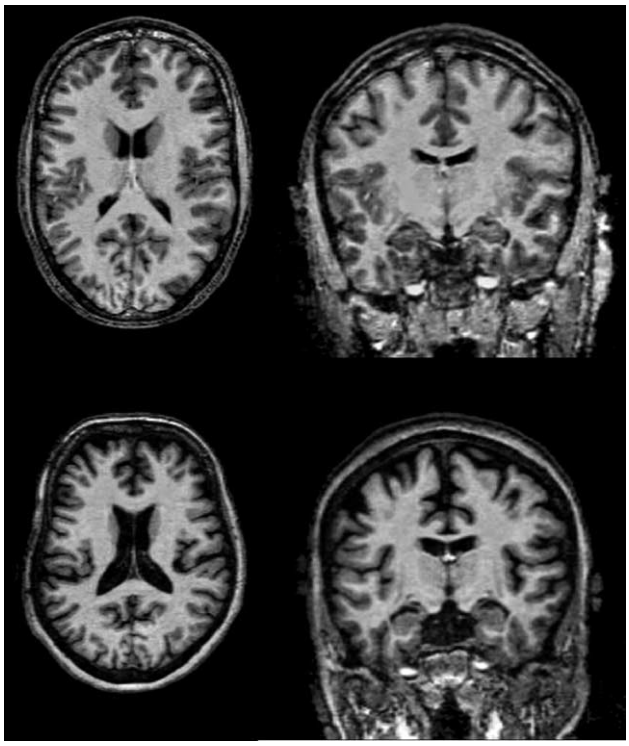

Fig. 7. Example of the use of z-transformed ratios for the quantitative description of a brain. EX1 (top) has a z-transformed ratio BRV/ICV of +2.64 (corresponding to an unusual high brain volume inside the cranium), EX2 (below) has a z-transformed ratio BRV/ICV of −1.77 (in the transition zone to a brain atrophy).

Table 4
Two example cases from our database, a 20-year-old male (EX1, left) and a 60-year-old female (EX2, right)

Parameter	male, 20 y	female, 60 y
HDV [ml]	3377	2837
ICV [ml]	1767	1423
BRV [ml]	1634	1134
GMV [ml]	769	607
WMV [ml]	865	527
CSFV [ml]	123	289
LHV [ml]	709	507
RHV [ml]	712	510
LCV [ml]	89	45
RCV [ml]	82	48
BSV [ml]	41	28

Parameter	ratio	z score	ratio	z score
ICV/HDV	0.523	−0.17	0.502	−0.22
BRV/ICV	0.925	2.64	0.797	−1.77
GMV/ICV	0.435	−0.57	0.427	0.52
WMV/ICV	0.495	1.78	0.370	−1.65
CSFV/ICV	0.070	−2.72	0.203	1.76
GMV/WMV	0.889	−1.30	1.150	1.08
LHV/ICV	0.401	2.30	0.356	−1.26
RHV/ICV	0.403	2.86	0.358	−1.01
LCV/ICV	0.050	1.73	0.032	−1.90
RCV/ICV	0.046	1.56	0.034	−1.92
BSV/ICV	0.023	1.25	0.020	0.62

In comparison with the MRI data (see Fig. 7), EX1 has a high ratio BRV/ICV (z score +2.64), EX2 a rather low ratio BRV/ICV (z score −1.77). Refer to the text for a discussion.

the past 100 years and is thought to result from improved nutrition.

It is also well known that the brain volume decreases with age in our sample by −113 ml/50 years (8.2%), which is similar to studies based on autopsy (Debakan and Sadowsky, 1978; Miller et al., 1980; Svennerholm et al., 1997) and MRI data (Blatter et al., 1995; Jernigan et al., 2001). This loss is more pronounced in the males than females and in the gray than the white matter compartment. The CSF compartment increased by 75 ml during this span. The difference between the brain loss and CSFV increase is explained by the secular effect discussed above.

The gray-to-white matter ratio GMV/WMV was consistently lower in our study in all three groups (e.g., females in group GEN: 1.062, males: 1.025) compared to published data: Blatter et al. (1995) reported GMV/WMV ratios of 1.11 for females and 1.05 for males, Schlaepfer et al. (1995) found 1.21 resp. 1.16, Peters et al. (1998) 1.21 resp. 1.15, Allen et al. (2003) 1.35 resp. 1.26. We tend to address this effect to the fact that this study was conducted on a 3 T high-field scanner. Image histograms differ significantly from those acquired on conventional 1.5 T scanners. However, the gender- and age-related differences are of similar magnitude in our study compared with data from reference above.

In some reports (Ge et al., 2002; Harris et al., 1994; Miller et al., 1980), a non-linear (quadratic or cubic) relationship between the GMV/WMV ratio and age was suggested. They indicated a relative minimum of this ratio during the 4th decade of life. In our data, a quadratic model offers a statistically significant improvement (adjusted R^2) over a linear model for females (of groups AGE and ALL) only.

Discussion

The present study included a reference population of about 500 healthy subjects aged between 18 and 70 to establish normative data for the size of several head compartments and their ratios as revealed by MRI data of the head. Gender-related differences and changes with age were determined. Compartment volumes were transformed into z scores by simple equations, offering the possibility to relate individual data to a larger population. Analysis procedures applied here do not require user interaction and required about 30 min computation time on a recent PC-type workstation. However, several factors influence our measurements and require a general discussion.

Table 5
Compartment volumes [ml] in young adults: comparison with published data

	Blatter et al. (1995)		Present study	
	Female	Male	Female	Male
ICV	1365 ± 102	1572 ± 92	1495 ± 96	1616 ± 91
BRV	1272 ± 91	1464 ± 94	1304 ± 88	1417 ± 86
GMV	670 ± 106	755 ± 95	668 ± 47	714 ± 48
WMV	602 ± 94	716 ± 98	636 ± 70	703 ± 69
CSFV	97 ± 34	99 ± 34	176 ± 28	184 ± 29

Table 6
Brain volume [ml] in young adults (20–30 years): comparison with published data

	Method	Female	*n*	Male	*n*
Chrzanowska and Beben (1973)	Autopsy	1286 ± –	–	1434 ± –	–
Debakan and Sadowsky (1978)	Autopsy	1283 ± 30	76	1420 ± 20	151
Blatter et al. (1995)	MRI	1365 ± 102	44	1464 ± 94	43
Filipek et al. (1994)	MRI	1325 ± 85	10	1435 ± 116	10
Present Study	MRI	1304 ± 88	145	1417 ± 86	145

Brain weights from autopsy studies were converted into volumes using a specific density of 1.02 g/ml (Miller et al., 1980).

First of all, scanner accuracy in terms of a mapping of the volume of interest onto correct physical dimensions has to be assured, best by phantom measurements. This is typically a part of the regular scanner quality control. However, the material-dependent susceptibility leads to non-linear local distortions in the images that are hard to assess because they are dependent on the actual probe (i.e., the subject under study). A reasonable ground truth could be established by combined CCT/MRI studies and non-linear correction of the MRI data based on suitable skull landmarks detected in the CCT dataset. However, this approach is hard to justify for ethical and economical reasons.

Second, the choice of the scanning protocol has an influence on the signal intensity of the different materials and thus on the mean and variance of the image intensity of the different compartments. Especially, the ratio of the T_1 relaxation times of gray and white matter is higher at 1.5 vs. 3.0 T (Bottomley et al., 1984). Histograms of T_1-weighted MRI data differ significantly when acquired at 1.5 vs. 3.0 T. With our T_1-weighted MDEFT protocol, we find a ratio GMV/WMV that is in the lower range of published data (here, females: 1.062, males: 1.025) but close to data from autopsy studies (1.10, Blinkov and Glezer, 1968).

Third, segmentation errors increase the variance of the measurements presented here. An evaluation of the ICV estimation procedure yielded an error for the IC volume of less than 1.5% (Hentschel and Kruggel, 2004). Phantom-based validation studies (Alfano et al., 1997) found a variance of 2.6–3.2% between phantom volumes and segmented compartments. From retest experiments using a segmentation approach similar to the one applied here, the mean and the variance of the difference between volumes from different scans were 0.4% resp. 1.2% (Lemieux et al., 1999). Thus, in total, the expected error on volume estimation for a given compartment is estimated as less than 4%, which is much less than the natural variance (see Table 1).

Of course, the question arises how much results obtained in our study group are generalizable to a larger population. Subjects included here were randomly selected from the local population if they fulfilled the admission criteria listed above. Results from our sample compare nicely with published data (see Tables 5 and 6). However, employing a different scanner type and protocol will lead to results that are similar in their characteristics, but different in magnitude. In addition to the subgroups described here, we selected random subgroups of 100 subjects from group ALL. Results compared nicely with data from the group ALL, indicating that measurements are stable. Thus, to establish site-dependent normative data, it might be sufficient to include data from 100 suitably chosen subjects.

In addition to the absolute compartment volumes, ratios normalized by the ICV are of special interest. Skull growth occurs along the suture lines and is determined by brain expansion that takes place during the normal growth of the brain. Thus, in healthy young adults, a close relationship between BRV and ICV is expected. The variance of the ratio BRV/ICV is only 2% in our sample (see Table 1). Thus, it may be used to estimate the premorbid brain size in degenerative brain diseases (e.g., Alzheimer's disease, anoxic encephalopathy, microangiopathy) or brain degeneration due to diffuse or focal brain damage (e.g., cerebral infarction or hemorrhage, after tumor removal). We prefer using the ratios GMV/ICV and WMV/ICV over GMV/WMV because estimation errors are much reflected much stronger in the latter quotient. This is supported by the lower variance of the ratios GMV/ICV and WMV/ICV compared with GMV/WMV (see Table 1). Both former ratios aid in a finer description of type of a brain atrophy.

It is well understood that this study presented brain descriptors at a coarse level only. It is useful – and possible – to break down compartments to, e.g., gyral substructures or basal ganglia and to study interhemispheric differences. Parameters for shape and texture will enhance the list of meaningful descriptors for brain structures. The emphasis of this work is providing a route to a patient-based analysis of brain data. Diagnostic and therapeutic decisions in neurobiology and clinical neuroscience are supported by quantitative parameters from single-case neuroimaging data.

Acknowledgments

This work was supported by the Bundesministerium für Bildung und Technology (BMB+F), Interdisziplinäres Zentrum für Klinische Forschung (IZKF) at the University of Leipzig, project C15.

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