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Effect of Non-rigid Registration Algorithms on Deformation Based Morphometry: A Comparative Study with Control and Williams Syndrome Subjects

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Abstract

Deformation Based Morphometry (DBM) is a widely used method for characterizing anatomical differences across groups. DBM is based on the analysis of the deformation fields generated by non-rigid registration algorithms, which warp the individual volumes to a DBM atlas. Although several studies have compared non-rigid registration algorithms for segmentation tasks, few studies have compared the effect of the registration algorithms on group differences that may be uncovered through DBM. In this study, we compared group atlas creation and DBM results obtained with five well-established non-rigid registration algorithms using thirteen subjects with Williams Syndrome (WS) and thirteen Normal Control (NC) subjects. The five non-rigid registration algorithms include: (1) The Adaptive Bases Algorithm (ABA); (2) The Image Registration Toolkit (IRTK); (3) The FSL Nonlinear Image Registration Tool (FSL); (4) The Automatic Registration Tool (ART); and (5) the normalization algorithm available in SPM8. Results indicate that the choice of algorithm has little effect on the creation of group atlases. However, regions of differences between groups detected with DBM vary from algorithm to algorithm both qualitatively and quantitatively. The unique nature of the data set used in this study also permits comparison of visible anatomical differences between the groups and regions of difference detected by each algorithm. Results show that the interpretation of DBM results is difficult. Four out of the five algorithms we have evaluated detect bilateral differences between the two groups in the insular cortex, the basal ganglia, orbitofrontal cortex, as well as in the cerebellum. These correspond to differences that have been reported in the literature and that are visible in our samples. But our results also show that some algorithms detect regions that are not

detected by the others and that the extent of the detected regions varies from algorithm to algorithm. These results suggest that using more than one algorithm when performing DBM studies would increase confidence in the results. Properties of the algorithms such as the similarity measure they maximize and the regularity of the deformation fields, as well as the location of differences detected with DBM, also need to be taken into account in the interpretation process.

Keywords

Non-rigid Registration; Deformation Based Morphometry; Williams Syndrome; Jacobian

1. Introduction

Non-rigid registration is a core component in many medical image analysis processes. Typical applications include spatial normalization, atlas-based segmentation, and deformation-based morphometry (DBM). Atlas-based segmentation refers to a technique in which structures of interest are first delineated in one or several reference image volumes. These reference volumes, also called atlases are registered to a new volume, often called the target volume, and the registration transformation is used to transfer labels from the atlases to the target volume. If the registration is accurate, accurate segmentation can thus be obtained. DBM commonly refers to a set of techniques in which features extracted from the deformation fields computed with non-rigid registration algorithms are used to detect differences between groups (Ashburner et al., 1998; Gaser et al., 1999; Chung et al, 2001). It is an alternative to the more widespread voxel-based morphometry (VBM) techniques (Ashburner and Friston, 2000).

Over the last five to ten years, a number of non-rigid registration algorithms have been proposed but their comparison and evaluation is a difficult task. As opposed to rigid-body problems for which a ground truth can be established and used to measure registration accuracy (West et al, 1997), evaluation of algorithms designed for non-rigid registration remains somewhat empirical. Several approaches have been proposed, and studies have compared these algorithms using metrics such as tissue overlap measures (Hellier et al., 2003; Christensen et al., 2006; Crum et al, 2004; Yass and Stark, 2009) or dispersion of homologous landmarks (Ardekani et al., 2005). Recently, Klein et al. (2009) conducted what is the most comprehensive study we are aware of in which 14 algorithms are compared using tissue overlap measures. However, evaluating the effect of non-rigid registration algorithms on DBM-derived findings remains largely unaddressed. One exception is the work of Yanosky et al. (2009) in which the power and stability of large-deformation registration schemes combined with various matching functionals were studied with tensor-based morphometry.

The goal of this work is to determine the sensitivity of DBM-based findings to the non-rigid registration algorithms used to conduct the study. To avoid the bias introduced by a single subject in DBM analysis, a group template with average anatomy is usually created (Yoon et al., 2006; Chiang et al., 2007; Borghammer et al., 2010) as the DBM atlas to which all volumes are subsequently registered. We thus begin by investigating whether or not the choice of a particular non-rigid registration algorithm affects the creation of this group atlas.

We then perform DBM analysis using five different non-rigid registration algorithms to detect regional differences between the groups. To do so we use two metrics, one is sensitive to volumetric differences, the other to anatomic variability. A major difficulty with comparative DBM studies is the lack of ground truth. One unique feature of this study is the fact that we have used samples from populations for which detailed anatomical differences have been studied and reported. We show that our group atlases preserve these characteristics. We can thus relate DBM findings to visible anatomical differences in these atlases. The remainder of this article is organized as follows: In the next section, we describe the data and methodology we have used. Section 3 reports our results. Our discussions are presented in Section 4.

2. Materials and Methods

2.1 Data and preprocessing

Our study was conducted on a set of 26 subjects. Thirteen of these (8 males, 5 females; mean age, 23.6 ± 4.2 years) were subjects with Williams Syndrome (WS) and thirteen were age-matched typically-developing Normal Control (NC) subjects (7 males, 6 females; mean age, 23.1 ± 5.8 years). Williams Syndrome is a rare genetic disorder caused by the deletion of approximately 25 genes in the 7q11.23 region of the genome (Reiss et al., 2000; Korenberg et al., 2000). WS subjects have mild to moderate intellectual disability and particular deficits in visual-spatial skills, but they also display unique behavioral features such as hypersociability, hyperaffiliative behaviors, atypical, highly expressive language and enhanced fascination with music (Bellugi et al., 2000). There are well-documented anatomical differences between NC and WS subjects, including decreased overall brain and cerebral volumes (Reiss et al., 2000; Chiang et al., 2007), differences in corpus callosum shape (Schmitt et al., 2001a), shortened dorsal end of the central sulcus (Galaburda et al., 2001; Jackowski et al., 2005), anomalous sylvian fissure morphometry (Eckert et al., 2006a), enlarged cerebellar vermis (Schmitt et al., 2001b), and a bilateral reduction in anterior and posterior insular volume (Cohen et al., 2011).

Images were acquired with a 3T Philips Achieva MRI scanner with an 8-channel receiver head coil and 80 mT/m gradients (100mT/m/ms slew-rate). For each subject, a 3D T1-weighted anatomic volume was obtained with a turbo field echo (TFE) sequence with matrix size of $256 \times 256 \times 170$ and voxel size of 1mm^3 . All scans were acquired at the Vanderbilt University Institute of Imaging Science. All scans were corrected for intensity non-uniformity using the N3 algorithm (Sled, 1998). To orient all the volumes in a standard pose, one of the volumes was registered to the MNI template (Collins et al., 1994). This was done by registering one volume to the MNI atlas with an affine transformation and then using the rigid body component of the transformation. (This was done because differences in head coverage and head size did not permit accurate registration with only a rigid body transformation.) All the other volumes were then registered to this first one using a rigid-body transformation computed with a standard intensity based registration algorithm (Maes et al., 1997). The Normalized Mutual Information (NMI) was used as similarity measure (Studholme et al., 1999). All the computations in this study were carried out on the

Advanced Computing Center for Research and Education (ACCRE) cluster at Vanderbilt University.

2.2 Creation of group atlases

To determine whether or not the choice of registration algorithm affects the shape of group atlases, we have used each registration algorithm to create two atlases, i.e., one for the WS group and the other for the NC group. This was done also to determine the extent to which group atlases would capture anatomic differences that have been documented previously. A number of procedures have been reported in the literature to create group atlases (Guimond et al., 2001; Bhatia et al., 2004; Kochunov et al., 2002; Kovacevic et al., 2004). We have selected a widely used iterative method put forth by Guimond et al. (2000). For a group of image volumes, one volume is first randomly chosen as an initial atlas to which all the other volumes in the dataset are registered. The forward (i.e., from the subjects to the atlas) and the backward (i.e., from the atlas to the subjects) deformation fields are computed. As will be discussed further, some registration algorithms produce both fields when others require additional computations to obtain one from the other. The subject images are deformed with the forward fields and intensity averaged. The average of the backward fields is then applied to this intensity average to produce an updated group atlas. The process is repeated until convergence, which is typically achieved after three or four iterations.

The group atlas creation process was performed in two steps. First, one WS volume and one NC volume were selected to initialize an affine atlas creation process. One affine WS atlas and one affine NC atlas were computed with only affine transformations to mitigate the potential bias introduced by the starting volumes. Then all the volumes were registered to their respective affine atlas with nine-parameter affine registrations adjusting for the brain size differences. Second, one of the affinely registered volumes was randomly selected within each group as initial volumes for the iterative creation of the non-rigid atlases. The non-rigid atlases were computed with each of the five non-rigid registration techniques used in this study (these algorithms are described below). Overall ten atlases based on non-rigid registration algorithms were thus computed, five WS and five NC.

To investigate the impact of registration algorithms on DBM results, one single DBM atlas had to be produced. This was done as described above except that all the volumes were pooled together. This process started with the calculation of an overall affine atlas and all the 26 volumes were affinely registered to this overall affine atlas. Then an overall average intensity and shape volume, called the DBM atlas, was computed. As will be shown in section 3.1, the choice of non-rigid registration algorithm has little impact on the creation of atlases. The overall DBM atlas was thus created with one single non-rigid registration algorithm. The Adaptive Bases Algorithm (ABA) (Rohde et al., 2003) that was developed in-house and described below has been used for this purpose. Once the overall DBM atlas was computed, five non-rigid registration algorithms were used to calculate the non-rigid transformations that register the 26 affinely registered volumes to this DBM atlas. For each registration algorithm, we thus produced 26 deformation fields; these were then analyzed and compared.

2.3 Non-rigid registration algorithms

We selected five well-established non-rigid registration algorithms for comparison: 1) the Image Registration Toolkit (IRTK) (Rueckert, et al. 1999); 2) the FMRIB Nonlinear Image Registration Tool (FSL) (Anderson et al., 2008); 3) the Automatic Registration Tools (ART) (Ardekani et al., 2005); 4) the Adaptive Bases Algorithm (ABA) (Rohde et al., 2003); 5) SPM normalization (Ashburner and Friston, 1999). IRTK and ART were among the best-ranked registration algorithms in Klein's study (Klein et al., 2009). We added ABA because we have developed it and FSL and SPM because they are widely used. Each algorithm is described briefly in the following subsections. Each algorithm outputs deformation fields in a different format and some but not all generate both the forward and the backward fields. Techniques that were used to obtain these are detailed below.

2.3.1 IRTK—IRTK uses the Normalized Mutual Information (NMI) as the image similarity measure to maximize (Rueckert, 1999). The deformation field is modeled as a linear combination of 3D B-splines. The executable for IRTK *nreg* can be downloaded from: <http://www.doc.ic.ac.uk/~dr/software>. Utilities are provided to generate the forward deformed images and the associated deformation fields. There is no utility provided to produce the inverse deformation field. In this study, we have generated these fields with the FSL *inwarp* facility. This required modifying the format of the forward deformation fields produced by IRTK to make them compatible with *inwarp*.

2.3.2 FSL—The FSL non-linear image registration (FNIRT) tool is included in the FMRIB Software Library (FSL) (<http://www.fmrib.ox.ac.uk/fsl/>). The deformation field is modeled as a linear combination of basis-functions that can be quadratic or cubic B-splines. The similarity measure is the sum-of-square difference between the images. The algorithm produces a series of coefficients that can be used to produce the deformed images with a utility called *applywarp*. The forward and reverse deformation fields are obtained with the utilities *fnirtfileutils* and *invwarp*, respectively.

2.3.3 ART—The Automatic Registration Toolbox (ART) is a non-parametric method (Ardekani, 2005) that maximizes the local cross-correlation between the two images. The ART tool can be found at NITRC: <http://www.nitrc.org/projects/art/>. The *3dwrapper* utility generates the deformed images and forward deformation fields. Computing the inverse deformation fields requires an additional step performed with the utility *ivf*. Both the forward and inverse deformation fields are in the NIFTI format. As such, the real displacement fields need to be computed from those stored in the file using a scale factor called *scale_slope* that is found in the file header.

2.3.4 ABA—The ABA algorithm (Rohde, 2003) models the deformation field as a linear combination of radial basis functions and optimizes the normalized mutual information between two images. The ABA executable *cspline* generates the forward and inverse deformed image and deformation fields automatically. The forward and inverse deformation fields are constrained to be inverses of each other.

2.3.5 SPM—The normalization utility in SPM8 is an algorithm that minimizes the mean square difference between a template and a warped source image using a deformation field generated with a linear combination of about 1000 low frequency three-dimensional cosine bases (Ashburner and Friston, 1999). The forward and inverse deformation fields can be obtained with the Deformations Toolbox in SPM8.

2.4 Features used in our DBM analysis

We have used two features estimated from the deformation fields to perform our DBM analysis: the Jacobian determinant of the transformation and the magnitude of the local displacement.

Jacobian determinant: The Jacobian determinant (referred to as JAC in the remainder of this article) of a 3D transformation is defined as follows:

$$JAC(x, y, z) = \begin{vmatrix} \frac{\partial(Dx)}{\partial x} & \frac{\partial(Dx)}{\partial y} & \frac{\partial(Dx)}{\partial z} \\ \frac{\partial(Dy)}{\partial x} & \frac{\partial(Dy)}{\partial y} & \frac{\partial(Dy)}{\partial z} \\ \frac{\partial(Dz)}{\partial x} & \frac{\partial(Dz)}{\partial y} & \frac{\partial(Dz)}{\partial z} \end{vmatrix}$$

in which the vector $[Dx, Dy, Dz]$ is the vector of displacements at position (x, y, z) . The *JAC* measures local volume changes. Values greater than one indicate tissue expansion and values smaller than one indicate tissue compression. A value of one indicates no volume change. It is a measure that is commonly used in DBM-based studies (Davatzikos et al., 1996; Gaser et al., 1999; Chung, et al., 2001; Chiang et al., 2007; Wang et al., 2007; Cardenas et al., 2007).

Magnitude of the deformation field: The magnitude of the deformation field (referred to as *DFM* in the remainder of this article) is defined as follows:

$$DFM(x, y, z) = \sqrt{Dx^2 + Dy^2 + Dz^2}$$

The *DFM* has been used (Kovacevic et al., 2004; Yoon et al., 2006; Han et al., 2008) as a measure of variability in a set of image volumes. If all the volumes in a set were exactly identical, the group atlas would be identical to the volumes, and the magnitude of the deformation field would be zero. The larger the difference between volumes the larger their “distance” from the atlas volume and the larger the displacement needed to register a particular volume to this atlas.

2.5 Statistical Analysis

Statistical comparison of *JAC* and *DFM* across groups was carried out using the general linear model regression implemented in SPM8. For each registration algorithm, two sample voxel-wise t-tests were computed between the NC subjects and the WS subjects, leading to one T map for each of the two DBM features. Family Wise Error (FWE) corrections based on the random field theory (Worsley et al., 2004) was performed to address the multiple

comparison issues at both peak and cluster level inferences. Peak-level correction permits identification of focal differences between groups while cluster-level correction reveals more diffuse differences. In all the results presented in this study an uncorrected p value of 0.001 was used to threshold the T maps ($T > 3.47$, $df = 24$). A corrected p value of 0.05 was used as the significance threshold at both peak and cluster levels. Clusters that survived after either peak or cluster level correction were deemed statistically significant.

2.6 Comparisons of DBM Results

Every registration algorithm used in this study produced statistically significant clusters. However, the number, size, and position of these clusters varied across algorithms. Thus, comparing these algorithms is difficult. Even answering the simple question “Are these algorithms detecting the same region of interest?” is complicated because regions produced by several algorithms may overlap partially or several small regions produced by one algorithm may overlap with a single larger region produced by another algorithm. To address this issue, we have developed the following scheme. First, for each algorithm, binary images were produced in which a voxel value is one if the voxel is within a significant cluster and zero otherwise. This is illustrated schematically in Figure 1 for three registration algorithms. Then these binary images were added with each other, producing an image in which voxel values range from zero to N with N the number of registration algorithms. We call this image the membership map and it is shown on the bottom left of Figure 1. Here, values in the membership map range from 0 to 3 and voxels are color-coded to reflect this (1 = blue, 2 = green, 3 = red). This membership map has three connected regions R1, R2, and R3. Regions in the membership maps are then filtered using a membership value threshold. In the example shown in Figure 1, regions that do not contain voxels with a value of 3 are eliminated. The final region of interest is defined as the union of the binary masks that overlap with the connected region that contains voxels with a value of 3. Following the example illustrated in Figure 1, the rectangular regions produced by algorithms A and B and the two small bottom regions produced by algorithm C would be considered to be the same region across algorithms. In our study, we compare five algorithms and we use a membership threshold of 4 to select regions of interest.

Since our analysis is performed in DBM atlas space, the localization of the statistically significant clusters is not based on standard Talairach coordinates. Instead the names of the regions are obtained by visual comparisons of our DBM clusters with labeled MRI images using two apps for the iPhone: the iSurf Brainview v3.0.0 (<http://itunes.apple.com/app/isurf-brainview/id381072423?mt=8>, Netfilter, Rio de Janeiro, Brazil) based on the MRI automatic segmentation produced by FreeSurfer and the Brain Tutor 3D (<http://www.brainvoyager.com/iOS/iphonebraintutor3d.htm>).

3. Results

3.1 Effects of Registrations on Group Atlas

Figure 2 presents ten group atlases that have been produced using the method described in Section 2.2. Each column shows the NC atlases (top), the WS atlases (middle), and the difference between the two (bottom) for each of the five algorithms used herein.

Qualitatively, there is little difference between the atlases except that the volumes produced by SPM are slightly blurrier. The difference volumes show that anatomic differences highlighted by ABA, IRTK, FSL, and ART are largely similar. One obvious difference is that the NC atlases are larger in size than the WS atlases; this is in accordance with what has been reported in the literature (Reiss et al, 2000).

It has also been documented (Galaburda et al., 2001; Jackowski et al., 2005) that WS subjects have shorter central sulci that do not come as close to the inter-hemispheric line as those in control subjects. These studies were performed manually on individual scans. Figure 3 shows cortical renderings of the group atlases in which the central sulcus has been delineated (red lines for the NC group and green lines for the WS group). This figure shows that the group atlases produced by different registration algorithms preserve such gross anatomical differences between the two groups that have been previously reported in this population.

The midline length and bending angles of the corpus callosum (CC) were defined by Schmitt et al. (2001a) and measured on individual subjects. Their work showed that WS have a shorter midline and a larger bending angle. In this study, we segmented the mid-sagittal CC, extracted the CC skeleton and measured the skeleton length and bending angles automatically on each individual as well as on the 10 group atlases. We confirmed that WS subjects have a statistically significant shorter CC midline length ($p=0.003$) and a larger CC bending angle ($p<0.001$) than NC subjects. Figure 4 illustrates CC shape differences between the WS and NC atlases using ABA as the registration method.

Figure 5 compares the CC measurements on group atlases using five registration algorithms and the group means of individual measurements. This figure shows that both the midline length and bending angles in the group atlases are representative of the values observed in the samples as a whole.

Based on our results, we can conclude that the choice of a particular registration algorithm has little effect on the resulting group atlases at both the cortical and deep brain structure levels. To simplify our analysis of DBM results, we have thus used a single algorithm to produce an overall DBM atlas based on the pooled WS and NC volumes. We have chosen ABA to do so because we are most familiar with this algorithm.

3.2 Raw T maps

Figure 6 shows the raw T maps that have been obtained with the five algorithms (columns) for both the JAC and DFM features (rows). In this figure, warm colors indicate that the feature values are larger for the NC subjects than the WS subjects; cold colors mean the opposite.

A number of observations can be made from these images. First, general patterns are somewhat similar across algorithms except for SPM. Second, the smoothness of the maps varies across algorithm. This is related to the smoothness of the deformation fields and it is more pronounced for the JAC than the DFM because the former is based on the derivative of the fields. These figures show that ART produces the least smooth T-maps. ABA comes

second, followed by FSL and then IRTK. We have used the SPM8 utility to estimate the smoothness of the JAC and DFM map expressed as full width at half maximum (FWHM) in the X, Y, and Z directions. These values, which are shown in Figure 7, are used to calculate FWE corrected p values using Random Field Theory (Worsley et al., 2004). Based on these results, one could anticipate that various algorithms will produce regions of statistical significance that not only vary in size but also in location, (e.g., ART could lead to small focal regions that are statistically significant when other algorithms may produce larger regions).

3.3 DBM Results Obtained with the JAC and DFM Features

Figures 8 and 9 show anatomical differences between the NC and WS groups uncovered by DBM with the JAC and DFM features after FWE correction for each of the non-rigid registration algorithm. In both figures, pixels with uncorrected p values smaller than 0.001 ($T > 3.467$, $df = 24$) that are part of a statistically significant cluster at either cluster/peak or both levels are shown in color based on their T values. Each column shows DBM results for one algorithm superimposed on the DBM atlas. As was the case earlier, warm colors mean that a larger value of the feature was observed in the NC subjects than in the WS subjects. Cold colors mean the opposite. Following the scheme detailed in section 2.6, common regions of interests across algorithms were identified using a membership threshold value of 4, i.e., at least 4 algorithms found this region to be statistically significant after FWE correction (corrected $p < 0.05$). A value of 4 was chosen rather than 5 because SPM detected very few significant voxels. Statistical results are overlaid on one subject deformed to the DBM atlas and statistical significance after FWE corrections are reported as follows. If a cluster in a region (there can be more than one cluster in a region for one specific algorithm) is significant at both peak and cluster level, a solid circle is drawn around the region. If only cluster level significance is found, a dashed line circle is drawn. If the clusters are significant only at the peak level, a starred line circle is drawn. Regions without circles are statistically significant regions at either peak/cluster level or both levels after FWE corrections that are found by less than four algorithms.

Three consistent regions of interests (ROIs) were found when the JAC feature is used. Two of them (R1 and R2) indicate volumetric enlargement in the NC subjects localized bilaterally around the insular cortex, Sylvian fissure, putamen, pallidum, and some white matter. R3 is localized in the center of the cerebellum and suggests that WS subjects show an enlargement of the cerebellum. These ROIs were found by DBM with ABA, IRTK, FSL, and ART. The DBM results based on the SPM normalization are qualitatively and quantitatively different. This algorithm only finds one large region located in the frontal lobe that is significant at both peak and cluster levels.

There are also a number of other statistically significant clusters found by less than four algorithms (see figure 8). ABA found a cluster around the anterior cingulate cortex close to the genu of the CC showing volumetric enlargement for NC subjects. ABA, IRTK and FSL all found clusters around the middle of the corpus callosum that indicate volumetric enlargement for NC subjects. FSL and ART found volumetric reduction for NC subjects around the splenium of the CC. These clusters are likely caused by differences in shape in

the CC between NC and WS groups. ABA, IRTK, FSL and ART all found different clusters in the brain stem, but these regions do not overlap. FSL also found one cluster around the posterior part of the superior frontal sulcus showing a volumetric reduction in NC subjects.

Two consistent regions of interests (R1 and R2) were found when using the DFM feature. ABA, IRTK, FSL, and ART found clusters significant after peak level and/or cluster level correction bilaterally across the insular cortex, orbitofrontal gyrus and temporal pole. These blue patches indicate more anatomical variations in WS subjects than in NC subjects, though the size and distribution of clusters vary across algorithms. SPM also found a cluster in R1 with an uncorrected p of 0.001, but this region was not significant after FWE correction (not shown). FSL found two other unique clusters around the left superior frontal gyrus (significant at both levels) and left inferior frontal gyrus (significant at only cluster level).

Tables 1 and 2 list all the clusters found in each ROI by different algorithms and their levels of significance after FWE corrections for the JAC and the DFM features, respectively. For example, in region 1 in table 1, ABA found two clusters significant at cluster level, IRTK found one contiguous region significant at both peak and cluster levels, FSL found one contiguous cluster significant at both peak and cluster levels (note that this cluster is very large and extends across hemispheres; we separated the voxels in the left and right hemispheres for analysis purpose), and ART found three isolated clusters all significant at cluster level and two of them are significant at peak level. The rest of tables 1 and 2 can be interpreted in the same way. The significance information in table 1 and 2 is also reflected in the circle line types in figure 8 and 9 respectively.

3.4 Relating DBM findings to observable anatomical differences

The group atlases provide us with a means of relating findings produced by DBM analysis to visible anatomical differences between two groups. Indeed, section 3.2 has shown that the group atlases preserve group anatomical differences across normalization algorithms at both cortical and deep brain structure levels. To correct for size differences between the groups and thus permit observation of local differences between these groups, the WS and NC group atlases were registered to the DBM atlas with a nine-degree freedom transformation. Figure 10 schematizes the process. The top panel shows an axial view in the NC atlas (left) and the WS atlas (right) obtained with the ABA algorithm. The bottom panel shows the deformed group atlases (NC on the left and WS on the right) registered to the DBM atlas (middle) with affine transformations. The horizontal lines have been drawn on the deformed group atlases (pink for NC while cyan for WS) to show that affine transformations have compensated for width differences in the atlases. Group differences, after affine transformations, are clear and highlighted with curved lines drawn on the deformed group atlases. The anterior end of the right insular cortex (shown with red arrows) extends further in the NC atlas than it does in the WS atlas. On both hemispheres, there are lateral displacements between the NC and WS groups along the coursing of the cortical area circumscribed by the sylvian fissure, the superior temporal gyrus and the inferior insular cortex. Notably, the DBM atlas is somewhere in the middle.

Figure 11 compares visible anatomical differences between groups and regions of statistically significant differences found by DBM with ABA, IRTK, FSL, and ART. In this

figure, the top panel shows the zoomed view of the bottom panel in figure 10 (subpanel A–C), as well as the color-coded intensity differences between the deformed NC and WS atlases (subpanel D). The bottom panel displays the DBM results of JAC based on different registration methods superimposed onto the DBM atlas over region R1 (see figure 8).

To interpret these results, one needs to keep in mind that all the non-rigid registration algorithms that have been used in this study are intensity-based. Typically, these algorithms will be driven by regions of high contrast, i.e., edges in the images. The transformations in regions of low contrast are plausible interpolations whose smoothness depends on the regularization scheme or the mechanism used by each algorithm to model the deformation fields. As seen on the top panel figures, a larger area of gray matter is present in the anterior part of right insular cortex in the NC atlas than in the WS atlas (marked with red arrows). This is also reflected as a blue blob in subpanel D. Thus, the DBM atlas had to be expanded in this region to match the NC group and contracted to match the WS group. The DBM results based on all four algorithms indeed found that the NC group has a larger volume than the WS group in the right anterior insular cortex. DBM results also show that this statistically significant different region spans the putamen, pallidum, and some white matter. Subpanel D doesn't show obvious differences between group atlases around the basal ganglia (putamen and pallidum), however the lateral displacements of the cortical area (shown with yellow arrows) between the group atlases are apparent. Registration algorithms need to displace this particular cortical area laterally and medially when matching the DBM atlas to the NC and WS groups, respectively by stretching or compressing the low-contrast region of basal ganglia. DBM results have detected areas of such expansion, whose patterns are a function of the transformation smoothness (e.g., ART detects several localized regions of expansion when IRTK detects one single large one).

Figure 12 compares the cerebella in the WS and the NC atlases after these have been registered to the DBM atlas with a nine-degree freedom transformation. The cerebellum contours have been drawn in pink on the deformed NC atlas and in cyan on the deformed WS atlas, showing that the cerebellum is larger in the WS group than it is in the NC group after adjusting for brain size differences. It also shows that the lobes are better separated in the NC atlas than in the WS atlas. In the bottom panel, colored clusters of statistically significant differences between JAC values in the NC and WS groups are superimposed on the DBM atlas. Here, the algorithms had to expand the cerebellum in the DBM atlas to make it match the cerebellum in the WS group and compress it to make it match the cerebellum in the NC group. The blue patches reflect JAC values larger for the WS group than the NC group. Smoothness of the deformation fields computed by each algorithm influences the location and extent of the patches. The lack of contrast inside the cerebellum and good contrast with the surrounding CSF explains that ABA, IRTK, and FSL find regions in the middle of the cerebellum, which would be expected if a structure with uniform intensity was expanded and the algorithms were driven by the edges of this structure. FSL and ART both find another region of statistical significance in the anterior vermis. ART producing the least smooth deformation fields also leads to the most local differences. ABA, IRTK, and ART also find some regions of expansion over the brainstem region. These differences are likely caused by the compression over the cerebellar region.

Figure 13 relates observable group differences with the DBM results obtained with both the DFM and the JAC features with the different registration algorithms. The top panel shows a sagittal view of the atlases that cover a sub-region of the right anterior insular cortex, the only region over which statistically significant differences are found with both the DFM and JAC features. Pink and cyan lines were drawn to highlight the boundary of the anterior right insular sulcus on the deformed NC and WS atlases respectively, showing that the two groups have distinct sulcal patterns around this area. The middle panel shows areas of statistical significance obtained with the DFM feature over this region for all registration algorithms. These results indicate that the WS group has more anatomical variation around the anterior insular cortex, the orbitofrontal gyrus and the temporal pole than the control group. The bottom panels show the regions of statistical significance when the JAC feature is used. These results indicate a region of enlargement around the right anterior insular sulcus in NC subjects. DBM results obtained with the DFM and JAC features thus indicate that there are more anatomical variations and a volumetric reduction around the anterior portion of the insular cortex in the WS group compared to the NC group.

4. Discussion

We have used five different non-rigid registration algorithms (ABA, IRTK, FSL, ART and SPM) to study the effect of registration on atlas creation and on results produced by DBM analysis. We have shown that the choice of a particular registration algorithm has little effect on the creation of group atlases. Using data sets acquired from population samples with documented anatomical differences, we have also shown that all the algorithms we have studied as well as the method used to produce the atlases preserve anatomical differences between groups at both cortical and deep brain structure levels. Previous work on structural differences in WS samples relies on volumetric measurement and shape delineation performed manually or semi-automatically on individual subjects. Most of these measurements were carried out on two data sets acquired by Reiss and colleagues (Reiss, et al., 2000; Galaburda et al., 2001; Schmitt et al., 2001a) and by Jackowski and colleagues (Jackowski et al., 2005). Differences observed between our group atlases correlate well with these findings. This indicates both that morphological characteristics of WS brains are stable across samples and that group atlases that capture these characteristics can be created automatically.

The effects of non-rigid registration algorithms on DBM analysis using both the JAC and the DFM features were compared both qualitatively and quantitatively using voxel-wise regression analysis. All the algorithms we studied except for SPM produce generally similar T maps. After FWE corrections at both peak and cluster level inferences (uncorrected $p < 0.001$; corrected $p < 0.05$), different registration methods generate statistically significant clusters that are different, both in terms of size and location. This is more pronounced for the JAC than the DFM feature. These differences can be explained, in part, by the smoothness of the deformation fields produced by each algorithm and the similarity measure used to drive the algorithms.

ABA and IRTK both maximize the normalized mutual information between the images and both model the deformation field with spline-like basis functions. There is more agreement

between these two algorithms than between other pairs of algorithms. FSL also models the deformation field with spline functions but uses the intensity difference between the images as its similarity measure. This may explain several unique clusters found around the cortical area by this algorithm. ART leads to smaller and more scattered clusters compared to the other algorithms. This is because this algorithm optimizes a local similarity metric in a non-parametric fashion. It may permit the detection of small structural differences but our results suggest that it leads to regions that are artificially broken into several small pieces. Even though the normalization utility in SPM is widely available and easy to use, our results show that it is not the best approach to use when performing DBM studies due to the low degree of freedom in the modeling of deformation fields.

Our study shows that the interpretation of DBM results needs to be done carefully and that the characteristics of the registration algorithm used in the study need to be taken into consideration in the interpretation process. For instance, DBM results obtained with the JAC show that the NC group has higher JAC values around the anterior insular cortex and the basal ganglia (putamen and pallidum) than the WS group. Without looking at the anatomic group atlases we have generated, one may be tempted to conclude that the relative volumes of the anterior insular cortex, putamen and pallidum are larger in the NC group than they are in the WS group. Another Jacobian-based morphometry study (Chiang, et al., 2007) performed with the ANIMAL (Collins et al., 1995) registration algorithm concluded that WS subjects have disproportionally decreased volumes around the basal ganglia and the thalamus. However, drawing such conclusion from JAC differences in DBM results alone is not prudent. Indeed, as was discussed earlier, the group atlases show obvious bilateral displacements of the sulcus regions surrounding the inferior insular sulcus, sylvian fissure, and superior temporal gyrus as well as differences in the anterior part of the insular cortex (Figure 11). Previous work showed anomalous sulcal and gyral morphometry in the sylvian fissure (Eckert et al., 2006) as well as increased cortical thickness around the right perisylvian area in a WS sample (Thompson, et al, 2005). Cohen et al. (2011) measured the morphometry of the insular cortex on individual subjects and found that both the anterior and posterior insular volume were reduced bilaterally after accounting for reduced total brain volumes in WS subjects. Our DBM results reveal consistent findings for the anterior insular cortex, and the group atlases also showed a more anterior orientation of the anterior insular sulcus in the NC atlas than that in the WS atlas (Figure 13). However, there is a lack of contrast around the basal ganglia (the putamen and the pallidum), where the deformation is thus somewhat arbitrary and a function of the normalization scheme used in the non-rigid registration algorithm. Thus, it is possible that apparent volume differences in these regions are caused by displacements driven by the cortical areas. To the best of our knowledge no measurement of the putamen and pallidum have been made in individual subjects. We thus cannot verify that areas of statistical differences detected by DBM in these regions are real.

Results obtained over the cerebellar area also show that drawing very specific conclusions on group differences based on DBM analysis alone is difficult. ABA, IRTK, FSL, and ART all find differences in this region but little can be said except that the overall volume of the cerebellum is larger in the WS group than in the NC group. Schmitt et al. (2000b) examined the cerebellar vermis on 20 subjects with WS and 20 age and gender matched NC subjects, showing that the posterior vermis is significantly larger in WS. Our JAC-based DBM results

only found differences in the center of the cerebellum showing that the algorithms we have compared can only detect gross volumetric changes over the cerebellum and not substructure differences.

Although not used as often as the JAC, the magnitude of the deformation field (DFM) may be a useful feature to use to find anatomical variation differences in groups that cannot be detected by an approach that is only sensitive to volumetric changes. All registration algorithms except for SPM detect more anatomical variations in WS subject around the anterior insular cortex and orbitofrontal gyrus in both hemispheres using the DFM. Several VBM studies have shown bilateral differences in gray matter density around the orbitofrontal area (Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Eckert et al., 2006b), which may be related to our findings. Also, surface-based analysis performed on cortical folding showed that the WS subjects have generally shallower olfactory sulcus compared to NC subjects (Van Essen, et al., 2006). However, we do not know of any work that has compared anatomical variability in WS and control samples, so we cannot relate our findings to previous reports. Our results suggest that a detailed analysis of this general orbitofrontal area may reveal other differences between NC and WS subjects.

In conclusion, to the best of our knowledge, this is the largest study that compares DBM results obtained with various well-established registration schemes. The subjects on which this study has been conducted permits comparison of DBM findings to observable anatomical differences, thus providing us with a good ground truth surrogate. Our study shows that the effect of non-rigid registration algorithms on the creation of atlases is negligible, meaning that all the algorithms we have evaluated are able to produce warped images that look alike with the exception of SPM that produces slightly more blurred images because of the smoothness of the deformation field it produces. Comparing differences between the group atlases with previously published results, we can conclude that our atlases are representative of their respective group. But our study also shows that registration algorithms have a substantial effect on DBM results both qualitatively and quantitatively. Even though general trends are similar across algorithms, specific conclusions that may be drawn when using one algorithm versus the other may vary substantially. When performing DBM analysis, our suggestion would thus be to use more than one algorithm and to look for regions that are consistently labeled as significant across these algorithms. Interpretation of the DBM results also requires taking into consideration the location of the detected regions of compression or extension, e.g., in a region of high or low contrast, the way the algorithms operate and the properties of the deformation field. While DBM results based on DFM and JAC can be used as good screening tools to identify differences between groups, specific conclusions on the nature and the location of these differences should only be drawn after careful analysis and possibly after correlating these findings with other biological or behavioral measurements.

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Figure 1.
Region selection for DBM results comparison.

Figure 2.

The creation of group atlas for NC (top panel) and WS (middle panel) group using registration algorithms (from left to right): ABA, IRTK, FSL, ART, SPM. The image differences are shown at the bottom.

Figure 3.

Central sulcus tracing on the group atlases for NC (top panel, red lines) and WS (bottom panel, green lines) groups using registration algorithms (from left to right): ABA, IRTK, FSL, ART, and SPM.

Figure 4.
CC shape differences between NC and WS.

Figure 5.
Effects of registration on Corpus Callosum (CC) shape differences for NC and WS atlases.

Figure 6.
T maps on JAC (top row) and DFM (bottom row) using different registration algorithms.

Figure 7. Smoothness estimation (FWHM in X, Y and Z directions) for DFM and JAC T maps for different registration algorithms (from left to right): ABA, IRTK, FSL, ART, and SPM.

Figure 8.
DBM results based on JAC differences between NC and WS groups using registration algorithms.

Figure 9. DBM results based on DFM differences between NC and WS groups using registration algorithms.

Figure 10.
Scheme of affine transformation of group atlases to the DBM atlas (highlight of observable differences).

Figure 11.

Top panel: A) deformed NC atlas, B) DBM atlas, C) deformed WS atlas, and D) Image differences between A and C (Colormap range: $[-160, 160]$). Bottom panel: The DBM results of JAC based on a) ABA, b) IRTK, c) FSL, and d) ART. The pink and cyan lines were drawn on the deformed NC and WS atlas respectively.

Figure 12.

Top panel: A) deformed NC atlas, B) DBM atlas, C) deformed WS atlas, and D) Image differences between A and C (Colormap range: $[-160, 160]$). Bottom panel: The DBM results of JAC based on a) ABA, b) IRTK, c) FSL, and d) ART. The pink and cyan lines were drawn on the deformed NC and WS atlas respectively

Figure 13.

Top panel: A:) deformed NC atlas, B) DBM atlas, C) deformed WS atlas, D) Image differences between A and B (Colormap range: $[-160,160]$). Middle panel: The DBM results obtained with the DFM feature with different registration algorithms superimposed on the DBM atlas. Bottom panel: The DBM results obtained with the JAC feature with different registration algorithms superimposed on the DBM atlas. The cyan and pink lines delineate the boundary of the right anterior insular cortex drawn on the deformed WS and NC atlas respectively.

Table 1

Summary of DBM results based on JAC over three ROIs

Region Name	Methods	T_max	Corr.P_pk	Corr.P_cl	Cluster size
R1: right hemisphere: insular cortex, sylvian fissure, putamen, pallidum, and white matter. (NC>WS)	<i>ABA</i>	6.21	0.087 [*]	<000	4639
		6.16	0.095 [*]	0.008	1535
	<i>IRTK</i>	6.08	0.018	<000	11995
	<i>FSL</i>	6.15	0.038	<000	25896 [†]
R2: left hemisphere: insular cortex, sylvian fissure, putamen, pallidum, and white matter. (NC>WS)	<i>ART</i>	8.48	0.004	<000	3724
		7.2	0.045	0.001	725
		5.61	0.649 [*]	0.001	700
	<i>ABA</i>	6.49	0.05	<000	3301
R3: cerebellum (NC<WS)		9.48	<000	<000	3530
	<i>IRTK</i>	7.82	0.006	<000	13148
	<i>FSL</i>	6.15	0.038	<000	25896 [†]
	<i>ART</i>	7.88	0.013	<000	3619
	<i>ABA</i>	5.97	0.136 [*]	<000	4901
	<i>IRTK</i>	5.71	0.043	0.043	3928
	<i>FSL</i>	6.15	0.038	0.145 [*]	1435
	<i>ART</i>	5.75	0.548 [*]	0.025	430

^{*} means corrected p bigger than 0.05.[†] means FSL has a contiguous region, and we treated it as two clusters divided by the inter-hemisphere fissure.

Table 2

Summary of DBM results based on DFM over two ROIs

Region Name	Methods	T_max	Corr.P_pk	Corr.P_cl	Cluster Size
R1: right hemisphere: insular cortex, orbitofrontal gyrus, and temporal pole. (NC<WS)	<i>ABA</i>	6.59	0.008	<.000	13664
	<i>IRTK</i>	6.19	0.006	0.003	20194
	<i>FSL</i>	5.18	0.087*	0.004	9817
	<i>ART</i>	6.22	0.041	<.000	5710
R2: left hemisphere: insular cortex, orbitofrontal gyrus, and temporal pole. (NC<WS)	<i>ABA</i>	5.91	0.029	0.003	8384
	<i>IRTK</i>	5.63	0.018	0.007	16146
	<i>FSL</i>	4.31	0.392*	0.009	8180
	<i>ART</i>	6.58	0.020	<.000	7035

* means corrected p bigger than 0.05.