ANTs-based pipeline for preprocessing structural neuroimaging data from stroke patients

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Background and Goals

- To do second level analysis with fMRI data, neuroscientists normalize their subjects' brains to a standard space.
- Various methods have been developed to normalize brains with lesions, which present challenges to standard normalization techniques.
  - These methods include affine and linear transformations (Friston, 1995), cost function masking (Brett et al., 2001), enantiomorphic normalization (Nachev et al. 2008) and spatial normalization in a single unified model (Ashburner & Friston, 2005).
- Recent work, such as Advanced Normalization Tools (ANTs) (Avants et al., 2008), has introduced algorithms that employ large deformations to assist with normalization.
  - These algorithms use Symmetric Normalization (SyN), a diffeomorphism-based method that uses a large deformation framework. Studies in healthy populations have shown SyN's superiority in normalization (Klein et al., 2009).
- Our goals are:
  1. To improve this method by using a study-specific template as an intermediate step.
  2. Assess the effects of normalization using ANTs on second level analysis in stroke patients.
  3. Propose solutions to remove the bias the normalization method induces on the second level analysis.

Summary and Recommendations

1. Be cautious using SPM when working with brains with lesions. We recommend ANTs.
2. Report normalization differences when working between groups.
   - Ensure your seeds/ROIs are not affected by your normalization method, as this may affect second level analysis.
3. For best normalization results, use a study-specific template (shown in Figure 6). This means registering everything to the template space (instead of MNI space) to alleviate between-group normalization differences.

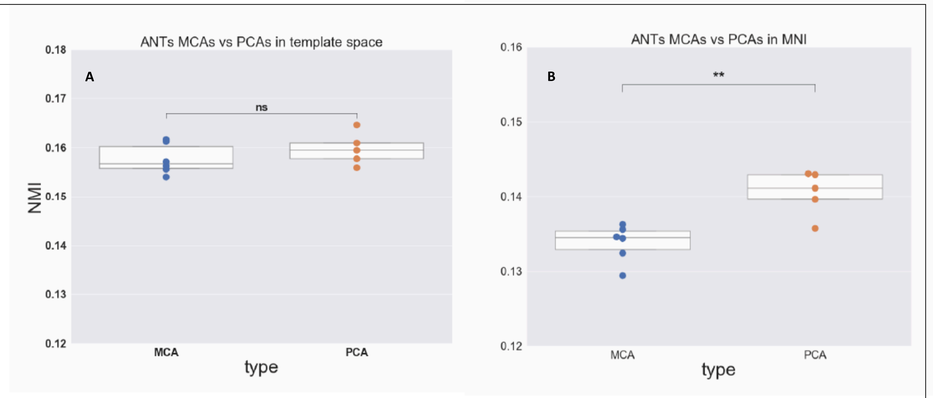

Figure 9: Normalization accuracy of MCA vs. PCA strokes when registering to MNI space compared to template space. We observed different patterns in normalization accuracy when brains from stroke patients (MCAs and PCAs) were registered to the template space (A) compared to MNI space (B). This suggests that registering to a template might reduce between patient group differences in normalization. **P<0.01 paired-t signif., n.s.: p>0.05.

Problems with SPM

- We compared our "ANTs template" method to the SPM unified segmentation method in a set of virtual lesion brains (Brett et al., 2001). We inserted lesion masks chosen randomly from a set of stroke patients into healthy control subjects' MRI scans (Figure 3). We compared normalization error (in terms of NMI difference) of the virtual lesion patients compared to the "baseline" normalization of the healthy brains (Figure 4).

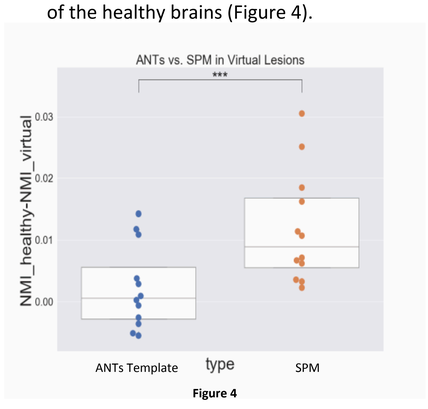

Figure 4

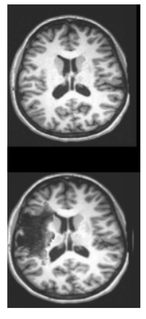

Figure 3

Our "ANTs Template" Approach to Normalization

- We used data from 11 patients (6 middle cerebral artery, 5 posterior cerebral artery strokes) and 6 healthy controls to assess normalization accuracy using our "ANTs template" method. Because ANTs outperformed SPM on the virtual lesion subjects, we chose to compare our method to the recently proposed method by the ANTs group, namely their direct normalization to MNI using CCFM ("ANTs native").

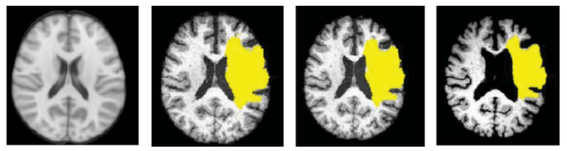

Figure 5: Example of normalization on a left MCA stroke using ANTs template, ANTs native, and SPM methods.

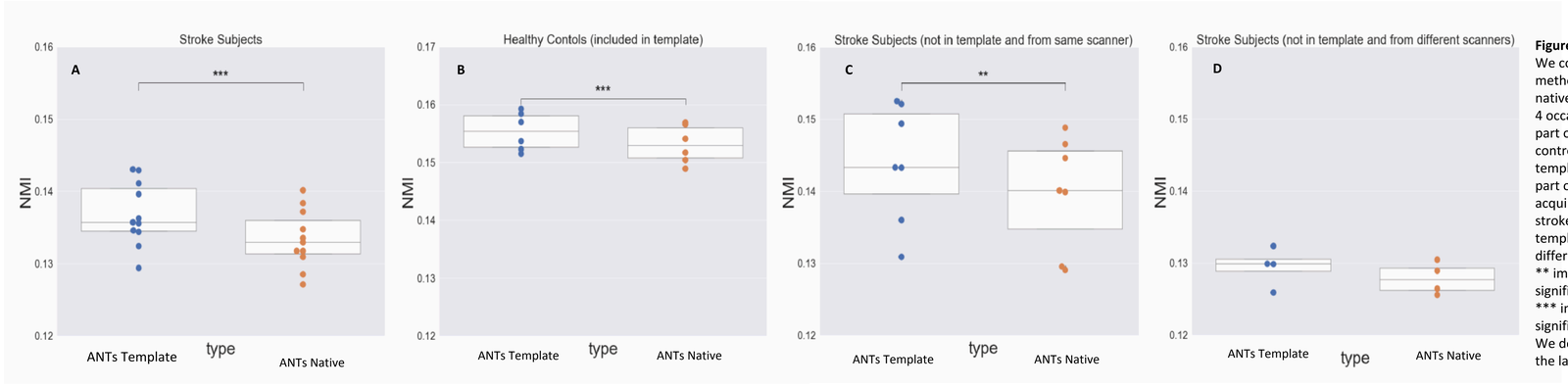

Figure 6:
We compared the "ANTs template" method's accuracy to the "ANTs native" method in terms of NMI on 4 occasions: (A) strokes that were part of our template, (B) healthy controls that were part of our template, (C) strokes that were not part of our template but were acquired on the same scanner, (D) strokes that were not part of our template and were acquired from a different scanner.
** implies P<0.01 paired t-test significance.
*** implies p< 0.001 paired t-test significance.
We do not report significance for the last case due to limited sample.

Normalization May Bias Second Level Analysis

- Normalization may effect second level analysis in stroke studies.
  - For example, ANTs and SPM give different clusters of activation when analyzing functional connectivity with the right motor cortex in 6 stroke patients compared to controls (figure 7).
- Even between groups of stroke patients, there could be induced confounds resulting from different normalization accuracies in the different groups.
  - We noticed a dependency of NMI on lesion size (figure 8) that can result in statistical differences in NMI between, for example, PCA and MCA strokes (figure 9).

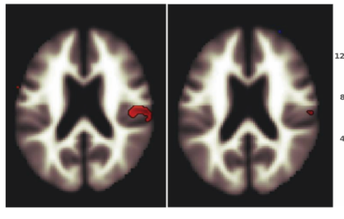

Figure 7: The significance cluster (p-uncorrected < 0.001) of right motor connectivity was different for the contrast controls > MCAs using "ANTs template" compared to the contrast controls > MCAs using SPM for normalizing brains.

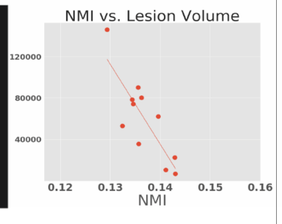

Figure 8: Anti-correlation of normalization accuracy with lesion size (in voxels) using our ANTs template method. We saw similar results using SPM and ANTs.

Methods

- We applied a two-step approach for our "ANTs template" method:
  - First, we registered individual T1s to a study-specific template.
  - Then, we registered them from the template space to MNI space.
- Our first step uses Affine and SyN, while the second step uses Affine, SyN, and CCFM.
  - The study template was constructed using an iterative method.
  - Initially, we constructed an average image. We used SyN and Affine to map each T1 to the average template.
  - Next, we made a template that minimized mean deformation error between the original images and the template.
  - This was repeated until convergence.
- Normalization accuracy was assessed using Normalized Mutual Information (NMI), which captures the shape of the joint histogram of the source and target by calculating the individual joint entropies (figure 2).

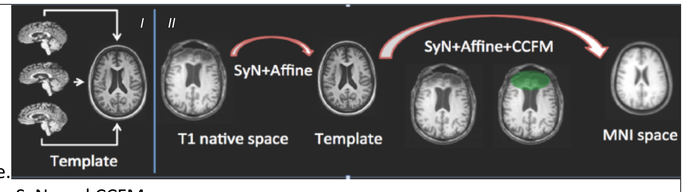

Figure 1

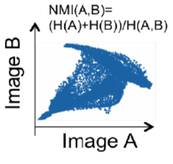

Figure 2

References: 1) Friston KJ, 1995 Human Brain Mapp 2:165–189. 2) Brett M et al., 2001 NeuroImage 14:486–500. 3) Nachev P et al., 2008 Neuroimage 39:1215–1226. 4) Ashburner J, Friston KJ, 2005 NeuroImage 26:839–851. 5) Avants et al., 2008 Image Anal 12:26–41. 6) Klein et al., 2009 Neuroimage 46:786-802.