Spatial normalization of injured brains for neuroimaging research: An illustrative introduction of available options

Junghoon Kim, PhD, Brian Avants, PhD, Sunil Patel, MS, and John Whyte, MD, PhD[1]

Recent advances in neuroimaging methods have allowed researchers to obtain various structural and functional parameters from an individual in a whole-brain, voxel-wise manner. To conduct group level analyses utilizing such data, a one-to-one correspondence between *voxels*[2] across individuals must be identified. The most common approach to this problem is registering individual brains to a standard template. Many sophisticated spatial registration methods are available for this purpose. However, when individual variability of the brains in the study population is substantially increased by injury or disease, achieving a satisfactory alignment across individual brains using the currently available registration protocols becomes a challenging task. Resorting to manual region-of-interest (ROI) drawing or using *affine-only transformation* may not be viable options because precise *spatial normalization* is a prerequisite for various powerful voxel-based techniques such as voxel-based *morphometry* (VBM; Ashburner & Friston, 2000), tensor-based (or deformation-based) morphometry (TBM or DBM; Ashburner et al., 1998; Gaser, Volz, Kiebel, Riehemann, & Sauer, 1999; Thompson, Woods, Mega, & Toga, 2000), voxel-based lesion-symptom mapping (VLSM; Rorden & Karnath, 2004), and coordinate-based voxel-wise meta-analyses (Fox, Laird, & Lancaster, 2005).

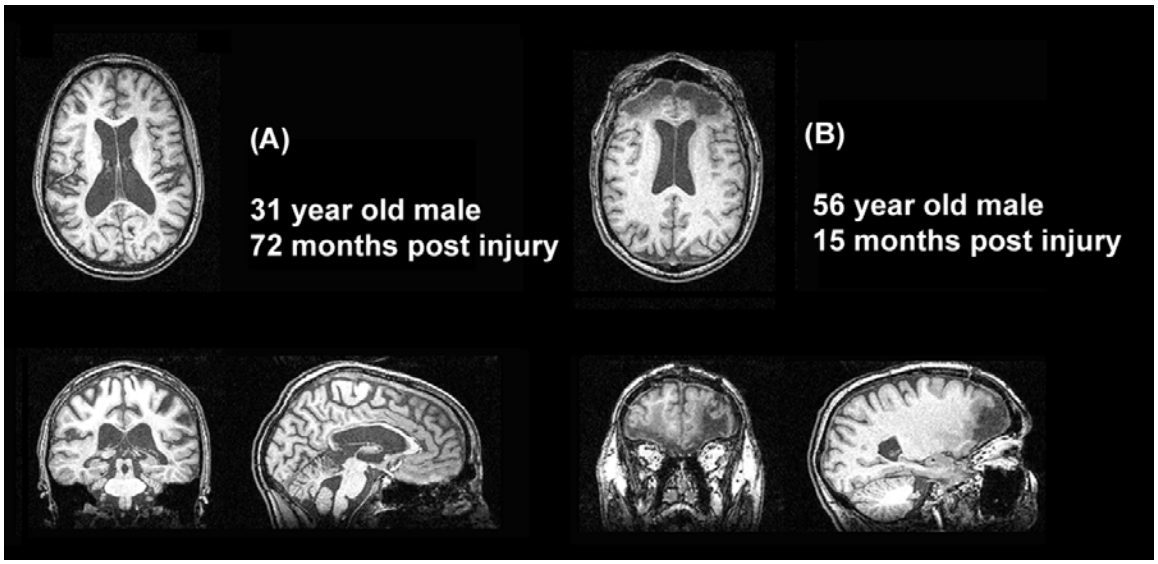

Figure 1. High-resolution anatomical scans from two survivors of TBI are used in the current study. (A) A brain with prominent diffuse injury. (B) A brain with large bilateral prefrontal focal lesions in addition to atrophy.

[1] We thank Edwardo Europa, BA and John Slattery, BA for their help in making figures, composing the glossary, and English editing.

[2] Some terms related to image registration and mathematics are explained in the glossary at the end of this document. When such terms occur for the first time, they are italicized.

The purpose of the present document is to briefly review available strategies for spatially normalizing lesioned brains to a standard template and to conduct case experiments on representative brains with severe traumatic brain injury (TBI) in order to qualitatively illustrate the relative effectiveness of each method. We chose the brains of TBI survivors for our case experiments because they show large and variable lesions. Due to the diverse etiology of TBI and complicated nature of injury progression, the brain of a TBI survivor frequently demonstrates both diffuse and focal brain lesions (Figure 1). These two types of injury patterns pose unique challenges for spatial normalization and require different approaches.

1. Normalizing brains with diffuse injury

Diffuse injury is characterized by widespread brain parenchymal atrophy accompanied by ventricular enlargement. Due to this 'non-linear' nature of diffuse injury (i.e., shrinkage in one part of the brain and enlargement in another part), a substantial amount of *non-linear transformation* is required to compensate the mismatch between the injured brain and the standard template. The more severe the atrophy, the larger degree of image *transformation* is necessitated. Until recently, most neuroimaging studies of clinical conditions with diffuse brain atrophy (e.g., TBI and neurodegenerative diseases) have used conventional non-linear normalization protocols (affine plus non-linear registration) originating from Statistical Parametric Mapping (SPM; Friston, 1995) or Automated Image Registration (AIR; Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998; Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998) software. In these implementations, the normalization process begins with affine-only transformations that involve only translating, rotating, scaling, and shearing. Then the *source image* is further matched to the template by non-linear transformation models, such as the linear combination of discrete cosine basis functions (in SPM) or polynomials (in AIR). An important limitation of these conventional protocols, however, is that they cannot fully normalize the atrophied brain due to their small *deformation* assumption (for mathematical introductions on the small and large deformation frameworks, see Ashburner, 2007; Miller et al., 1997). Essentially, the small deformation framework assumes that image matching can be done successfully with a small degree of image transformation. As a result, when large deformations are required to match the source image to the *target image*, a distortion of the original image or even a breakage in *topology* can occur (e.g., a tear or overlap in the source image). In contrast, the large deformation framework (e.g., Avants & Gee, 2004; Beg, Miller, Trouvé;, & Younes, 2005), while allowing large deformation, preserves image topology. In other words, while structures in the source image go through a large degree of transformation, structures that are neighbors are also neighbors after spatial normalization. Although not yet widely used, there has been a recent emergence of spatial normalization applications using large deformation, including the high-dimensional warping Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) toolbox (Ashburner, 2007) in SPM5, the FMRIB's Linear Registration Tool (FLIRT) in FSL, and Symmetric Normalization (SyN) in Advanced Normalization Tools (ANTS). These algorithms use a *diffeomorphism* (a differentiable map with differentiable inverse) to implement a large deformation framework. Here, we focus on SyN as a representative

method of the large deformation framework because a recent large-scale evaluation study has demonstrated its robustness compared to other state-of-the-art algorithms (Klein et al., submitted for publication).

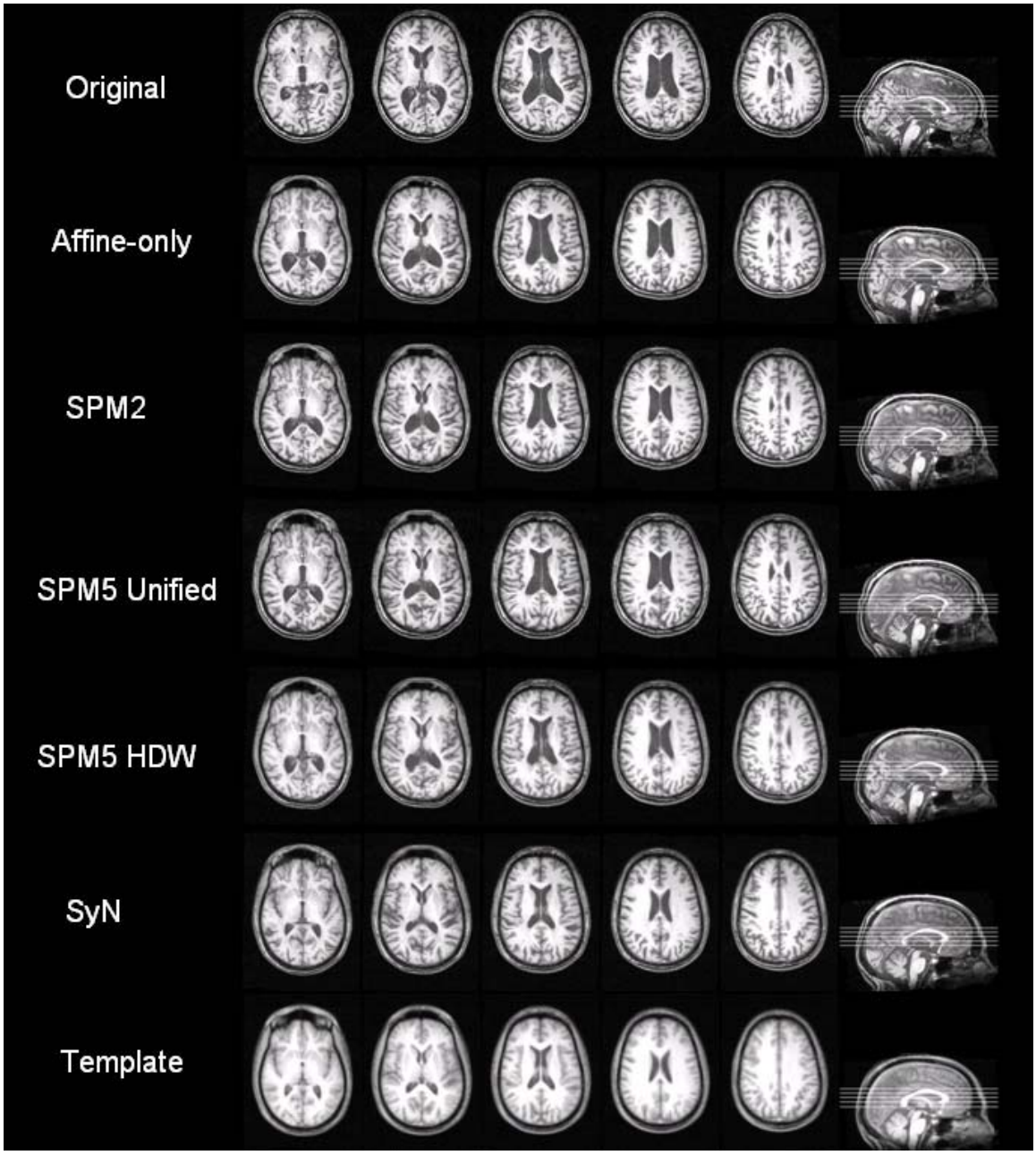

Figure 2. Spatial normalization results for the brain with diffuse pathology (see text for details). Unified = Unified Segmentation. HDW = High-dimensional Warping. SyN = Symmetric Normalization

To illustrate the effectiveness of a large deformation normalization protocol in dealing with diffuse injury, we normalized our case brain (Figure 1, A) utilizing SyN. For comparison purposes, we also processed the same brain with four more protocols: affine-

only transformation, SPM2 non-linear warping, SPM5 unified segmentation protocol, and SPM5 high-dimensional warping algorithm. These protocols implemented in SPM are utilized because SPM is the most widely used *image registration* package among clinical researchers. All SPM normalizations were conducted with default settings. The results are illustrated in Figure 2. At the top row, the original brain without any transformation is presented. At the bottom row, a customized template brain to which the original brain was registered is shown. As expected, affine-only transformation did not perform well in terms of the similarity judged by visual inspection (e.g., the comparison of the size and shape of the ventricles between the normalized brain and the template). The two low-dimensional algorithms, SPM2 and SPM5 Unified, have performed better but not as well as the two high dimension algorithms, SPM5 HDW and SyN. It seems that SyN yields better performance between the two latter protocols (e.g., in terms of matching both the ventricle size and shape to the size and shape of the ventricles in the template). These results suggest that the brains characterized with severe diffuse injury can best be normalized by large deformation algorithms using diffeomorphisms.

2. Normalizing brains with focal injury

Focal abnormalities in the injured brains pose a difficult challenge for the nonlinear models. This is due to the fact that most of the spatial registration algorithms try to match the voxel intensities across the whole brain through minimizing the *cost function*, a single output measuring the mismatch between two images. Since a focal lesion with abnormal intensity values contributes disproportionately to the cost function, it is possible that the algorithm attempts further transformation to minimize the cost function even in cases where optimal matching for other healthy areas is achieved. This starts to cause a distortion of images. The five most widely used ways to deal with this problem are described below.

First, some researchers have conducted only affine transformations that do not introduce such distortion. In an affine-only transformation, the source image is matched to the template using only a *linear transformation* involving rotation, translation, scale, and shear. Since detailed non-linear warping is not being performed by the algorithm, distortions are not introduced in and around the lesion area. However, this gain is offset by the cost of poorer matching of detailed structure between the source and template images globally.

A second method is manually applying a lesion on the standard template at the location corresponding to its location in the source image. This has the effect of reducing the difference between the source and template image attributable to the lesion that is captured in the cost function. However, the reasoning for using this approach is somewhat circular. The location of the lesion in the template space is what the algorithm is intending to reveal. However, the user must determine the location of the lesion in the template prior to running the algorithm.

A third method of dealing with focal lesions is called enantiomorphic normalization (Nachev, Coulthard, Jager, Kennard, & Husain, 2008). It is a new method which essentially involves replacing the lesion volume with the homologous volume from the contralateral hemisphere of the brain and then estimating the normalization parameters from this “artificial” brain. The resulting parameters can then be applied to

the original brain. However, this method has many limitations. For example, the lesion must be unilateral. In addition, it makes an assumption that the brain is symmetric and there is clear evidence for brain asymmetry at least in some areas. Furthermore, large unilateral lesions frequently distort across the midline, violating the symmetry assumption.

A fourth method is called a 'unified segmentation' approach. Introduced with SPM5, this approach basically combines *segmentation*, *bias correction*, and spatial normalization in a single unified model (Ashburner & Friston, 2005). Since parameter estimation alternates these three processes, spatial normalization of lesions can benefit from segmentation and bias correction steps. For example, multiple Gaussian models for tissue segmentation can help to distinguish lesioned and healthy areas. Bias correction, which includes an *inhomogeneity field*, also can help isolating a lesioned area. The unified segmentation approach is conceptually attractive because it is fully automated. However, it is implemented using a small deformation model, limiting its use for normalizing brains with diffuse pathology.

Finally, the most widely used method of dealing with focally lesioned brains to date is cost function masking (CFM; Brett, Leff, Rorden, & Ashburner, 2001). The key idea in cost function masking is that the voxels representing a lesion are not used in the calculation of the difference between two images, the cost function. Brett et al. (2001) found that cost function masking significantly improved non-linear normalization results, outperforming affine-only transformation. However, cost function masking has limitations when the lesion is large or bilateral. In addition, later work has not clearly shown a difference between the results of affine only normalization and those of a non-linear algorithm using cost function masking (Crinion et al., 2007). Recently, we developed a method that can be combined with SyN to deal with focally lesioned brains. It is tentatively called SyN with constrained cost function masking (CCFM). In essence, the method formulates brain matching in the presence of the lesion as a "missing data" problem. Because diffeomorphic mappings are defined by the *velocity field*, this formulation leads to unknown velocity field parameters within the lesioned region. The "missing" velocity field parameters are estimated by a smooth inference from the velocity field parameters outside of the lesion, in particular, near the lesion boundaries. Thus, the lesioned regions deform in the most probable way, given the deformation of the healthier surrounding tissue. This approach is related to, but markedly more 'constrained' than the original cost function masking approach; the original technique does not particularly specify the nature of the deformation within the lesion. The advantage of this method compared to the original implementation of cost function masking is that our approach performs well in cases of bilateral and/or large lesions. Figure 3 shows essential steps in SyN with constrained cost-function masking. The original brain, which is rigidly transformed (leftmost), is labeled as lesion (green) and healthy (red) areas. Then, the lesion area is 'constrained' while healthy areas go through a large deformation normalization process. The Jacobian map (middle) shows the degree of deformation. The normalized case brain (second from right) and the template (rightmost) are also shown.

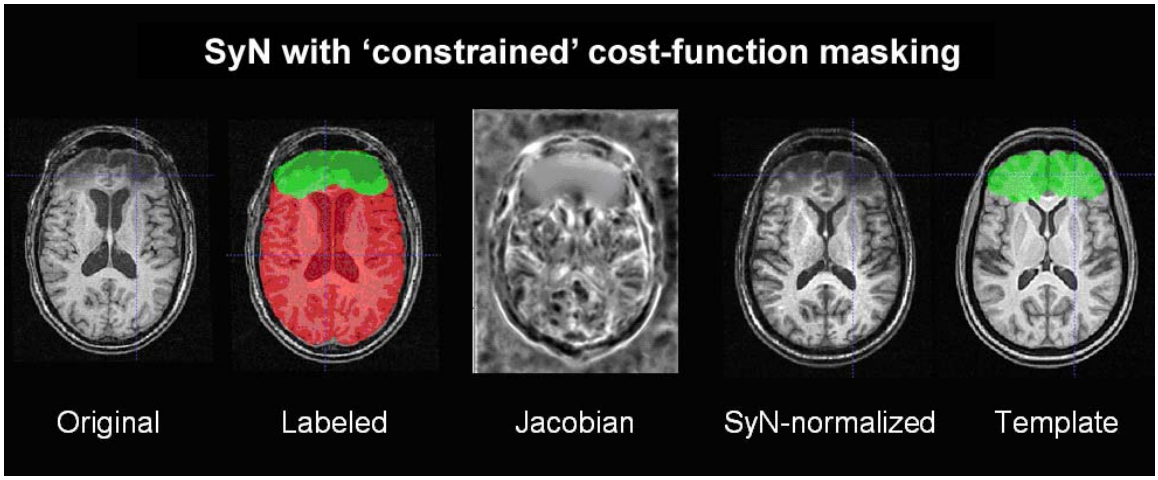

Figure 3. Steps for constrained cost-function masking (see text for detailed description).

To illustrate the effectiveness of our CCFM approach combined with SyN in dealing with focal (and diffuse) injury, we spatially normalized our case brain (Figure 1, B) utilizing different protocols. Among the protocols included are affine-only transformation, SPM2 non-linear warping with and without CFM, SPM5 unified segmentation protocol, and SyN with and without CCFM. The results are illustrated in Figure 4. At the top row, the original brain without any transformation is presented. At the bottom row, a customized template brain to which the original brain was registered is shown. As expected, affine-only transformation did not perform well in terms of the similarity judged by visual inspection. The cost function masking in each algorithm (SPM2, SPM5 Unified, and SyN) seems to have worked reasonably well without causing any lesion-related distortion. However, the two low-dimensional algorithms, SPM2 and SPM5 Unified, have not performed as well as the large deformation algorithm, SyN, in terms of matching the healthy regions. These results suggest that the brains characterized with severe focal *and* diffuse injury may best be normalized by large deformation algorithms in combination with constrained cost-function masking.

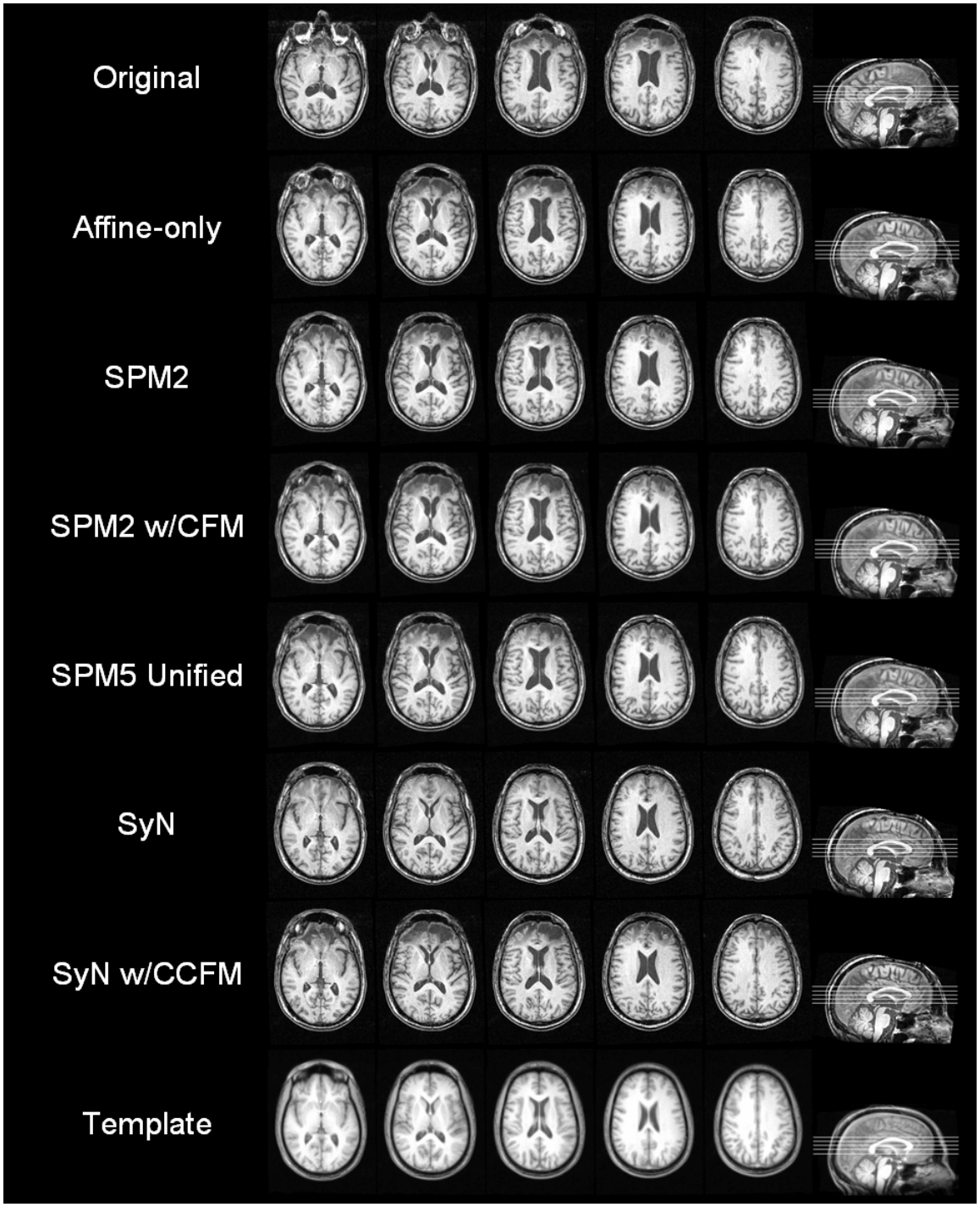

Figure 4. Spatial normalization results for the focal lesion brain with or without cost function masking. CFM = Cost function masking. CCFM = Constrained cost-function masking.

3. Concluding remarks

In this document, we have presented qualitative evidence on the performance of various normalization protocols. However, visually inspecting the similarities between the normalized source images and the template is not sufficient for evaluating the capabilities of a normalization protocol. Quantitative performance evaluation is necessary. Existing evaluation studies suggest that large deformation methods should be used for normalizing brains characterized by diffuse injury. Focal injury, frequently co-existing with diffuse injury in the case of TBI, has been found to be best dealt with by cost function masking. We have introduced a variation of the original cost function masking by directly constraining the deformation in the masked lesion area. Our method, called 'constrained' cost-function masking, is expected to improve the performance of normalization, especially in the presence of large and/or bilateral focal lesions. Finally, a fundamental limitation of the spatial normalization procedure should be acknowledged. That is, because of individual variations in functional localization, spatial normalization in terms of anatomical features does not guarantee the alignment of functionally homologous areas across subjects. Thus, caution should be exercised when anatomical normalization is applied to functional data.

4. Glossary[3]

Affine Transformation: A linear transformation (scaling, shearing, rotation) followed by a translation that preserves collinearity and ratios of distances. Such changes are imposed onto the whole brain image rather than certain portions.

Bias correction: The process of correcting intensity non-uniformities from magnetic resonance images.

Cost function: A mathematical measure of mismatch between two images. For example, SPM uses the sum of the squared differences between the voxel intensity values.

Deformation: Image transformation.

Diffeomorphism: A differentiable map with a differentiable inverse. A diffeomorphic transformation is a smooth (invertible and differentiable) transformation that preserves structure (topology) maps.

Field: An algebraic structure in which mathematical operations are performed.

Image registration: The alignment of one image to another image.

Inhomogeneity field: A spatial distribution of values across an image describing the deviation between original intensity values from corrected values.

Linear (transformation): One or a combination of the following: moving an image about a fixed point in a circular motion (e.g. rotation), enlarging/diminishing an image (e.g. scaling), stretching an image with the same magnitude and direction on both sides of a defined axis (e.g. shearing).

Morphometry: The evaluation of the variation and change in the size and shape of (parts of) the brain.

[3] In defining the terms, we tried to avoid replacing one technical term with another. This sometimes sacrificed the rigor of the definition.

Non-linear (transformation): Transformations not involving rotations, scaling or shearing. Typically, these functions are characterized by polynomials or are trigonometric functions (i.e. sine and cosine).

Segmentation: The classification of different tissues (i.e. white matter, grey matter, CSF) in the brain.

Source image: The original brain image of the subject prior to registration.

Spatial normalization: The process of mapping voxels from a subject brain onto specific locations of a template brain. Essentially, the obtained MRI images are transformed to fit the template. The purpose of normalization is to reduce brain structure variability between the various subjects.

Target image: The template brain image or what the source image will be aligned to.

Topology: A collection of points in space whose relative positioning remains unchanged by deformation transformations.

Transformation: A calculable function that alters the relative positioning and size of points in an image.

Velocity field: A summary of values spatially distributed across an image describing the speed and direction of moving fluid in particular regions.

Voxel: A 3-D element that serves as a unit of raw neuroimaging data collection.

6. References

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *Neuroimage, 11*(6 Pt 1), 805-821.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851.

Ashburner, J., Hutton, C., Frackowiak, R., Johnsrude, I., Price, C., & Friston, K. (1998). Identifying global anatomical differences: deformation-based morphometry. *Hum Brain Mapp, 6*(5-6), 348-357.

Avants, B., & Gee, J. C. (2004). Geodesic estimation for large deformation anatomical shape averaging and interpolation. *Neuroimage, 23 Suppl 1,* S139-150.

Beg, M. F., Miller, M. I., Trouvé;, A., & Younes, L. (2005). Computing Large Deformation Metric Mappings via Geodesic Flows of Diffeomorphisms. *Int. J. Comput. Vision, 61*(2), 139-157.

Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage, 14*(2), 486-500.

Crinion, J., Ashburner, J., Leff, A., Brett, M., Price, C., & Friston, K. (2007). Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. *Neuroimage, 37*(3), 866-875.

Fox, P. T., Laird, A. R., & Lancaster, J. L. (2005). Coordinate-based voxel-wise meta-analysis: dividends of spatial normalization. Report of a virtual workshop. *Hum Brain Mapp, 25*(1), 1-5.

Friston, K. J. (1995). Commentary and opinion: II. Statistical parametric mapping: ontology and current issues. *J Cereb Blood Flow Metab, 15*(3), 361-370.

Gaser, C., Volz, H. P., Kiebel, S., Riehemann, S., & Sauer, H. (1999). Detecting structural changes in whole brain based on nonlinear deformations-application to schizophrenia research. *Neuroimage, 10*(2), 107-113.

Klein, A., Anderson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M., et al. (submitted for publication). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration.

Miller, M., Banerjee, A., Christensen, G., Joshi, S., Khaneja, N., Grenander, U., et al. (1997). Statistical methods in computational anatomy. *Stat Methods Med Res, 6*(3), 267-299.

Nachev, P., Coulthard, E., Jager, H. R., Kennard, C., & Husain, M. (2008). Enantiomorphic normalization of focally lesioned brains. *Neuroimage, 39*(3), 1215-1226.

Rorden, C., & Karnath, H. O. (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nat Rev Neurosci, 5*(10), 813-819.

Thompson, P. M., Woods, R. P., Mega, M. S., & Toga, A. W. (2000). Mathematical/computational challenges in creating deformable and probabilistic atlases of the human brain. *Hum Brain Mapp, 9*(2), 81-92.

Woods, R. P., Grafton, S. T., Holmes, C. J., Cherry, S. R., & Mazziotta, J. C. (1998). Automated image registration: I. General methods and intrasubject, intramodality validation. *J Comput Assist Tomogr, 22*(1), 139-152.

Woods, R. P., Grafton, S. T., Watson, J. D., Sicotte, N. L., & Mazziotta, J. C. (1998). Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr, 22*(1), 153-165.

Acknowledgement

"Supported in part by Grant # H133G050219 from the National Institute on Disability and Rehabilitation Research, United States Department of Education (J. Whyte, Principal Investigator)"