



## Effects of spatial transformation on regional brain volume estimates

John S. Allen<sup>a,b,\*</sup>, Joel Bruss<sup>d</sup>, Sonya Mehta<sup>d</sup>, Thomas Grabowski<sup>d,e</sup>, C. Kice Brown<sup>f</sup>, Hanna Damasio<sup>a,c,d</sup>

<sup>a</sup> Dornsife Cognitive Neuroscience Imaging Center, University of Southern California, Los Angeles, CA 90089-2520, USA

<sup>b</sup> Department of Anthropology, University of Southern California, Los Angeles, CA 90089-0032, USA

<sup>c</sup> Brain and Creativity Institute, University of Southern California, Los Angeles, CA 90089-1061, USA

<sup>d</sup> Department of Neurology, Laboratory of Computational Neuroimaging, University of Iowa, Carver College of Medicine, 200 Hawkins Drive Iowa, City, IA 52242, USA

<sup>e</sup> Department of Radiology, University of Iowa, Carver College of Medicine, 200 Hawkins Drive Iowa, City, IA 52242, USA

<sup>f</sup> Lone Tree Biostatistics, LLC 203 West Pioneer Road, Lone Tree, IA 52755-9553, USA

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### ABSTRACT

Spatial transformation of MR brain images is a standard tool used in automated anatomical parcellation and other quantitative and qualitative methods to assess brain tissue volume, composition, and distribution. Despite widespread use, the quantitative effects of spatial transformation on regional brain volume estimates have been little studied. We report on the effects of transformation on regional brain volumes of 38 (17M, 21F) manually parcellated brains. After tracing in native space, regions of interest were transformed using a classic piecewise-linear Talairach transformation (Tal) or a nonlinear registration (AIR 5th order nonlinear algorithm, 158 parameters) to one of three Talairach-based templates: 1) Tal50, constructed from 50 Talairach-transformed normal brains, 2) the MNI 305 atlas, 3) IA38, constructed from MNI305-transformed scans of the 38 subjects used in this study. Native volumes were compared to the transformed volumes. We found that: 1) significant group-level differences can be obtained in transformed data sets that are in the opposite direction of effects obtained in native space; 2) the effects of transformation are heterogeneous across brain regions, even after covarying for total brain volume and age; 3) volumetric intra-class correlations between native and transformed brains differ by registration method and template choice, region, and tissue type; and 4) transformed brains produced hippocampus and corpus callosum volume proportions that were significantly different from those obtained in native space. Our results suggest that region-based volumetric differences uncovered by spatial-transformation-based methods should be replicated in native-space brains, and that meta-analyses should take into account whether volumes are determined using spatially-transformed images and/or specific automated methods.

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### Introduction

Volume is a fundamental property of mammalian brain tissue (Caviness et al., 1999). For decades, comparative anatomists have tried to make sense of brain size differences among species in the contexts of physiology, phylogeny, and function (Jerison, 1973; Striedter, 2005). Within our own species, debates about the importance of the relationship between brain size and cognitive ability extend back to the 19th century (Gould, 1978; Michael, 1988). Such inquiries continue today with investigations, for example, into the relationship between overall brain size (as measured *in vivo* with MRI) and performance on IQ tests (McDaniel, 2005). Global and regional brain volumes are also examined in relation to the expression of various psychiatric and neurological diseases, such as

schizophrenia (Antonova et al., 2004), autism (Lainhart, 2006), and Alzheimer disease (Kantarci and Jack, 2003). Although the precise functional role of increased brain size continues to be debated (Aboitz, 1996), there can be no doubt that brain volumetrics constitutes an important paradigm in contemporary neuroimaging research (Caviness et al., 1999).

Brain volumetric studies using MRI can be influenced by a number of methodological variables. One of the most critical is whether or not spatial transformation or normalization is performed on the data *before* estimates of global or regional volumes are made. Transformation methods are used in the study of regional brain volumes to provide a means to “correct” for overall brain or head size (e.g., Penhune et al., 2003; Collins et al., 1994; Buckner et al., 2004) or to facilitate the automated parcellation of regions of interest (e.g., Nopoulos et al., 2000; Andreasen et al., 1996; Quarantelli et al., 2002). Low-dimensional transformations will account for global brain size differences, but transforms beyond rigid-body and global rescaling parameters are capable of accounting for regional

\* Corresponding author. Dornsife Cognitive Neuroscience Imaging Center, University of Southern California, Los Angeles, CA 90089-2520, USA. Fax: +1 859 887 0912.

E-mail addresses: [jsallen38@aol.com](mailto:jsallen38@aol.com), [jsallen@usc.edu](mailto:jsallen@usc.edu) (J.S. Allen).

differences as well. While transformation approaches can be expected to produce reliable results, the nature and extent of volumetric distortion inherent in these results is rarely quantified or even addressed. Spatial transformation is also an essential component of tissue-density-based statistical techniques, such as voxel-based morphometry (Ashburner and Friston, 2000) and other tissue-based assessment tools (Mega et al., 2005). Lastly, group-level functional neuroimaging analyses rely on spatial normalization (Fox et al., 1985; Mazziota et al., 2000; Kochunov et al., 2002).

Since manual tracing of MR images requires anatomical expertise and a considerable investment of labor, the development of automated volumetric methods has been a priority. MRI volumes determined by automated methods are generally validated against volumes determined by manual tracing — the “gold standard.” The necessity for such validation studies arises because spatial normalization and co-registration inevitably alter brain anatomy. This alteration can occur at two levels: first, anatomical structures may not be colocalized correctly in transformed brains (imperfect registration described by Bookstein, 2001; see also Uylings et al., 2005); second, the volume or shape of regions of interest may become significantly distorted, potentially leading to erroneous interpretations of neuroanatomical findings. Colocalization errors (or biases) and shape distortions are distinct but often interrelated factors affecting the performance of tools for the automated assessment of brain tissue.

Several methods of comparing manual and automated measures have been suggested: percent overlap and percent volume difference between automated and manual tracings (Collins et al., 1995; Iosifescu et al., 1997; Fischl et al., 2002); comparing automated versus traced volume means within a subject group (Andreasen et al., 1996; Quarantelli et al., 2002); measures of sensitivity (proportion of automated region included in manual region) and specificity (proportion of automated tracing properly excluded from the region based on the manual tracing) (Andreasen et al., 1996; Quarantelli et al., 2002); Pearson correlations between automated and manual measures (Iosifescu et al., 1997); ability of the automated methods to reproduce well-established results derived from manual volumetry, e.g., to detect age-related changes in brain anatomy (Dade et al., 2004).

Image analysis in automated volumetry typically begins with atlas-based spatial transformation of the native MR brain dataset. The methods of Andreasen et al. (1996), Kates et al. (1999), and Quarantelli et al. (2002) incorporate classic piecewise-linear Talairach transformations (Talairach and Tournoux, 1988), while Dade et al. (2004) make use of a proportional Talairach transformation based on each individual subject's AC-PC aligned image.

Alternatively, intensity-based registration methods can be used to transform brain volumes to a standard template space. Transformation to a single-brain-based atlas potentially preserves the resolution of the neuroimaging technology; however, this is at the cost of incorporating the idiosyncrasies of the target brain (Fischl et al., 2002). Spatial transformation using a probabilistic brain atlas derived from an appropriate population of brains produces a more generalized registration template. The Montreal Neurological Institute (MNI) template created from more than 300 brain image volumes is the most widely used of these atlases (Collins et al., 1994). Such probabilistic brain atlases can be used in combination with linear and higher-order nonlinear

warps to coregister MR volumes for automated volumetry (Fischl et al., 2002; Mega et al., 2005).

In this study, we examined the effects of spatial transformation on regional brain volumes and gray matter/white matter ratios, focusing particularly on the effects of transformation in the assessment of group (in this case, male vs. female) differences in brain volume. The regions we assessed include the cerebral hemispheres, frontal lobe, parietal lobe, temporal lobe, occipital lobe, cingulate gyrus, insula, hippocampus, and corpus callosum. Regions of interest (ROI) were previously manually traced on high resolution MRI scans in native space, and gray and white matter volumes for each region were determined (Allen et al., 2002, 2003, 2006). Subsequently, the ROIs and tissue segmentation images were spatially normalized using four different approaches: 1) a classic piecewise-linear Talairach transformation (Tal); 2) applying the deformation field obtained by nonlinear registration of brain scans to a Talairach-compatible atlas generated by iterative 5th order nonlinear warping of 50 normal (Talairach-transformed) brains (Tal50); 3) transformation to the MNI atlas (MNI305); and 4) transformation to an atlas constructed from MNI305-transformed scans of the 38 subjects used in this study (IA38). This final transformation method is similar to those often employed in VBM studies, in which an atlas is constructed from the subject groups of interest (Good et al., 2001a; Senjem et al., 2005). Following each transformation, the volume of gray and white matter in each region was recalculated. The results of this study therefore primarily address the issue of ROI volumetric distortion during transformation, not the issue of errors in colocalization.

Protocols similar to ours have been used by investigators interested in validating automated volumetric (e.g., Andreasen et al., 1996) or tissue density assessment methods (e.g., Ashburner and Friston, 2000, 2001; Good et al., 2001a,b; Mega et al., 2005). Naturally, in these validation studies, the results that indicated a strong level of agreement between the gold standard of manual tracing and automated processing were emphasized (however, see Kennedy et al., 2008). We take a somewhat different perspective, in that we are interested in more fully exploring the ramifications of spatial transformation in the assessment of regional brain volumes, without the *a priori* goal of validating a transformation-based automated method. We will therefore tend to emphasize the differences that arise due to spatial transformation, rather than focus on the fact that considerable amounts of information about individual brain structure are clearly maintained following spatial transformation. Our goal in evaluating the effects of spatial transformation is to broaden the interpretive neuroanatomical framework for assessing results from automated approaches and to enable better integration of results from automated and manual-based brain volumetric studies.

## Methods

### Subjects

Subjects were 17 men (mean age=31.7, SD=9.6, range 22–49) and 21 women (mean age=33.0 years, SD=7.3, range 23–47). All were right-handed (scores on the Oldfield–Geschwind Handedness Inventory greater than +90) with no left-handedness in first-degree relatives, healthy, and with no history of neurological or psychiatric illness. All gave informed consent in accordance with institutional and federal rules.

### Image acquisition

Thin cut MR images were obtained on a 1.5 T GE Signa scanner, using the following protocol: SPGR/50, TR 24, TE 7, NEX 1 matrix 256 X 192, FOV 24 cm. We obtained 124 contiguous coronal slices, with an interpixel distance 0.94 mm and slice thickness of 1.5 or 1.6 mm. The slice thickness was adjusted to the size of the brain so as to sample the entire brain, while avoiding wrap artifacts. For each subject, three individual 1NEX SPGR brain scans were obtained. These scans were coregistered and averaged post hoc using Automated Image Registration (AIR 3.03, UCLA, Woods et al., 1992), to produce a single dataset of enhanced quality with voxel dimensions of 0.7 mm in plane and 1.5–1.6 mm through plane (Holmes et al., 1998).

Volumetric analysis of the brains was accomplished using Brainvox (Damasio and Frank, 1992; Frank et al., 1997), an interactive family of programs designed to reconstruct, parcellate, and measure brains from MR acquired images. An automated program, extensively validated against human experts (Grabowski et al., 2000), was used to segment the images into white matter, gray matter, and CSF. Before tracing ROIs, brains were reoriented (but *not* resized) along a horizontal plane, perpendicular to the hemispheric fissure, running through the anterior and posterior commissures (i.e., the AC-PC line); this ensured that coronal slices in all subjects are perpendicular to a uniformly and anatomically defined axis of the brain.

### Manual tracing of regions of interest

Regions of interest were traced by hand on contiguous coronal slices of the brain. Anatomical landmarks to guide parcellation were identified and marked on the surface of 3D reconstructions. The parcellation of the brain was based on a scheme modified from Rademacher et al. (1992), with additional consultation of several anatomical texts (Ono et al., 1990; Duvernoy, 1991; Damasio 2005). Parcellation of the hemispheres, frontal lobe, parietal lobe, temporal lobe, occipital lobe, cingulate gyrus, insula, and corpus callosum are described in detail in Allen et al. (2002, 2003) and Damasio (2005). Note that basal gray matter structures are included in the frontal and parietal lobe ROIs; basal gray volumes were excluded from these ROIs in Allen et al. (2002, 2003). A description of the parcellation of the hippocampus can be found in Allen et al. (2005). Volume determinations from ROIs were made using image analysis programs developed in our laboratory (Frank et al., 1997).

### Piecewise-linear Tal transformation

MR images were reconstructed in three dimensions using Brainvox. Extracerebral voxels were edited away manually. The (piecewise-linear) Talairach transformation was implemented using Brainvox. The user selected three points: the anterior and posterior commissures and a single point in the midline of the brain. An automated planar search routine computed the Talairach bounding box by scanning volume slices taken perpendicular to the Talairach axes for voxels with opacities above a user-defined threshold. The accuracy of the bounding box was confirmed by visual inspection. The brain image was then resampled into the 1988 Talairach atlas space (Talairach and Tournoux, 1988) in accordance

with the original definition, with two scaling factors each along the right-left and top-bottom axis and three scaling factors along the anterior-posterior axis.

### Tal50 transformation

We created the Tal50 brain template as follows. We used fifty brains representative of those used in this study, obtained on the same scanner using the same pulse sequence. We began by piecewise-linear Talairach transformation of these 50 brain volumes, and then averaged them. Next, the individual native-space brains were aligned to this 50-brain average using a 12-parameter affine model, and the resulting transformation parameters used to initialize a 5th order polynomial nonlinear warp (158 parameters) of each native-space brain to the 50-brain average. This registration was based on an intensity matching algorithm that uses a least squares cost function. These 50 transformed brains were then averaged. Another iteration of nonlinear warping individual brains to this new average was then performed (cf. Woods et al., 1999), followed by averaging of the transformed brains to produce the final Tal50 template.

We registered each of the 38 brains used in this study to the Tal50 template using the aforementioned 5th order polynomial nonlinear warp (158 parameters) supported by AIR 3.03.

### MNI305 transformation

We registered each of the 38 brains used in this study to the MNI305 template using the 5th order polynomial nonlinear warp (158 parameters) supported by AIR 3.03, analogous to the procedure used to perform the Tal50 transform.

### IA38 transformation

Finally, we created a study-specific atlas based on the MNI305 space as follows. The 38 brains used in this study were individually aligned to the MNI305 template using procedures parallel to those described in the Tal50 transformation section, i.e. nonlinear registration followed by averaging the 38 transformed brains, and then another iteration of nonlinear warping to the 38 brain average.

### Spatial transformation of ROIs

Bitmaps derived from manually-traced ROIs (as well as gray and white matter segmented volumes) were transformed separately into Tal, Tal50, MNI305, or IA38 space, using transformation scaling factors (Tal) or parameters (Tal50, MNI305, IA38) derived from the transformation of the whole brain images. Nearest-neighbor interpolation was used. Transformed gray and white matter volumes were then recalculated for each ROI, and these volumes were compared to the native-space volumes. We visually inspected the transformed ROIs to verify that they maintained their proper anatomical positions in the transformed brains.

### Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 9.0.0) and SAS (version 8.0). Independent samples *t*-tests, pairwise *t*-tests, and univariate ANCOVA

(with total volume as a covariate) were used to compare group (i.e., males versus females) means within native and transformed datasets. A mixed-model analysis of covariance (ANCOVA), with sex as an among-subject factor and registration template choice (native, Tal Tal50, MNI305, and IA38) as a within-subject factor, was used to assess the effect of transformation on ROI mean differences. The covariables used in the ANCOVA were age and total native-space volume (i.e., gray and white matter volumes summed) (Table 3). Expected individual deviations for ROIs from native to each transformed volume were calculated by taking the square root of the mean square error between the two groups (Tables 4a, b). A “proportional accuracy” (referred to as “percent accuracy” by Mega et al. 2005) measure was also used to quantify volumetric differences between native and transformed ROIs. This measure was calculated with the following equation:  $1 - (|native\ vol. - transformed\ vol. / native\ vol.)$  (Tables 5a, b). We use intra-class correlation coefficients (ICC), with 95% confidence intervals calculated according to Snedecor and Cochran (1980; equivalent to Shrout and Fleiss, (1979) ICC [1, 1]), to assess the intensity of agreement between individual native and transformed ROI measures (Tables 6a, b) (rather than using the Pearson correlation coefficient). The Pearson correlation coefficient is an index of the direction and degree of the linear relationship between a measurement pair and indicates nothing concerning agreement per se between the two measurements. The closer a Pearson correlation coefficient is to 1.0 the closer the

association is to a straight line; the closer an ICC is to 1.0 the closer the agreement is to complete.

## Results

Native and transformed volumes (gray and white matter) for each subject are presented in Appendix Tables A–G.

### Mean group differences

In Table 1, the mean gray and white matter, native and transformed, volumes for each ROI are presented by sex and hemisphere. Note that the mean volumes for the MNI305 and IA38 transformed brains are consistently larger than those for the native, Tal, or Tal50 transforms. (The larger observed size in the MNI305 [and thus IA38] is well-known, and relates to the method of construction of the MNI template [Louis Collins thesis and personal communication; see also <http://imaging.mrc-cbu.cam.ac.uk/imaging/Cbulmaging>, A. C. Evans and D. L. Collins and S. R. Mills and E. D. Brown and R. L. Kelly and T. M. Peters, “3D statistical neuroanatomical models from 305 MRI volumes,” Proc. IEEE-Nuclear Science Symposium and Medical Imaging Conference, 1813–1817, 1993].

In Table 2, the results of *t*-tests assessing volume differences between the sexes are presented. As expected, in native space, male brains are consistently significantly larger than female brains for almost every region and for both gray and white matter. After transformation, for either the Tal or Tal50

**Table 1**  
Native, Tal, and Tal50 volumes by region, sex, tissue type, and hemisphere

Region	Sex	Native volume		Tal volume		Tal50 volume		MNI305 volume		IA38 volume		
		Gray	White	Gray	White	Gray	White	Gray	White	Gray	White	
Cerebral hemisphere	M	Left	328.7 (7.1)	252.9 (7.8)	295.9 (3.7)	225.6 (3.3)	302.7 (4.0)	244.9 (3.4)	348.4 (5.5)	326.7 (4.6)	357.7 (5.2)	346.8 (4.3)
		Right	329.7 (7.8)	251.5 (7.3)	295.6 (4.4)	226.1 (3.1)	298.6 (3.9)	242.0 (3.3)	354.8 (5.5)	326.9 (4.8)	365.5 (5.4)	352.9 (4.3)
	F	Left	292.8 (7.1)	206.6 (4.1)	304.3 (3.0)	219.0 (2.7)	310.3 (2.5)	238.6 (2.4)	358.0 (3.3)	316.5 (3.5)	367.4 (3.2)	336.9 (3.5)
		Right	292.6 (5.9)	209.2 (4.5)	307.9 (3.5)	219.5 (2.8)	311.1 (2.5)	236.4 (2.2)	369.1 (3.1)	319.1 (2.9)	379.2 (3.1)	344.1 (2.9)
Frontal lobe	M	Left	114.3 (3.0)	104.2 (3.7)	104.8 (1.6)	94.4 (1.9)	105.3 (1.7)	102.9 (1.8)	142.7 (2.7)	143.8 (2.5)	145.5 (2.4)	152.5 (2.4)
		Right	113.9 (2.9)	106.0 (3.6)	104.3 (1.8)	96.2 (1.6)	102.8 (1.7)	103.2 (1.5)	141.7 (2.7)	144.5 (2.2)	146.2 (2.6)	146.4 (1.3)
	F	Left	101.6 (1.8)	86.7 (1.8)	106.9 (1.4)	90.6 (1.1)	107.4 (1.3)	99.0 (0.9)	145.0 (1.8)	137.9 (1.2)	149.0 (1.9)	154.8 (2.1)
		Right	100.5 (2.7)	90.0 (2.0)	107.3 (1.4)	94.0 (1.5)	106.2 (1.1)	101.5 (1.0)	147.9 (1.7)	141.9 (1.4)	151.3 (1.7)	152.0 (1.4)
Parietal lobe	M	Left	68.2 (1.9)	73.8 (2.1)	62.3 (1.6)	66.6 (1.5)	61.9 (1.7)	73.5 (1.7)	79.3 (2.2)	101.2 (2.6)	81.1 (2.1)	107.1 (2.3)
		Right	68.1 (1.5)	75.2 (1.8)	61.4 (1.3)	67.0 (1.2)	60.3 (1.3)	73.1 (1.5)	82.3 (1.8)	101.6 (2.2)	83.8 (1.8)	110.4 (2.2)
	F	Left	59.8 (1.3)	60.3 (1.6)	64.4 (1.2)	64.1 (1.4)	64.0 (1.0)	71.7 (1.4)	83.1 (1.3)	97.8 (2.1)	84.3 (1.1)	104.1 (2.2)
		Right	62.6 (1.6)	62.6 (1.9)	66.2 (1.5)	65.4 (1.4)	64.8 (1.1)	72.2 (1.3)	89.1 (1.9)	99.8 (2.0)	90.2 (1.7)	108.6 (2.1)
Temporal lobe	M	Left	77.6 (2.2)	45.2 (2.6)	68.5 (1.5)	39.0 (1.2)	69.2 (1.4)	40.9 (1.3)	94.3 (1.9)	57.9 (1.7)	99.0 (1.9)	63.8 (1.9)
		Right	78.6 (2.6)	44.9 (2.0)	69.0 (1.7)	39.6 (1.1)	69.1 (1.3)	41.0 (1.0)	96.6 (1.8)	59.0 (1.4)	101.4 (1.8)	65.7 (1.6)
	F	Left	66.0 (1.3)	35.9 (0.7)	69.5 (1.3)	38.6 (0.7)	69.9 (1.0)	40.8 (0.7)	95.0 (1.4)	57.3 (1.0)	99.5 (1.4)	62.8 (1.0)
		Right	66.0 (1.1)	35.7 (0.8)	68.9 (1.1)	37.7 (0.9)	68.5 (0.9)	38.9 (0.9)	96.4 (1.2)	56.5 (1.3)	101.4 (1.2)	62.5 (1.4)
Occipital lobe	M	Left	28.7 (1.1)	21.8 (1.9)	26.6 (0.9)	19.1 (0.7)	26.9 (0.6)	19.4 (0.7)	33.0 (1.1)	23.8 (0.8)	32.3 (1.1)	23.3 (0.8)
		Right	30.0 (0.8)	18.8 (0.9)	28.0 (0.8)	17.9 (0.9)	27.9 (0.8)	17.9 (0.9)	34.2 (0.9)	21.8 (1.0)	34.1 (1.0)	22.1 (1.2)
	F	Left	26.5 (1.0)	17.2 (0.8)	29.2 (0.9)	19.4 (0.8)	28.1 (0.7)	19.1 (0.7)	34.9 (1.0)	23.5 (0.8)	34.5 (1.0)	23.7 (0.9)
		Right	27.5 (1.0)	15.4 (0.8)	30.1 (0.9)	17.2 (0.8)	29.5 (0.7)	17.0 (0.6)	36.7 (0.9)	21.0 (0.8)	36.3 (0.8)	21.0 (0.8)
Cingulate gyrus	M	Left	15.4 (0.6)	7.1 (0.3)	13.6 (0.5)	5.9 (0.2)	16.6 (0.5)	7.4 (0.3)	22.9 (0.8)	10.2 (0.4)	25.0 (0.8)	11.0 (0.4)
		Right	14.4 (0.6)	5.0 (0.2)	12.4 (0.5)	4.2 (0.1)	15.5 (0.6)	5.3 (0.2)	21.3 (0.8)	7.3 (0.3)	23.3 (0.8)	8.0 (0.3)
	F	Left	13.4 (0.6)	5.9 (0.2)	13.5 (0.6)	6.0 (0.2)	16.9 (0.6)	7.4 (0.2)	23.1 (0.9)	10.1 (0.4)	25.3 (1.0)	11.0 (0.4)
		Right	14.1 (0.5)	4.3 (0.2)	14.2 (0.6)	4.2 (0.2)	17.8 (0.6)	5.4 (0.2)	24.3 (0.8)	7.3 (0.3)	26.7 (0.9)	8.0 (0.3)
Insula	M	Left	8.2 (0.2)	0.8 (0.06)	6.7 (0.1)	0.6 (0.05)	8.0 (0.2)	0.8 (0.06)	11.9 (0.3)	1.1 (0.09)	13.5 (0.3)	1.2 (0.10)
		Right	8.2 (0.2)	1.5 (0.09)	6.7 (0.2)	1.1 (0.06)	7.8 (0.2)	1.5 (0.07)	11.5 (0.2)	2.1 (0.11)	13.2 (0.3)	2.4 (0.10)
	F	Left	7.0 (0.1)	0.6 (0.03)	6.7 (0.1)	0.5 (0.03)	8.0 (0.1)	0.7 (0.04)	11.8 (0.2)	1.0 (0.06)	13.5 (0.2)	1.1 (0.06)
		Right	7.0 (0.1)	1.2 (0.04)	6.7 (0.1)	1.1 (0.04)	7.8 (0.1)	1.4 (0.05)	11.5 (0.2)	2.0 (0.07)	13.1 (0.2)	2.2 (0.08)
Hippocampus	M	Left	3.5 (0.11)		2.7 (0.09)		3.1 (0.09)		5.0 (0.15)		5.1 (0.16)	
		Right	3.8 (0.12)		2.8 (0.10)		3.3 (0.11)		4.8 (0.17)		5.2 (0.18)	
	F	Left	3.2 (0.09)		2.9 (0.07)		3.4 (0.07)		5.0 (0.12)		5.5 (0.11)	
		Right	3.5 (0.09)		3.1 (0.07)		3.5 (0.08)		5.2 (0.13)		5.7 (0.13)	
Corpus callosum	M											
				10.7 (0.4)		9.0 (0.3)		10.7 (0.4)		14.3 (0.7)		14.2 (0.6)
	F											
				9.2 (0.3)		9.0 (0.2)		10.9 (0.3)		14.9 (0.5)		14.9 (0.5)

All measures in cubic centimeters (standard error).

**Table 2**  
Results of *t*-tests comparing male and female native and transformed regional volume means

Region		Native Volume				Transformed Sample Means							
		Sample means		Adjusted means		Tal volume		Tal50 volume		MNI305 volume		IA38 volume	
		Gray	White	Gray	White	Gray	White	Gray	White	Gray	White	Gray	White
Cerebral hemisphere	Left	m > f**	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Right	m > f**	m > f**	ns	ns	f > m*	ns	f > m*	ns	f > m*	ns	f > m*	ns
Frontal lobe	Left	m > f**	m > f**	ns	ns	ns	ns	ns	ns	ns	m > f*	ns	m > f*
	Right	m > f**	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Parietal lobe	Left	m > f**	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	f > m*	ns
	Right	m > f*	m > f*	ns	ns	f > m	ns	f > m*	ns	f > m*	ns	f > m*	ns
Temporal lobe	Left	m > f**	m > f**	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Right	m > f**	ns	m > f*	ns	ns	ns	ns	ns	ns	ns	ns	ns
Occipital lobe	Left	ns	m > f*	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Right	ns	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Cingulate gyrus	Left	m > f*	m > f**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Right	ns	m > f**	f > m*	ns	f > m*	ns	f > m**	ns	f > m*	ns	f > m**	ns
Insula	Left	m > f**	m > f*	m > f*	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Right	m > f**	m > f**	m > f*	ns	ns	ns	ns	ns	ns	ns	ns	ns
Hippocampus	Left	m > f*		ns		f > m*		F > m*		ns		ns	
	Right	m > f*		ns		ns		ns		f > m*		ns	
Corpus callosum			m > f**		ns		ns		ns		ns		ns

Sample means as reported in Table 1.

Native volume adjusted means derived from ANCOVA using the appropriate hemispheric total gray or white matter volume (total tissue volume was used as covariate for cerebral hemisphere volumes). m, male; f, female; ns, not significant. (*t*-test, \**p* < 0.05; \*\**p* < 0.01).

transforms, there are no significant differences between the sexes for white matter volume. However, for several ROIs, gray matter volumes are significantly larger in females than males after transformation by either method. For example, after Tal transformation, the male means for gray matter cerebral hemisphere volumes decline by about 30 cm<sup>3</sup> – to about the size of the female native means – while the transformed female means increase by about 15 cm<sup>3</sup>, resulting in an inversion of the result obtained in native space. Similar patterns are obtained for the MNI305 and IA38 transformations. For the most part, white matter sex differences are eliminated, but for several gray matter regions, female means are significantly larger than male means. In general, the results in Table 2 indicate that transformation can affect the significance of group difference in volume depending on region and tissue type.

It is reasonable to suppose that regional native volume differences between the sexes are largely a function of an overall difference in brain volume. To test this, a univariate ANCOVA analysis (with either gray or white matter of the hemisphere or cerebrum as covariate) of the native-space ROIs was undertaken to assess male–female differences after correcting for overall brain size (“adjusted means” in Table 2). As expected, many of the group-level differences are attenuated. For the white matter in general, significant differences are eliminated in native brains after correcting for size, which matches the results obtained for the transformed brains. For the gray matter, the native adjusted mean for the right cingulate gyrus shows that females are larger than males, a result that is also seen in all the transformed brains. In native space, the right cingulate gyrus gray matter volumes in males and females are approximately equal; it is not surprising therefore that after correcting for overall volume, the female volume is significantly larger. For this region, transformation appears to provide a size correction that is equivalent to a statistically size-corrected native-space result. However, for several gray matter regions, there is no match between the native adjusted means and the transformed means. The adjusted native means for the gray matter of the temporal

lobe and insula still show that males have greater volumes than females; no similar results were obtained in any of the transformed brains. In addition, there were several gray matter regions in the transformed brains in which females were greater than males; these were not matched in the adjusted native-space volumes.

A mixed-model ANCOVA analysis was undertaken to examine the regional effects of transformation while covarying for total native cerebrum volume and age (in the age range of this subject group, age will be a modest contributor to the total observed variation in brain size; see Allen et al. 2005). A summary of the ANCOVA results for the regional gray and white matter volumes is presented in Table 3. A significant effect of transformation method can be seen in the cerebral hemispheres, frontal, parietal, and temporal lobes, the insula, and cingulate gyrus; in other words, transformation method introduces significant variation to regional brain volumes even after covarying for age and total volume. It is equally important to note that there are several regions in which transformation does not produce significant differences in volume. These results highlight again the different effects that transformation can have on different regions of the brain. The “method by sex interaction” results indicate that in several regions male and female brains are affected differently by the transformation. The “method by age” interaction demonstrates that for a few regions – most notably the frontal lobe – the different transformation methods produce significantly different relationships between age and regional brain volume.

*Expected deviations from native volumes*

Expected deviations at the individual level of the transformed volumes from the native volume are presented in Table 4a. These are derived from the within-subject mean square error differences between the transformed and native volumes. Two patterns are immediately apparent. First, the Tal-based transformations have substantially smaller expected deviations from native volume than the MNI-based transforms, suggesting that the 1988 atlas brain is closer to the

mean normal brain size than the MNI template. Second, the difference between the two is relatively less pronounced in the occipital lobe compared to the other structures.

Expected deviations for the gray matter/white matter (G/W) ratio are presented in Table 4b. Again, the MNI-based transforms tend to have larger deviations, although the pattern is not as strong as for the volume difference. In general, the Tal transform has the lowest deviation for G/W ratio, with the exception of the insula. For the MNI-based transform, the occipital lobe again has a relatively low deviation compared to the other major lobes and the cerebral hemispheres as a whole.

### Proportional accuracy

Proportional accuracy statistics are presented in Tables 5a, b. Absolute differences between native and Tal-transformed brains tend to fall in the 10–20% range, without any systematic difference in proportional accuracy between the Tal or Tal50 transformation (Table 5a). Compared to the Tal-transformed values, proportional accuracy means for the MNI-transformed brains show substantially greater differences with the native values (Table 5b), and some of the scores (such as for the cingulate gyrus and insula) are very low (<0.5). Proportional accuracy scores for the MNI305 and IA38 are roughly similar, although the IA38 values are uniformly somewhat lower. The proportional accuracy scores by region are more variable in the MNI-transformed brains compared to the Tal-transformed brains. In addition, the MNI-transformed brains show greater variation between gray and white matter proportional accuracy.

The Tal and MNI proportional accuracy scores indicate substantial differences in the treatment of the male and female subject groups (i.e., for two groups known to have a mean difference in size). For the Tal transformations, the proportional accuracy is essentially the same for males and females. The only somewhat anomalous pattern is seen in the cingulate gyrus. For the Tal transformation, the proportional accuracy is significantly higher for females than males, while in the Tal50 transformation, it is significantly higher for the men. The male proportional accuracy score stays about the

same for both transformations; however, the female accuracy score is significantly lower for Tal50 than for Tal (pairwise *t*-test,  $p < .0001$ ), producing the conflicting results. For the MNI-transformed brains, the male proportional accuracy scores are significantly higher than the female scores for every region and tissue.

### Intra-class correlations and gray/white ratio

Intra-class correlation coefficients between the native and transformed volumetric measures and gray matter / white matter ratio are presented in Tables 6a, b. For the Tal-transformed brains, the volumetric ICCs vary substantially by region and tissue. For both the Tal and Tal50 transforms, the occipital lobe measures are strongly correlated to the native measures. The other regions range from moderately correlated to essentially uncorrelated, again with the results varying according to transformation method, tissue type, and gender (i.e., group membership).

In contrast to the volumetric measures, the Tal-transformed G/W ratio ICCs are almost uniformly high. The only exceptions are for the frontal lobe and parietal lobe native-Tal50 ICCs: even where these correlations are significant, they are not particularly strong.

The ICCs for the MNI-transformed brains present an entirely different picture. Nearly all of the volumetric ICCs, for both MNI305 and IA38, are negative, and in many cases significantly so. The G/W ratio ICCs are generally much lower than for the Tal-transformed brains, with the exception of the occipital lobe, cingulate gyrus, and insula, where the ICCs are quite high (>0.8) and statistically significant.

### Hippocampus and corpus callosum proportion

Spatial transformations based on global brain landmarks may cause disproportionate changes in different, especially smaller, regions of the brain. We examined this issue by looking at the ratios of hippocampus volume/total gray matter volume and corpus callosum volume/total white matter volume in native and transformed brains.

**Table 3**  
Mixed-model ANCOVA results for regional volume by hemisphere with “sex” as an among-subject factor and transformation template (native, Tal, Tal50, MNI305, or IA38) as a within-subject factor

Region		Method effect		Method by sex interaction		Method by age interaction	
		Gray	White	Gray	White	Gray	White
Cerebral hemisphere	Left	<0.001 (7.73)	0.001 (4.85)	<0.001 (7.51)	0.004 (4.12)	<0.001 (4.38)	0.003 (2.69)
	Right	<0.001 (6.16)	<0.001 (7.67)	<0.001 (7.16)	0.002 (4.60)	<0.001 (3.81)	<0.001 (4.02)
Frontal lobe	Left	<0.001 (7.18)	0.002 (4.47)	0.009 (3.54)	ns (1.70)	<0.001 (4.06)	0.022 (2.08)
	Right	0.001 (4.73)	<0.001 (5.91)	0.008 (3.62)	0.041 (2.57)	<0.001 (3.24)	0.002 (2.86)
Parietal lobe	Left	ns (1.00)	ns (1.10)	0.048 (2.47)	ns (1.60)	ns (0.74)	ns (0.95)
	Right	ns (1.36)	0.020 (3.02)	ns (2.43)	ns (1.39)	ns (1.00)	ns (1.61)
Temporal lobe	Left	0.021 (3.00)	ns (1.09)	0.014 (3.24)	ns (1.56)	0.039 (1.91)	ns (0.69)
	Right	0.016 (3.18)	ns (1.22)	0.006 (3.78)	ns (1.35)	ns (1.75)	ns (0.70)
Occipital lobe	Left	ns (0.82)	ns (0.54)	ns (1.02)	ns (0.80)	ns (0.38)	ns (0.30)
	Right	ns (0.76)	ns (0.30)	ns (1.42)	ns (0.43)	ns (0.40)	ns (0.19)
Cingulate gyrus	Left	ns (0.51)	ns (1.06)	ns (0.22)	ns (0.41)	ns (0.61)	ns (0.88)
	Right	0.038 (2.62)	0.047 (2.62)	ns (1.07)	ns (0.37)	ns (1.16)	ns (1.22)
Insula	Left	0.011 (3.42)	ns (0.37)	ns (1.32)	ns (0.10)	ns (1.48)	ns (0.20)
	Right	0.009 (3.53)	ns (0.67)	ns (1.67)	ns (0.26)	ns (1.59)	ns (0.35)
Hippocampus	Left	ns (1.03)		ns (1.57)		ns (0.69)	
	Right	ns (1.18)		ns (1.46)		ns (0.69)	
Corpus callosum			ns (1.40)		ns (0.78)		ns (0.71)

Covariables were age and native total brain volume (gray plus white matter); *p* values are provided when significant, “ns” when not significant; *F* values are provided for all regions in parentheses.

**Table 4a**  
Expected deviations from native volumes (in cubic millimeters)

Region			Tal		Tal50		MNI305		IA38	
			Gray	White	Gray	White	Gray	White	Gray	White
Cerebral hemisphere	Males	Left	±26857	±22975	±25746	±16479	±46486	±62638	±52711	±76016
		Right	±27816	±24478	±27981	±19573	±49451	±61056	±56457	±78593
	Females	Left	±17120	±13510	±17678	±24051	±75269	±83092	±81694	±97410
		Right	±19909	±14305	±18105	±21269	±81365	±82279	±88416	±99864
Frontal lobe	Males	Left	±10808	±19596	±9969	±7441	±21076	±29025	±23585	±34749
		Right	±10604	±10705	±10899	±8488	±21485	±28500	±24476	±35348
	Females	Left	±6822	±5634	±7412	±10045	±31626	±36559	±34367	±42527
		Right	±9876	±6437	±9247	±9548	±34111	±37049	±37086	±44157
Parietal lobe	Males	Left	±6017	±7087	±6154	±5267	±8861	±20450	±10089	±24252
		Right	±6586	±7886	±6615	±6283	±10904	±20093	±12021	±26066
	Females	Left	±4918	±4673	±4498	±8790	±16879	±26910	±17713	±31331
		Right	±4687	±4447	±3959	±7684	±19319	±26588	±19945	±32744
Occipital lobe	Males	Left	±8253	±4246	±7806	±3199	±13154	±10545	±16084	±14647
		Right	±8760	±4948	±8518	±4255	±13865	±10329	±16918	±14907
	Females	Left	±4651	±2874	±5139	±4317	±21143	±15474	±24205	±19286
		Right	±4505	±2637	±4417	±3328	±21968	±14999	±25491	±19282
Cingulate gyrus	Males	Left	±2309	±1447	±2551	±1585	±3928	±3073	±3720	±2919
		Right	±2266	±1273	±2457	±1426	±3692	±2575	±3758	±2873
	Females	Left	±2158	±1665	±1736	±1566	±6058	±4544	±5779	±4636
		Right	±2327	±1485	±2154	±1395	±6686	±4030	±6443	±4066
Insula	Males	Left	±1745	±964	±1618	±726	±5733	±2516	±7033	±2943
		Right	±1742	±633	±1581	±569	±5351	±1838	±6577	±2185
	Females	Left	±716	±307	±2612	±1160	±7034	±3057	±8595	±3617
		Right	±794	±242	±2787	±829	±7343	±2175	±9058	±2656
Hippocampus	Males	Left	±1213	±139	±584	±47	±2741	±277	±3852	±364
		Right	±1170	±296	±709	±142	±2499	±445	±3616	±607
	Females	Left	±491	±62	±779	±70	±3393	±305	±4597	±391
		Right	±481	±133	±689	±125	±3215	±559	±4372	±717
Corpus callosum	Males		±1420		±1190		±3142		±2882	
	Females		±546		±1379		±4209		±4116	

In the native brains, the hippocampus proportion (for males and females combined) is 1.19% (s.d. 0.11); in Tal brains, the proportion 0.97% (s.d. 0.10); in Tal50 brains, the proportion is 1.16% (s.d. 0.12); in MNI305 brains, the proportion is 1.25% (s.d. 0.15); in IA38 brains, it is 1.33% (s.d. 0.15). Pairwise *t*-tests indicate that compared to the native proportion, the hippocampus proportions are significantly smaller for both Tal ( $p < 0.001$ ) and Tal50 brains ( $p < 0.001$ ). In contrast, for both MNI305 and IA38, the proportions are significantly larger ( $p < 0.001$ ). Although the overall mean hippocampal proportional size in the native and Tal50 brains is not that different, it is larger in native brains in 29 of the 38 subjects, indicating a systematic trend towards decreased proportional hippocampal size in the transformed brains; this trend is even more apparent in the Tal brains, where the proportional size of the hippocampus is smaller in every subject. Of the MNI305 proportions, 33 of 38 are larger than in the native space, as are all but one of the IA38 proportions.

A different pattern was observed for the corpus callosum proportion. The corpus callosum proportion for the native brains (males and females combined) is 2.17% (s.d. 0.22); for Tal brains, it is 1.97% (s.d. 0.25); for Tal50, 2.24% (s.d. 0.30); for MNI305 brains, it is 2.21% (s.d. 0.36); and for IA38 brains, 2.05% (s.d. 0.29). Pairwise *t*-tests indicate that the difference between the native and the Tal proportion is significant ( $p < 0.001$ ), as is the difference between the native and Tal50 proportions ( $p = 0.014$ ). It is important to note, however, that the two Tal transformations produced proportional changes in the opposite direction. Compared to native corpus callosum proportion, the Tal proportion was lower in every

subject, while for the Tal50 brains, the proportion was higher in 28 of 38 subjects. The native and MNI305 corpus callosum proportions are not significantly different. The IA38

**Table 4b**  
Expected deviations from native gray:white volumes ratios

Region			Tal	Tal50	MNI305	IA38
Cerebral hemisphere	Males	Left	±0.007	±0.066	±0.099	±0.120
		Right	±0.007	±0.064	±0.079	±0.111
	Females	Left	±0.008	±0.072	±0.100	±0.128
		Right	±0.026	±0.069	±0.082	±0.117
Frontal lobe	Males	Left	±0.010	±0.061	±0.088	±0.130
		Right	±0.008	±0.062	±0.074	±0.122
	Females	Left	±0.011	±0.064	±0.087	±0.106
		Right	±0.010	±0.067	±0.088	±0.096
Parietal lobe	Males	Left	±0.011	±0.065	±0.105	±0.122
		Right	±0.011	±0.064	±0.078	±0.108
	Females	Left	±0.012	±0.072	±0.103	±0.130
		Right	±0.009	±0.076	±0.080	±0.122
Occipital lobe	Males	Left	±0.028	±0.076	±0.118	±0.171
		Right	±0.016	±0.057	±0.090	±0.153
	Females	Left	±0.031	±0.091	±0.132	±0.181
		Right	±0.020	±0.068	±0.105	±0.163
Cingulate gyrus	Males	Left	±0.027	±0.040	±0.041	±0.048
		Right	±0.028	±0.037	±0.034	±0.046
	Females	Left	±0.027	±0.053	±0.047	±0.062
		Right	±0.025	±0.038	±0.033	±0.047
Insula	Males	Left	±0.056	±0.028	±0.089	±0.103
		Right	±0.044	±0.049	±0.077	±0.105
	Females	Left	±0.038	±0.024	±0.037	±0.050
		Right	±0.054	±0.027	±0.055	±0.058
Corpus callosum	Males	Left	±0.864	±0.188	±0.207	±0.337
		Right	±0.437	±0.104	±0.172	±0.214
	Females	Left	±1.101	±0.277	±0.218	±0.314
		Right	±0.528	±0.121	±0.100	±0.174

**Table 5a**  
Proportional accuracy means (standard errors) by region and sex

Region		Proportional accuracy native vs. Tal		Proportional accuracy native vs. Tal50	
		Gray	White	Gray	White
Cerebral hemisphere	Males	0.901 (0.018)	0.901 (0.017)	0.903 (0.018)	0.915 (0.018)*
	Females	0.917 (0.016)	0.919 (0.016)	0.919 (0.016)	0.853 (0.016)
Frontal lobe	Males	0.898 (0.020)	0.894 (0.016)	0.910 (0.021)	0.915 (0.019)*
	Females	0.908 (0.018)	0.918 (0.014)	0.909 (0.019)	0.858 (0.017)
Parietal lobe	Males	0.903 (0.017)	0.893 (0.017)	0.894 (0.016)	0.906 (0.018)**
	Females	0.908 (0.016)	0.912 (0.015)	0.923 (0.015)	0.821 (0.017)
Temporal lobe	Males	0.878 (0.017)	0.888 (0.017)	0.885 (0.017)	0.911 (0.019)
	Females	0.920 (0.015)	0.915 (0.016)	0.916 (0.015)	0.870 (0.017)
Occipital lobe	Males	0.921 (0.017)	0.926 (0.016)*	0.906 (0.016)	0.909 (0.017)
	Females	0.894 (0.015)	0.871 (0.015)	0.907 (0.014)	0.874 (0.015)
Cingulate gyrus	Males	0.872 (0.016)**	0.851 (0.017)**	0.863 (0.026)**	0.855 (0.026)**
	Females	0.933 (0.014)	0.935 (0.014)	0.730 (0.023)	0.731 (0.023)
Insula	Males	0.827 (0.016)**	0.760 (0.019)**	0.915 (0.020)	0.905 (0.019)
	Females	0.919 (0.015)	0.867 (0.017)	0.870 (0.018)	0.874 (0.017)
Hippocampus	Males	0.752 (0.019)**		0.864 (0.015)**	
	Females	0.884 (0.017)		0.924 (0.013)	
Corpus callosum	Males		0.845 (0.017)**		0.868 (0.024)
	Females		0.934 (0.015)		0.810 (0.022)

Left and right hemisphere volumes are combined. Significant difference (*t*-test) between males and females indicated by \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ).

proportion is significantly lower ( $p < .001$ ) than the native proportion.

## Discussion

The diverse results reported in this paper reflect the many ways in which spatial normalization of MRI scans can affect the measurement of regional brain volumes. To briefly summarize our findings: 1) group-level mean native volume differences can be attenuated by spatial normalization; in some cases, significant group-level differences are obtained in transformed data sets that are in the opposite direction of those obtained in native space (Tables 1 and 2); 2) ANCOVA analyses indicate that transformation affects different brain regions in different ways, even after covarying for total brain volume (Table 2) or brain volume and age (Table 3); MNI-transformed brain volumes are substantially larger than native or Tal-transformed volumes (Tables 1 and 4a, b); 4) proportional accuracy statistics indicate that both the Tal and Tal50 templates provide volumes that differ absolutely by about 10–20% from

those measured in native space (Tables 5a, b); for some regions, there are significant gender differences in proportional accuracy measures; proportional accuracy scores are relatively low for the MNI-transformed brains and male scores are significantly higher than female scores; 5) volumetric intra-class correlations between native and transformed brains differ by template, region, and tissue type (gray or white matter) (Table 6a, b); G/W ratios generally have much higher ICCs ( $> 0.9$ ), although there were some Tal50 regions with lower ICCs; almost all of the volumetric ICCs for MNI-transformed brains are negative, although G/W ratio ICCs for some regions are positive and significant; 6) All four of the transformation templates produced hippocampus and/or corpus callosum volume proportions that were significantly different from those obtained from native brains; in some cases the proportions were larger, in others smaller.

Our results highlight the contribution of shape distortion in producing volume differences between native and transformed brains. The effects of this distortion appear to be heterogeneous, varying by region, tissue type, and transformation

**Table 5b**  
Proportional accuracy means (standard errors) by region and sex

Region		Proportional accuracy native vs. MNI305		Proportional accuracy native vs. IA38	
		Gray	White	Gray	White
Cerebral hemisphere	Males	0.779 (0.029)**	0.643 (0.032)**	0.744 (0.030)**	0.547 (0.034)**
	Females	0.566 (0.026)	0.416 (0.029)	0.528 (0.027)	0.303 (0.030)
Frontal lobe	Males	0.749 (0.036)**	0.611 (0.034)**	0.712 (0.036)**	0.520 (0.036)**
	Females	0.542 (0.032)	0.406 (0.031)	0.500 (0.033)	0.299 (0.032)
Parietal lobe	Males	0.810 (0.025)**	0.630 (0.034)**	0.786 (0.027)**	0.529 (0.036)**
	Females	0.585 (0.023)	0.383 (0.031)	0.565 (0.024)	0.259 (0.032)
Temporal lobe	Males	0.766 (0.031)**	0.660 (0.033)**	0.705 (0.031)**	0.516 (0.036)**
	Females	0.543 (0.028)	0.404 (0.030)	0.470 (0.028)	0.242 (0.032)
Occipital lobe	Males	0.844 (0.027)**	0.815 (0.029)**	0.846 (0.027)**	0.812 (0.030)**
	Females	0.661 (0.024)	0.618 (0.026)	0.674 (0.024)	0.612 (0.027)
Cingulate gyrus	Males	0.495 (0.051)**	0.517 (0.055)**	0.359 (0.049)**	0.409 (0.051)**
	Females	0.270 (0.046)	0.280 (0.050)	0.096 (0.044)	0.130 (0.046)
Insula	Males	0.553 (0.034)**	0.585 (0.036)**	0.352 (0.038)**	0.420 (0.037)**
	Females	0.331 (0.031)	0.348 (0.032)	0.089 (0.034)	0.159 (0.033)
Hippocampus	Males	0.712 (0.034)**		0.587 (0.037)**	
	Females	0.467 (0.031)		0.325 (0.033)	
Corpus callosum	Males		0.642 (0.050)**		0.662 (0.044)**
	Females		0.374 (0.045)		0.380 (0.040)

Left and right hemisphere volumes are combined. Significant difference (*t*-test) between males and females indicated by \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ).

**Table 6a**

Intra-class correlation coefficients between native vs. Tal and native vs. Tal50 volumes and gray/white ratios

Region			ICC native vs. Tal volume			ICC native vs. Tal50 volume		
			Gray	White	G/W	Gray	White	G/W
Cerebral hemisphere	Males	Left	-0.223	0.111	0.995*	-0.101	0.428	0.663*
		Right	-0.072	0.075	0.994*	-0.069	0.278	0.667*
	Females	Left	0.155	0.339	0.989*	0.032	-0.276	0.400
		Right	0.086	0.320	0.901*	0.096	-0.103	0.436*
Frontal lobe	Males	Left	0.021	0.340	0.988*	0.162	0.610*	0.702*
		Right	0.057	0.251	0.993*	0.042	0.439	0.690*
	Females	Left	0.237	0.344	0.980*	0.064	-0.295	0.473*
		Right	0.071	0.390	0.982*	0.084	-0.110	0.432*
Parietal lobe	Males	Left	0.416	0.279	0.981*	0.425	0.550*	0.545*
		Right	0.007	-0.100	0.976*	0.080	0.155	0.492*
	Females	Left	0.387	0.552*	0.975*	0.382	0.020	0.374
		Right	0.592*	0.662*	0.985*	0.625*	0.239	0.304
Temporal lobe	Males	Left	0.151	0.590*	0.973*	0.177	0.751*	0.842*
		Right	0.262	0.506*	0.990*	0.221	0.595*	0.891*
	Females	Left	0.436*	0.296	0.937*	0.186	-0.155	0.531*
		Right	0.208	0.591*	0.980*	0.076	0.405	0.783*
Occipital lobe	Males	Left	0.722*	0.815*	0.967*	0.637*	0.761*	0.929*
		Right	0.570*	0.890*	0.980*	0.503*	0.862*	0.966*
	Females	Left	0.785*	0.817*	0.965*	0.823*	0.809*	0.875*
		Right	0.750*	0.842*	0.982*	0.721*	0.831*	0.960*
Cingulate gyrus	Males	Left	0.497*	0.381	0.962*	0.563*	0.626*	0.989*
		Right	0.461*	0.288	0.970*	0.574*	0.452	0.966*
	Females	Left	0.927*	0.905*	0.970*	0.339	0.193	0.988*
		Right	0.899*	0.912*	0.977*	0.211	0.326	0.994*
Insula	Males	Left	-0.305	0.637*	0.950*	0.496*	0.962*	0.997*
		Right	-0.112	0.317	0.825*	0.348	0.813*	0.987*
	Females	Left	0.381	0.855*	0.899*	-0.113	0.839*	0.991*
		Right	0.366	0.632*	0.819*	-0.021	0.682*	0.988*
Hippocampus	Males	Left	-0.248			0.419		
		Right	-0.220			0.285		
	Females	Left	0.415			0.661*		
		Right	0.259			0.768*		
Corpus callosum	Males		0.249			0.438		
	Females		0.770*			0.259		

Statistically significant values indicated by \* (i.e., 95% confidence interval did not include zero).

template. Given that the assessment of group differences in global and regional volumes is one of the fundamental goals of structural neuroimaging research, it is with some peril that we neglect to seriously address the potential effects spatial transformation has on our ability to accurately and consistently estimate volume from MR images.

#### Transformation and group differences in ROI volumes

Spatial transformation causes a reduction in the magnitude of group-level volume differences, therefore it is no surprise that there are fewer significant gender differences in regional brain volumes in the transformed compared to the native-space brains (Tables 1 and 2); this is a pattern that is similar in both the Tal- and MNI-transformed brains. For the native brains, in almost all ROIs and tissues, males are significantly larger than females. This was not true of any of the transformed ROIs. Indeed, the only significant volume differences found in transformed brains were in cases where the female mean became significantly greater than the male mean (e.g., hemispheric GM, parietal GM, right cingulate gyrus GM, left hippocampus). In the cases where transformed regions in females are larger than those in males, it may be possible that these results reflect “real,” size-corrected shape or proportional differences between the sexes (although proportional sizes of the major lobes are remarkably similar in the two sexes in native-space brains, Allen et al., 2002). Alternatively, these differences may reflect the specific effects of transformation into Talairach space in our groups of larger (i.e., male)

and smaller (i.e., female) brains. Nevertheless, the ANCOVA results (Table 3) indicate that size is not the only critical factor, since it is clear that transformation method introduces significant variation to regional brain volumes even after covarying for overall native brain volume. It is important to remember that although the MNI transformation differs in several ways from the Talairach transformation (Collins et al. 1994), the creation of the MNI template began with brains transformed into an approximation of Talairach space. This may account for some of the similarities we see in these volumetric results across transformation methods.

The native, transformed, and native adjusted means in Table 2 indicate that statistically size-corrected native brains do not provide results that are equivalent to those obtained with transformed brains, especially for gray matter regional volumes. The size corrections introduced by spatial normalization are therefore not equivalent to the volume adjustments introduced by standard statistical methods such as the ANCOVA or multiplicative scaling. Again, this could be indicative of a real biological difference between men and women in the gray matter volume of these regions; conversely, it could be indicative of a tendency for the spatial transformation to volumetrically compensate differently for relatively smaller and larger brains.

The reason that size corrections introduced by spatial normalization are not equivalent to those introduced by standard statistical methods is that nonlinear transformations introduce local expansions and contractions in the transformed image. In applications where nonlinear warping

transforms are used routinely (e.g. voxel-based morphometry), these local distortions can be isolated from global differences, and volume measurements can be adjusted accordingly using the Jacobian determinants of the non-affine transformation matrix (Goldszal et al., 1998; Ashburner and Friston, 2000; e.g., using VBM5.1 Toolbox). Local effects of the transform are frequently neglected, however, in applications that involve region-based measurements on data subjected to low-order transforms (beyond rigid-body and global rescaling parameters). The data presented here show that these effects are non-negligible.

Dozens of studies investigating group-level differences in regional brain volumes have made use of the automated Talairach atlas-based parcellation method of Andreasen et al. (1996) and modifications of that method, such as that provided by Kates et al. (1999). Validation studies of these methods indicate that group-level differences may be maintained following Tal transformation, and therefore it is legitimate to use them to examine changes in brain structure (relative to normal comparison subjects) that may arise due to disease (such as schizophrenia) or age. Our results cannot address the validity of these methods directly, since our Tal-based spatial transformations of manually-traced ROIs are not equivalent to the transformation-followed-by-parcellation of the automated methods. However, our study points to several issues that should be kept in mind when assessing the results derived from automated methods that use spatial transformation as a means of colocalization or as a size correction: group-level differences may be underestimated; spatial transformation will affect different regions in different ways; gray and white matter may be affected differently by transformation; and spatial transformation may have different effects on different

groups of brains depending on how their native structures compare to the target template brain or atlas. It is especially important to pay attention to the composition of groups (i.e., age and gender of the subjects) used to validate methods. Of course, the parameters used in the spatial transformation (e.g., linear vs. nonlinear warp, number of basis functions in a nonlinear warp, specific atlas used as the target) should also be accounted for (Salmond et al., 2002; Keller et al., 2004).

As Dade et al. (2004, p. 1495) point out, after spatial transformation “important subtleties of structural information about an individual’s brain can be lost.” Due to the reduction in variability in transformed brains, structural-functional relationships may be more difficult to uncover. For example, correlations between regional brain volumes and IQ test score performance were higher when studied in a group of subjects whose MRI brain scans were not transformed (Andreasen et al., 1993) compared to those in which an automated, Tal-based parcellation method was used (Flashman et al., 1998). Group-level differences in brain structure that must be discovered by quantitative volumetry of small regions are almost by definition “subtle,” thus there should be some concern about the ability to detect such differences in the “noise” introduced by spatial transformation. Conversely, a real or native difference in brain structure between two groups may engender subtly different responses to spatial transformation outside of the region of interest, which could obscure the ability to detect the real difference. Whether either of these possibilities is more or less true is difficult to determine. But they point to the necessity for volumetric differences uncovered by spatial-transformation-based methodologies to be replicated in native-space brains assessed using appropriate statistical tools (Smith, 2005).

**Table 6b**

Intra-class correlation coefficients between native vs. MNI305 and native vs. IA38 volumes and gray/white ratios

Region			ICC native vs. MNI305 volume			ICC native vs. IA38 volume		
			Gray	White	G/W	Gray	White	G/W
Cerebral hemisphere	Males	Left	-0.478*	-0.652*	0.395	-0.598*	-0.745*	0.153
		Right	-0.452	-0.626*	0.573*	-0.557*	-0.766*	0.224
	Females	Left	-0.866*	-0.876*	0.137	-0.887*	-0.909*	-0.159
		Right	-0.869*	-0.871*	0.287	-0.888*	-0.911*	-0.100
Frontal lobe	Males	Left	-0.381	-0.504*	0.481*	-0.529*	-0.613*	0.270
		Right	-0.420	-0.560*	0.622*	-0.541*	-0.694*	0.371
	Females	Left	-0.848*	-0.905*	0.204	-0.860*	-0.927*	-0.055
		Right	-0.822*	-0.868*	0.296	-0.841*	-0.909*	0.087
Parietal lobe	Males	Left	0.245	-0.490*	0.161	0.087	-0.644*	-0.101
		Right	-0.224	-0.668*	0.417	-0.328	-0.805*	0.006
	Females	Left	-0.663*	-0.699*	0.094	-0.721*	-0.768*	-0.198
		Right	-0.557*	-0.671*	0.261	-0.610*	-0.762*	-0.222
Occipital lobe	Males	Left	0.387	0.398	0.924*	0.442	0.435	0.895*
		Right	0.209	0.653*	0.971*	0.235	0.619*	0.947*
	Females	Left	0.048	0.163	0.896*	0.094	0.173	0.819*
		Right	-0.108	0.228	0.969*	-0.111	0.220	0.936*
Cingulate gyrus	Males	Left	-0.484*	-0.321	0.892*	-0.577*	-0.413	0.860*
		Right	-0.403	-0.409	0.919*	-0.556*	-0.541*	0.864*
	Females	Left	-0.374	-0.478*	0.972*	-0.503*	-0.573*	0.949*
		Right	-0.492*	-0.377	0.975*	-0.628*	-0.531*	0.972*
Insula	Males	Left	-0.615*	0.428	0.997*	-0.782*	0.231	0.991*
		Right	-0.644*	0.195	0.967*	-0.773*	-0.076	0.944*
	Females	Left	-0.876*	-0.014	0.995*	-0.939*	-0.202	0.989*
		Right	-0.865*	-0.405	0.992*	-0.925*	-0.543*	0.975*
Hippocampus	Males	Left	-0.120			-0.390		
		Right	-0.007			-0.284		
	Females	Left	-0.591*			-0.734*		
		Right	-0.551*			-0.682*		
Corpus callosum	Males		-0.179			-0.225		
	Females		-0.512*			-0.545*		

Statistically significant values indicated by \* (i.e., 95% confidence interval did not include zero).

### Comparing transformation methods

Since some volumetric studies are based on classic Talairach transformation (e.g., those using the [Andreassen et al., 1996](#) method), while others base their volumetry on templates from multiple averaged brains (e.g., the MNI template, [Collins et al., 1994](#)), it is important to compare the differential effects on transformation that can arise depending on the nature of the target template. Of course, there should be no expectation that the two approaches, which also employ different warping methods (piecewise-linear versus nonlinear), should produce identical results. Templates based on averaging multiple brains (e.g., Tal50, MNI305, IA38) should incorporate fewer spatial biases than the classic, single-brain based Tal transformation ([Kochunov et al., 2002](#)). We found that while the different transformations provide similar results, there were many instances in which the templates provided somewhat divergent patterns of transformation from the native space.

We consistently found that MNI volumes are on the order of 25% larger than the native or Tal-transformed volumes. The reason the MNI305 template is so large is that it was based initially on a simple linear transformation to the space defined by the Talairach brain, which is 25% taller than normal ([Collins et al., 1994](#); D.L. Collins, pers. com., 2007). This resulted in an increase in all linear dimensions, which in turn led to the creation of a template that is approximately 25% larger than a typical brain, with an overall intracranial volume of about 1.9 L. The effects of this increase in overall size is manifest in the reliability results we present in [Tables 5a, b and 6a, b](#).

Different transformations may introduce regionally heterogeneous variation in absolute size, and it also appears to be true that changes in proportional size can also vary widely. For example, we found that the proportional representations of two small structures, the corpus callosum and hippocampus, could stay the same, be larger, or be smaller, depending on the transformation template. Proportional changes of this kind could pose a problem in comparing studies using different methodologies, especially those concerned with structural-behavioral relationships (e.g., [Van Petten, 2004](#), [Allen et al., 2006](#), regarding the hippocampus and memory). Even with neuroanatomical criteria and volumetric methodology carefully defined, morphometric studies of smaller structures such as the hippocampus ([Pedraza et al., 2004](#)) or the orbitofrontal cortex ([Lacerda et al., 2003](#)) often produce discrepant results. One thing to be concerned about is that the introduction and widespread adoption (because of ease of use) of an automated, spatial-transformation-based volumetric method for smaller anatomical structures could have a disproportionate influence on the field as a whole. Future meta-analyses should take into account if volumes are determined using spatially-transformed images or specific automated methods.

The proportional accuracy scores for the MNI-transformed brains ([Table 5b](#)) were quite different from the Tal-transformation results reported here and from those reported by [Mega et al. \(2005\)](#), who performed native volume transformation with three different Talairach-compatible sub-volume probabilistic models ([Table 5a](#)). For every region and tissue type, the MNI-transformation proportional accuracies were substantially lower than for the Tal transformations. These results are perhaps not surprising given that proportional accuracy is a volumetric measure and the large size of the MNI template, which is essentially outside the normal range of volumes, ensures that transformation will cause large shifts in

volume. It is also important to note that the proportional accuracy scores for the MNI-transformed brains are more variable across regions than for the Tal-transformed brains; this is especially apparent when comparing the larger with some of the smaller structures. (e.g., compare the scores for the frontal lobe versus the insula). This suggests that above and beyond the expected changes in volume due to the large MNI template, there are also relative distortions in volume that are difficult to predict.

Another way to examine volumetric agreement among methods is the intra-class correlation coefficient ([Table 6a, b](#)). For the Tal transformations, the intra-class correlation coefficients for regional GM and WM volumes were quite variable ([Table 6a](#)). The occipital lobe GM and WM volumes had the highest ICCs after transformation. This may reflect the position of the occipital lobe relative to the Talairach landmarks; since the occipital lobe is almost entirely posterior to the position of the posterior commissure, it is apparently less deformed during the process of spatial normalization. In contrast to the volumetric ICCs, the Tal-transformed G/W ratio ICCs were almost uniformly high. This result indicates that both the Tal and Tal50 spatial transformation conserve regional gray and white matter densities, despite disparate patterns of regional volume change. The relative preservation of G/W ratio we observed is consistent with the results of [Mega et al. \(2005\)](#), although they used somewhat different measures).

The MNI-transformation ICC results ([Table 6b](#)) are in some ways similar to the Tal-transformation results, but there are some notable differences. The volumetric ICCs for the MNI-transforms are not only low, but in almost all cases negative. The ICC is sensitive to differences in scale (which the Pearson correlation is not), so the low and negative volumetric ICCs for both Tal- and MNI-transformed brains probably reflect the rescaling that spatial transformation entails, and this rescaling is much more profound for the MNI transformation. The negative volumetric ICCs of the MNI transformations are an arithmetic result of the expected variance between the native and MNI305/IA38 brains being greater than the variance among brains. That said, the MNI volumetric ICC results are similar to the Tal results in that there is not strong agreement between the native and transformed measures, and relatively speaking, the occipital lobe shows the strongest agreement for both types of transformation.

The MNI-transformation G/W ratios are not as high as Tal transformations for the larger regions, but are comparable for the occipital lobe, insula, and cingulate gyrus. Unlike the frontal, parietal, and temporal lobes, none of these three regions contain much of the white matter core of the cerebrum. This would suggest that the MNI transformation is affecting the cerebral cortex and the white matter core in different ways. The G/W ratios for the cerebral hemispheres of the native and Tal-transformed brains are about 1.30–1.40, while for the MNI brains they are around 1.05–1.10 (see results in [Table 1](#) which would indicate that the white matter as a whole is scaled-up more so than the gray matter). The ICCs for G/W ratios for males are generally higher than those for females, which suggest that the scaling up varies according to starting G/W ratio or overall brain volume.

The explanation for this pattern probably lies in the fact that the two Tal-based spatial transformations we studied were low-order warps that were not capable of differentially affecting small gray matter structures (e.g., the cortical ribbon)

relative to the subjacent white matter. Generally, the cortical ribbon was affected in parallel with the white matter. On the other hand, the transformation methods were capable of altering the basic size and overall shape of larger structures (e.g., lobes). Note that for the Tal50 transformation, the G/W ICCs for the frontal lobe and for the parietal lobe, in particular, were significant but not especially high. Nonetheless, the general preservation of regional information about relative gray matter/white matter composition following Tal-based spatial normalization supports the use of tissue density-based tools, such as that developed by Mega et al. (2005) or VBM (Ashburner and Friston, 2000), although there may be other arguments against their adoption for general (Bookstein, 2001; Davatzikos, 2004) or particular (Mehta et al., 2003) uses.

### Limitations

Although the statistical results we present are generally quite robust, a sample size greater than the 38 employed here would probably produce more generalizable results. Interslice thicknesses were either 1.5 or 1.6 mm; 3 of the 21 female and 8 of the 17 male subjects had interslice thicknesses of 1.6 mm. This is a potential source of within-method variation although across-methods, since the group composition is the same, interslice thickness should have a limited influence on the comparative results. We tested the effects of spatial transformation on the manually-traced ROIs by transforming them according to the parameters derived from the global transformations. These results are therefore informative, but not directly comparable to results obtained in studies where there is manual or automated tracing of ROIs following spatial transformation. Finally, our ROIs were defined according to neuroanatomical criteria. More informative comparative data on spatial normalization may be obtained by sampling regions with simplified ROIs (i.e., cubes) according to their location vis-à-vis particular transformation landmarks (e.g., between the AC and PC), regardless of their neuroanatomical affinities.

### Conclusion

Our results justify two main conclusions: 1) volumetric measures and their relationships (between groups, male vs. female) will depend on whether data have been transformed and how the data have been transformed; 2) measures of local regions and the relationship between groups will vary as a function of the type of global normalization approach that was used (e.g., dividing by total size, piecewise linear vs. nonlinear, and template choice). We recognize that there are many reasons to use spatial transformation in the analysis of MR images, and that our comparisons between native and transformed volumes may not be relevant to all of them. Nonetheless, our results indicate that given the heterogeneous regional effects of transformation, results obtained from transformed brains should be regarded with due caution. At the very least, a more comprehensive and realistic perspective should be developed with regard to the potential sources of bias, error, and variability that are hidden in the “black box” of spatial transformation. Important individual and group differences may be lost as a result of transformation. Meta-analyses should be conducted in ways that are sensitive to this concern. Although automated parcellations of the MR brain images increases reliability among users, the validity of the findings – and not simply the reliability/validity of the method – should

be checked against other volumetric approaches. There is legitimate cause for concern when spatial transformation is used as a means of size correction, or when an automated method is based simply on individual co-registration to the Talairach or MNI template. The “gold standard” of volumetry conducted in native-space brains should still be sought to confirm or validate major structural-functional associations.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2008.05.047](https://doi.org/10.1016/j.neuroimage.2008.05.047).

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