Deformation Based Morphometry with Implicit Reference-Based Registration: Validation and Detection of Structural Changes in a Primate Model of Early-Life Stress

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Introduction

Deformation-based morphometry (DBM) has been used for examining brain structural changes during development and aging, and in various neuropathological states such as Alzheimer's disease[1,2]. However this technique has not been widely applied to cross-population morphological studies and little work has been done on its validation due to the difficulties of cross-subject registration and the lack of ground truth of the deformation field. In this work, we present a framework for the DBM technique using an implicit reference-based group (IRG) registration method[3]. Comparison between the proposed DBM method and a commonly used approach was made. Validation of cross-group volumetric comparisons using DBM was performed by simulating known volume change and deformation fields. The DBM technique was applied to a study of monkey brain morphological changes due to early life stress, and the results were compared with manual segmentation approach[4].

Methods

Framework of Deformation based morphology. Voxel-wise volumetric changes between two images can be measured by properties (e.g. the determinant) of the Jacobian of the deformation fields, which define the correspondences of the two images. Previous DBM methods used reference-based registration, which estimates transformations directly from one image to another. Here an implicit reference-based group (IRG) registration with a high-dimensional elastic deformation model was used, which simultaneously maps each image to an implicit reference space. This method does not need to select or compute the reference, resulting in smaller registration errors. For two groups of images, transformations h_{iR} from each image I_i to the reference I_R were computed using the IRG registration. To obtain the volume change from I_i to I_j, the Jacobian of the composed transformations of h_{iR} and h_{jR}^{-1} was computed: $vol(I_i)/vol(I_j)=Jac(h_{ij}^{IRG})=Jac(h_{iR}(h_{jR}^{-1}))=Jac(h_{iR})\times(1/Jac(h_{jR}))$. To compare structural differences between two groups, voxel-wise statistics on the Jacobian maps $Jac(h_{iR})$ were performed.

Validation by simulation. Two different simulation approaches were used. The first one analyzed the DBM performance under various degrees of volume change, and compared DBM using IRG with DBM using reference-based registration. Simulated human brain MRI data were downloaded from www.bic.mni.mcgill.ca/brainweb[5]; a ROI and a desired Jacobian map Jac^{des} were pre-defined; the deformation fields h_{12}^{sim} were simulated using a topology preserving transformation simulation tool[6] to match the desired volume change serving as the "ground truth"; DBM with reference-based and IRG registration was applied to estimate the Jacobian maps Jac^{ref} and Jac^{IRG}, respectively. The procedure was repeated with a set of different desired volume changes. The average Jacobian in the ROI was computed to provide the volume change obtained by DBM and simulation. The ratio of volume change (RVC) between DBM vs. simulation was also calculated. An RVC close to 1 indicates better performance. Another validation was to assess the sensitivity of the DBM method for detecting cross-group volume changes. Two groups of monkey brains were utilized. The left hippocampus (LHC) of each brain was manually segmented[4] and no significant volume difference between the two groups was found. For each image in the second group, a deformation field with a 10% atrophy (10% decrease of the original volume and $Jac(h)=0.9$) of the LHC was simulated using the same simulation tool, and was used to generate a new image with a smaller LHC. DBM was applied to the images of the first group and the second group before and after LHC shrinkage. T-tests were performed on the Jacobian maps to test for significant volume differences between the two groups before and after LHC shrinkage.

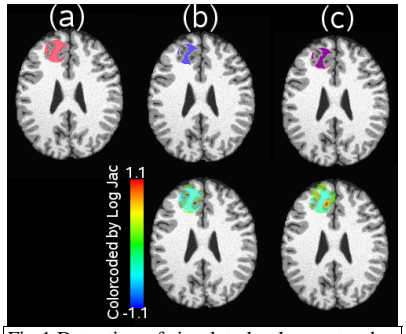

Fig.1 Detection of simulated volume atrophy. Top row: (a) a brain image (I_1) with a pre-defined ROI; (b) I_1 after a simulated 29.2% atrophy of the ROI (I_2); (c) deformed I_1 to I_2 using IRG overlaid by the simulated ROI. Bottom row: log Jacobian of the simulated transformation by IRG.

Monkey brain structural change by DBM. 28 Rhesus monkeys assigned at birth either into mother-reared (MR) or peer-reared (PR) group were used, matched for gender (7 males and 8 females vs. 6 males and 7 females), age (27.4±0.9 vs. 26.4±0.3 months) and weight (3.6±0.13 vs. 3.5±0.1 kgs). MRI images were acquired on a 3T Siemens scanner and 224 slices were prescribed to cover the whole brain with a TR of 2.5 s, a TE of3.49 ms and a spatial resolution of 0.3×0.3×0.6 mm^3. Data averaged from 4 runs were acquired using Nova DR dual surface coils. Affine registration was utilized to align each subject to a monkey brain template[7] to ensure that the overall brain volume of each subject was similar and the images were globally aligned. DBM was applied to generate Jacobian maps and voxel-wise t-tests performed. A threshold of corrected $p<0.0$ was used to generate the group difference map.

Results

Table 1 shows the DBM performance for detecting various degrees of structural change. The Jacobian maps of simulated deformations (Jac^{sim}) were set as the "ground truth" although they did not achieve Jac^{des} when the desired volume atrophy was large. As the volume atrophy decreased, DBM performed better, with RVC closer to 1. DBM with IRG registration always produced better RVC values than that with reference-based registration. An example of detecting the simulated atrophy is shown in Fig.1. The Jacobian from DBM had a similar distribution as the simulated one. Fig.2a shows that DBM did not detect any significant volume difference around the LHC between MR and PR in the original data, which is consistent with manual segmentation results, whereas a significant volume decrease was detected after simulating LHC atrophy in the PR group. Fig.2b shows significant volume increases in the PR group detected by DBM. The ROIs, which had significant volume increases in the PR group by the manual approach, are overlaid on the top, showing that DBM provides consistent but more anatomically-specific results.

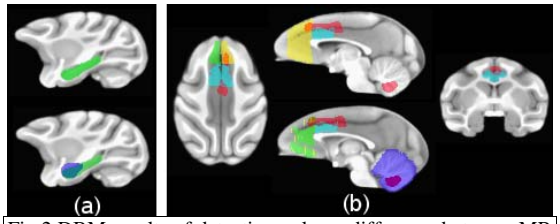

Fig.2 DBM results of detecting volume difference between MR and PR monkey brains. (a) Top: no significant difference detected; bottom: significant volume difference detected (blue) on LHC after atrophy simulation of the LHC (green) in the PR group. (b) Significant volume differences detected by DBM (red) overlaid by ROIs (yellow & green: right & left medial PFC, cyan: dorsal ACC, blue: cerebellar vermis) which were shown to have significantly large volumes in PR compared to MR.

Discussion and Conclusion

DBM with IRG registration was proposed and the performance was examined in this study. DBM results were consistent with the simulated "ground truth". IRG registration provides more accurate results compared to the commonly used reference-based registration. DBM accuracy decreases as the volume change increases. Structural changes in the monkey brain further showed that the proposed DBM is able to detect volume changes across groups and can improve upon the manual approach by providing more anatomically-specific information.

References 1.Camara et al. *Neuroimage.* 2008. 2.Verma et al. *PNAS* 2005. 3.Geng et al. *ISMRM* 2008. 4.Geng et al. *ACNP* 2008. 5.Kwan et al. *IEEE TMI* 1999. 6.Xue et al. *Neuroimage.* 2006. 7.Black et al. *Methods Enzymol.* 2004.

Jac^{des}	Jac^{sim}	Jac^{ref}	Jac^{IRG}	RVC^{ref}	RVC^{IRG}
0.5	0.708	0.835	0.755	0.564	0.837
0.7	0.778	0.864	0.796	0.613	0.916
0.8	0.836	0.895	0.8418	0.638	0.964
0.9	0.909	0.940	0.908	0.665	1.02
0.95	0.954	0.969	0.953	0.673	1.02

Tab.1 DBM performance at various volume atrophy levels.