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Cross-validation of Brain Segmentation by SPM5 and SIENAX

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Abstract

Volumes of cerebral grey (GM) or white matter (WM) are often used as clinical observations or statistical covariates. Several automated segmentation tools can be used for this purpose, but they have not been validated against each other. We used the most common ones, SPM5 and SIENAX 2.4, to derive volumes of grey and white matter in 56 healthy subjects (mean age 49 ± 13 , range 22–80) and compare the two methods. Both methods yielded significant correlations with age in the expected directions, and estimates of parenchymal volumes were highly correlated. However, without use of priors in SIENAX, GM was significantly underestimated in comparison to SPM ($0.52 \pm .06$ Vs $0.66 \pm .07$ L) and WM was significantly overestimated ($0.48 \pm .07$ Vs $0.46 \pm .07$ L). This error was associated with misclassification of GM as CSF, especially in deep grey matter. Invoking prior probabilities in SIENAX resulted in excellent agreement with SPM: GM and WM volumes were found to be 0.64 ± 0.07 L and 0.47 ± 0.07 L, respectively. We conclude that SIENAX requires priors for accurate volumetric estimates, and then provides close agreement with SPM5.

Keywords

MRI; Grey Matter; White Matter; segmentation; SPM; SIENAX

1. Introduction

Segmentation of the cranial contents into three main compartments of grey matter (GM), white matter (WM) and CSF is useful for spatial normalization operations, and is of substantial clinical research interest. Volumetric changes over time are sensitive markers of a range of neurological disease states and disease progression (Tofts, 2003). Brain volumes of one or more compartments are reduced due to chronic conditions such as multiple sclerosis (Miller et al., 2002; Pelletier et al., 2004; Zivadinov et al., 2005), normal aging (Good et al., 2001; Resnick et al., 2000; Smith et al., 2006), Creutzfeldt-Jakob disease (Fulbright et al., 2006) and Alzheimer's disease (Brunetti et al., 2000).

For practical reasons, semi-automatic or fully automatic segmentation is attractive. The most widely used automated tools are SIENAX 2.4 of FSL3.3 (FMRIB Image analysis Group) and unified segmentation of SPM5 (Wellcome department of Imaging Neuroscience). Both are

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fast, reproducible, and require minimal human intervention, but their outcomes can be influenced by technical factors such as electronic noise, poor contrast to noise ratio, bias field caused by inhomogeneity of magnetic field, and partial volume effect (Zhang et al., 2001). Despite their popularity, these methods have not been tested directly against each other in vivo. Here we report the first rigorous comparison between the two methods.

2. Methods

2.1 Subjects and Imaging

Fifty-Six normal subjects (age range 22-80 years) participating in a genetic study underwent MRI imaging. All subjects were healthy by history and neurological examination. The subjects included 26 females (age 50.3 ± 12.3) and 30 males (age 47.7 ± 13.0). MRI was performed on a GE 1.5T Signa scanner, using the SPGR sequence with 104 axial slices (acquisition matrix 256×256 , FOV=240mm, yielding reconstructed voxel dimensions $0.94 \times 0.94 \times 1.50$ mm). Imaging parameters were set to TR/TE/TI/FA 28/6/0/40. Further image processing (see below) was performed in Matlab 7.1. Statistical analyses were performed with JMP (SAS Institute, Inc., Cary, NC), and consisted of product-moment linear regressions and appropriate ANOVA and ANCOVA models.

2.2 Structural segmentation by SPM5 and SIENAX

The SPM5 segmentation algorithm is based on a probability map (<http://www.fil.ion.ucl.ac.uk/spm/>). The machinery of SPM5 segmentation employs tissue classification, bias correction, and non-linear registration into a single generative model (Ashburner and Friston, 2005). In this experiment, default parameters were used for all operations.

SIENAX is performed by a series of FSL utilities (Smith et al., 2004; Smith et al., 2002). By default, the segmentation does not rely on any tissue probability maps, or priors, but those can be invoked and aid the initial segmentation in the case of suboptimal bias-field. The default no-priors setting was used for the first SIENAX evaluation; in the second, due to the unexpected results, we used this option. The total number of tissue classes was set to the default value of three.

2.3 SPM and SIENAX comparison

We first compared the global compartmental volumes obtained by both methods across the entire sample, as well as their covariance with age and gender. We also tested the reproducibility of each method. Of 56 subjects included in this study, 23 subjects were imaged twice (mean interval 12.8 ± 0.74 months). These scans were analyzed to assess inter-session reliability of the segmentation methods.

To assess the concordance between the methods at the voxel level, we employed the Dice metric (Dice, 1945; Zijdenbos et al., 1994). This is a ratio between voxels that are in mutual agreement between the two segmentation methods and total number of voxels being sampled, expressed as $dice = 2V_{SIENAX+SPM} / (V_{SIENAX} + V_{SPM})$, where $V_{SIENAX+SPM}$, V_{SIENAX} , and V_{SPM} denote voxels that are in mutual agreement between the two methods, voxels in SIENAX, and voxels in SPM, respectively. The Dice metric has a range of 0 (no concordant voxels) to 1 (perfect agreement). Computing this metric requires classification of every voxel into pure GM, WM, or CSF; this was done by assigning the voxel to the compartment with the highest probability.

Although the Dice metric is voxel-based, it contains no information about the location and topographic distribution of disagreement. To develop spatially-specific discrepancy measures,

segmented images from both SIENAX and SPM were normalized to stereotactic space using normalization parameters derived from SPM. The averaged normalized images were then subtracted. This method was also applied to the bias-field images derived by both methods.

3. Results

3.1 Global GM, WM and CSF volumetric analyses of SIENAX and SPM

Our first experiment, using SIENAX in its default mode (without priors) resulted in surprising discrepancies between SIENAX and SPM, although the results were highly correlated between the two methods ($r=0.72$, $P<0.0001$ for GM, $r=0.80$, $P<0.0001$ for WM). GM volume was higher by SPM (0.66 ± 0.07 litre) than with SIENAX (0.52 ± 0.06 litre). This 27% difference was highly significant by paired t test ($t_{55}=20.15$, $P<0.0001$). For white matter, the volume was slightly higher by SIENAX (0.48 ± 0.07) than with SPM (0.46 ± 0.07). This 4% difference was again highly significant by paired t test ($t_{55}=3.89$, $P<0.0001$).

These discrepancies were considered unacceptable, and cast doubt on the validity of both SPM and SIENAX. One of the most prominent technical differences between the two methods was the use of prior probability maps, so we repeated the SIENAX analyses with the addition of priors. Figure 1 summarizes the mean group volumes and standard deviation for all three methods. When the priors were turned on, there is an excellent agreement between SIENAX and SPM in both GM and WM volumes. The correlations between them were also much better (GM: $r=0.95$, $P<0.0001$; WM: $r=0.95$, $P<0.0001$). The Dice metric was less sensitive, but it confirms these findings for GM: concordance rose with the use of priors (0.86 ± 0.02 Vs 0.81 ± 0.07 , $t_{55}=6.25$, $P<0.0001$).

Because age is known to significantly affect cerebral atrophy, we also examined age regressions of all three methods. Table 1 provides the numerical results. All three methods demonstrated reasonable and similar age regressions. Total CSF volume by SPM was also positively correlated with age, as expected ($r = 0.61$, $P<0.0001$). We also tested the effect of gender, since males are known to have larger brain volumes. A repeated-measure ANCOVA compared SPM and SIENAX (default values) derived volumes, using gender as a grouping factor and age as a covariate. For GM, there were significant main effects of method ($F_{1,53}=40.55$, $P<0.0001$), gender ($F_{1,53}=8.51$, $P<0.01$) and age ($F_{1,53}=29.85$, $P<0.0001$), and a significant method by gender interaction ($F_{1,53}=20.37$, $P<0.0001$). Males had larger mean volumes than females, and the difference was larger for SPM than the default SIENAX. For WM, there were significant main effects of method ($F_{1,53}=5.74$, $P<0.05$), gender ($F_{1,53}=18.95$, $P<0.0001$) and age ($F_{1,53}=10.36$, $P<0.005$), and a significant method by gender interaction ($F_{1,53}=14.49$, $P<0.0005$). Males had larger mean volumes than females, and the difference was larger for SPM than the default SIENAX. These differences between the methods disappeared with the use of priors in SIENAX; thus, without priors, SIENAX is also inferior to SPM in detecting gender differences.

Finally, our data demonstrate that priors are essential to achieve good reproducibility in SIENAX. Across the 26 subjects repeated in one year, the absolute volume differences for default SIENAX had a range of 15-17%, whereas the range was only 4-6% for SPM and SIENAX with priors. The correlations between the first and second measurement were lower for default SIENAX (0.72 GM and 0.67 WM) than for SIENAX with priors (0.95 GM and 0.92 WM) and SPM (0.87 GM and 0.96 WM).

3.2 Topographic Distribution of discrepancies between SPM and SIENAX

To visualize the regional pattern of volumetric discrepancies between SPM and SIENAX, the normalized difference images were evaluated as shown in Figure 2. The voxels with difference

value above 0.25 were overlaid onto a normalized anatomical image. Default SIENAX segmentation appears to misclassify deep grey matter as CSF. Further, the difference image of normalized bias-field correction is shown in Figure 3. In it, bright regions represent areas where SIENAX overestimated the bias-field compare to SPM. In the presence bias-field, true image intensity is modulated by $I_{acquired} = I_{true} \times I_{bias}$, where I_{bias} , I_{true} , and $I_{acquired}$ denote amount of bias, true image intensity, and acquired image intensity, respectively. Bias-field, I_{bias} , has a multiplicative effect on true image intensity, I_{true} , and therefore bright regions in the Figure 3 represent voxels where SIENAX's I_{true} was lower than SPM's I_{true} . In the case of SIENAX without priors, the discrepancy of bias-field correction lies in the deep cortical structures, corresponding to the areas of maximal GM underestimation. With priors turned on, the discrepancy in these regions is eliminated.

4. Discussion

Segmentation of the brain into its anatomical compartments is essential for several purposes. Diseases often involve predominantly one compartment, and a global 'brain atrophy' measure may be less sensitive than compartment-specific analysis. Biological processes may affect compartments in opposite directions (e.g., the increase of CSF and decrease of GM with aging), so that global volumes may be misleading. Segmentation is also extremely useful as an aid to spatial normalization, and differential volumetric values can enhance statistical models when used as covariates.

Despite the crucial importance of segmentation methods, we could not find any instance in which they were validated in vivo against an external 'gold standard', such as detailed postmortem analysis. We therefore chose to estimate their validity indirectly by testing their reliability against each other, their reproducibility and their ability to reflect the known aging effects on cerebral anatomy. The two methods we evaluated, SIENAX and SPM, are the most common and well known. Together, they represent the bulk of segmentation and volumetric work published to date.

In our first experiment, we deliberately used default values for all parameters in both SPM and SIENAX, since our aim was to evaluate their accuracy in the hands of a non-expert user. Under these conditions, we found that SIENAX demonstrated substantial underestimation of GM, which was misclassified as CSF. SIENAX also underestimated the volumetric differences between male and female subjects, and suffered lower reproducibility in a 12-months test-retest experiment. All of these problems disappeared when we turned on the option of using prior probability maps in SIENAX. With priors, there is excellent agreement between the volumetric estimates of SIENAX and SPM: the means are virtually identical, and the correlations was be excellent (0.95) for both GM and WM. Gender effects are seen equally well, and the one-year reproducibility is also similar. Therefore, we concluded that SIENAX should not be used in its default setting. Instead, the priors option should be employed in the absence of gross anatomical abnormality. With priors, the agreement between SPM and SIENAX is excellent under all conditions tested.

Reliability is necessary, but not sufficient, for validity: the very high agreement between SPM and SIENAX (with priors) may indicate that they are both equally wrong. However, our results are in good agreement with previous work (Good et al., 2001; Smith et al., 2006; Taki et al., 2004), indicating the validity of our methods. Global grey matter volume was previously reported in the range of 0.52 - 0.83 L; considering age and gender differences, our finding of 0.66 is consistent. For example, we found volumes of 0.69 L in males and 0.62 L in females, compared to 0.71 L and 0.58 L by (Blatter et al., 1995). Similarly, our global WM volumes of 0.49 L in males and 0.41L in females are very similar to the Good et al. (2001) values of 0.45 L in males and 0.40 L in females, and also Ge et al values of 0.49L in males and 0.47L in

females (Ge et al., 2002). Aging effects were also reasonably delineated by both methods. Grey and white compartmental volumes were reduced with age, and the regression slope was greater for GM than WM, as reported by previous investigators. We found a slope of 0.0032 for GM and 0.0019 for WM, compared to the previously reported range of 0.0024 - 0.0039 for GM and 0.0021 - 0.0048 for WM (Good et al., 2001; Smith et al., 2006; Taki et al., 2004). Our reproducibility results are also in agreement with previous findings (Reiss et al., 1998). We conclude, therefore, that our procedures and methodologies are valid, as well as reliable.

Visual examination of segmentation results showed that the GM discrepancy resulted from underestimation of GM volume by SIENAX, which misclassifies GM as CSF, especially in deep cortical structures such as the insula and cingulate gyrus. The same pattern was also observed in the difference image in normalized space. In searching for possible causes, one mechanism may be bias-field correction. Because SPM and SIENAX are both intensity-based segmentations with bias-field correction integrated into the algorithm, the end result is sensitive to the amount of correction. Bias-field correction algorithms attempt to correct for non-uniform image intensity and recover the true image intensity; it is difficult, however, to verify their accuracy without knowing the ground truth (Guillemaud and Brady, 1997; Van Leemput et al., 1999a, 1999b). We examined the actual bias-field correction magnitude between SIENAX and SPM in normalized space, and found good topographic agreement between the maximal discrepancy in correction magnitude and the degree of GM underestimation by SIENAX. SIENAX without priors, therefore, seems to overestimate the bias-field in deep grey matter, and then misclassify it as CSF. With priors turned on, bias-field correction was regularized by the spatial distribution of priors, bias field overestimation was prevented, and GM was correctly classified.

We conclude that a non-expert user, employing default parameter and option settings in SIENAX, is likely to encounter severe GM underestimation and CSF overestimation, especially in deep cortical structure. Prior probability maps are, therefore, essential for accurate segmentation with SIENAX, at least with normal brains as used here. There is ongoing debate in the literature regarding the use of priors in studies of grossly deformed diseased brains. To overcome some of the bias introduced by use of default MNI priors, some authors have implemented custom priors in Alzheimer's disease and Huntington's disease (Douaud et al., 2006; Good et al., 2001; Karas et al., 2003). In the unified segmentation model in SPM5, priors are no longer stationary and are warped to match individual scan, intended to reduce the bias. Note also that we did not test other available segmentation tools, such as Freesurfer (Fischl et al., 2002; Fischl et al., 2004; Makris et al., 2006), because our aim was only to test the two most common methods.

In the absence of an external 'gold standard', testing the concordance between two methods may help to validate both. Our results suggest excellent agreement between SIENAX and SPM when both use prior probability maps. However, if SIENAX is used in its default mode without invoking priors, it severely underestimates grey matter volume, especially in deep areas, possibly due to suboptimal bias-field correction. In this default mode, SIENAX suffered from significant errors in segmenting our data.

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Figure 1. Parenchymal (mean $\pm$ SD) volumes estimated by SIENAX and SPM5 for 56 healthy subjects studied (30 males and 26 females). Solid and dotted lines represent gray matter (GM) and white matter (WM), respectively.

SIENAX GM<SPM GM SIENAX CSF>SPM CSF

Figure 2. Normalized difference images of GM and CSF using 56 subjects. Bright voxels represent a difference value of 0.25 and higher.

Bias SPM < Bias SIENAX

Figure 3. Normalized difference images of bias-field image using 56 subjects. Bright voxels represent where SIENAX bias-field correction is greater than SPM.

Table 1

Parenchymal volumes against age regressions by SPM, SIENAX, and SIENAX with priors in Figure. 1.

Compartment/Method	r	P	Regression Equation
GM (Grey Matter)			
SPM	− 0.54	< 0.0001	0.8170652 - 0.0032097 Age
SIENAX	− 0.56	< 0.0001	0.6496466 - 0.0026568 Age
SIENAX with priors	− 0.58	< 0.0001	0.7998251 - 0.0033065 Age
WM (White Matter)			
SPM	− 0.33	0.01	0.5459458 - 0.0018545 Age
SIENAX	− 0.43	0.001	0.5868354 - 0.002232 Age
SIENAX with priors	− 0.30	0.02	0.5484376 - 0.0015588 Age