Automated VOI Analysis in $^{18}$F-FDDNPN PET Using Structural Warping: Validation Through Classification of Alzheimer's Disease Patients

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Abstract—In the field of quantitative imaging, the creation of accurate volumes of interest (VOIs) is often of central importance. However, the process of creating these VOIs for multiple subjects can be time-intensive and there are many chances to introduce variability on inter- and intra-investigator levels. Although previous work has shown that image normalization through cortical surface mapping can be helpful in VOI analysis, the process is complicated and labor-intensive. In this paper we present a method to eliminate this variability by warping structural and functional images to a common space in which valid VOIs already exist. We apply this method to a study of Alzheimer's disease (AD) and 2-1-[6-2-[18F]fluoroethyl](methyl)amino]-2-naphthylidene)malononitrile (FDDNP), which is known to co-localize with amyloid plaques and neurofibrillary tangles. We normalize the MRIs of control subjects and mild cognitive impairment (MCI) and AD patients, to a common space. The same normalization is applied to FDDNP PET images. The normalization technique reduces average voxel-to-voxel variance in MRIs by 54% as compared to linear normalization alone. Biologically important structures, such as the segmentation between white and gray matter, are maintained after normalization. Discriminant analysis shows that data extracted from VOIs in the common space out-performs data extracted from unnormalized PET images in classifying subjects as control, MCI, or AD. This suggests that image normalization may be useful in eliminating inter- and intra-investigator variability and increasing the predictive capability of data extracted from imaging modalities. Further study will examine the applicability of this method to predicting longitudinal changes in cognitive ability from functional imaging data.

I. INTRODUCTION

In the field of quantitative imaging, the creation of accurate volumes of interest (VOIs) is often of central importance. This process, however, can be time-consuming and is known to have variance introduced on inter- and intra-investigator levels. Prokas et al. [1] have shown that spatial normalization of 2-1-[6-2-[18F]fluoroethyl](methyl)amino]-2-naphthylidene)malononitrile (FDDNP) images to a common space, through the use of cortical surface maps, can be helpful in classifying subjects into healthy control and Alzheimer's disease (AD) groups. In both living patients, as well as in post mortem studies, FDDNP has been shown to co-localize with amyloid plaques and neurofibrillary tangles (NFTs), which are the characteristic pathologies associated with AD [1]. However, the procedure of cortical surface mapping is complex and labor intensive. An improved procedure suited for automated and streamlined operation is thus warranted. We present here an automated method of extracting regional data from functional PET images by warping co-registered structural MRI images to a common space in which valid VOIs have already been created. To examine the utility of this method, we applied it to the study of FDDNP in AD. We validated this method by examining the overlap between the common space and the warped MRIs in specific structures and regions. In addition, we used data extracted from warped functional images to create a statistical model categorizing subjects as normal control, mild cognitive impairment (MCI) [2], or AD.

II. METHODS

A. Subjects

The study group was comprised of 7 AD (76±10 years, 4:3 female/male), 6 MCI (73±13 years, 4:2 female/male) and 10 control (71±10 years, 7:3 female/male) subjects. All subjects (n=23) were given mini-mental state examinations (MMSE) to assess cognitive abilities. AD patients had an average MMSE score of 23±2, MCI had an average score of 27±1, and controls had an average score of 29±1.

B. Imaging

1) MRI: A T1-weighted gradient echo (MPRage) image was taken for each subject with a 3T Siemens Allegra MRI scanner. All MRIs were normalized using the cortical surface mapping method, and regions of interest (ROIs) were subsequently drawn over nine regions on an average cortical surface map of the subjects. The cortical surface mapping was then inverted to convert these ROIs to 3-dimensional VOIs for each individual in the study [1]. In addition, MRIs were segmented into white and gray matter using the automated segmentation algorithm in SPM8.

2) PET: Each subject was given a bolus injection of FDDNP (320-550 MBq) and a dynamic PET scan was taken for up to 125 min. (six 30s frames; four 180s frames; five 600s frames; and three 1200s frames). Imaging was performed using an ECAT EXACT HR+ scanner (Siemens Corp.). After the images were reconstructed using filtered back-projection with attenuation correction, a movement correction algorithm was applied [3]. Logan analysis was performed on images to create FDDNP distribution volume ratio (DVR) images [4].
C. Analysis

One control subject was designated as the common space, to which all others would be warped. For each subject’s MRI scan, a three-dimensional diffeomorphic warp was calculated to normalize it to the common space. This was done using the symmetric image normalization method (SyN) described by Avants [5], as implemented in the software package ANTs [6]. This warp was applied to all previously drawn VOIs, segmentation images, and coregistered FDDNP-DVR images for that subject. For each subject, average FDDNP-DVR values were measured in each of the nine VOIs. This measurement was first performed using an individual’s VOI to extract data from the respective unwarped PET image (unwarped data). Next, average DVR values were extracted from warped PET images using VOIs created for the common space MRI (warped data). The warping algorithm was evaluated using the Dice overlap statistic, $\kappa$, calculated between the VOIs of the common space image and the VOIs of subjects warped into the common space.

$$\kappa = \frac{2#(A \cap B)}{#(A) + #(B)}$$

This measure has a range of [0,1], and captures the overlap between two regions, A and B. The #($X$) operator returns the number of voxels contained in region $X$. Using the statistical software SPSS (SPSS 15.0 for Windows), discriminant analysis was performed to classify subjects as control, MCI, or AD. In addition to classifying subjects solely on MMSE scores, an exhaustive search of two classes of models was performed. In the first, models were built using unwarped FDDNP-DVR data extracted from all possible combinations of VOIs; the second was built similarly, except using warped FDDNP-DVR data extracted using the common space VOIs. In both classes, models were built with and without the use of MMSE as a predictor variable. Models in all categories were ranked by classification ability and leave-one-out cross validation.

III. RESULTS

Characteristic results of the SyN warping can be seen in Fig. 1. Images warped to the common space showed a 54% reduction in average voxel-by-voxel variance within the brain as compared to variance measured after only a nine parameter linear registration. The overlap ratio, $\kappa$, between structures in the common space, and those of the 22 remaining

Fig. 1. (a) (Left) Warping Results: Average of 22 subjects MRIs after linear registration only (Top); Average of 22 subjects after warping to common space (Middle); MRI of common space subject (Bottom). (b) (Right) Voxel-to-voxel variance of unwarped (Top) and warped (Bottom) MRIs. Warping reduces average in-brain variance by 54% from linear registration alone.

Fig. 2. Overlap Statistic by Region. Data shown is average overlap, ± SD, between common space regions and warped regions of remaining 22 subjects.
TABLE I

| Model                          | Classification % | Cross-Validation % | Regions Used |
|-------------------------------|------------------|--------------------|--------------|
| Unwarped PET Data Only        | 82.6             | 73.9               | 2,4,5,8,9    |
| Warped PET Data Only          | 87               | 73.9               | 4,5,8,9      |
| Unwarped PET Data & MMSE      | 91.3             | 87                 | 4,5,8,9      |
| Warped PET Data & MMSE        | 100              | 95.7               | 4,5,8        |

IV. DISCUSSION

As can be seen in Fig. 1, the SyN algorithm is a powerful tool in normalizing a set of structural images. The strength of this method is reinforced by the data shown in Fig. 2. Although there is no way of describing statistical significance of the overlap statistic in this situation, some investigators consider good results to be $\kappa > 0.6$ for smaller structures and $\kappa > 0.8$ for larger structures [5]. The fact that we see $\kappa > 0.9$ for white and gray matter is especially encouraging, as we are warping the MRIs of some AD patients with severe cortical degeneration. Table I shows that data extracted from FDDNP-DVR images using a single set of VOIs in a common space outperforms data extracted using individual VOIs for each subject in classifying subjects as control, MCI, or AD. In addition, the models using warped data use fewer predictor variables than those using unwarped data. It should also be noted that all the discriminant models shown in Table I use FDDNP-DVR information from regions closely associated with the classical pathological progression of AD, as described by Braak and Braak [7]. The regions used in all models are the occipital-parietal region, containing regions of the basal isocortex where initial deposits of amyloid plaques are found, with increasing deposition in stage B; and the upper temporal lobe and the posterior-cingulate gyrus, which see initial amyloid deposition in stage B, with increasing deposition in stage C. Many of the models also use data from the medial temporal lobe, which is the major site of accumulation for NFTs [7]. Furthermore, no special weighting was put on these regions in the search for best discriminant models.

V. CONCLUSION

We have shown that the SyN algorithm is not only a powerful tool in image normalization, but that it also maintains biologically important structures of the warped images. We have also shown that by normalizing data to a common space and using a set of VOIs drawn in that space, one can actually improve the predictive quality of data extracted from functional images. In addition to being able to better classify subjects into their diagnostic groups, we can do so using fewer predictor variables. This is perhaps due to an elimination of intra-investigator variability by using a single set of VOIs. Further study is warranted to examine the use of this method with respect to other PET tracers as well as its application to longitudinal studies of cognitive impairment.

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