

# Multivariate analysis of diffusion tensor imaging and cortical thickness maps in a traumatic brain injury (TBI) cohort using Advanced Normalization Tools (ANTs)

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## Introduction

TBI is a complex disease process involving mechanical disruption of neurological tissues and activation of secondary injury cascades, culminating in loss of function. Multiple neuroimaging approaches have recently been developed to detect white matter (WM) and gray matter injury following TBI. It is hypothesized that a multivariate analysis of these two imaging modalities may provide insight into the alteration of cortical and WM circuits following TBI. To address this hypothesis, we employ a novel multivariate technique, sparse canonical correlation analysis (SCCA), to quantify traumatically induced disruption of WM and cortical networks.

## Diffuse traumatic brain injury data

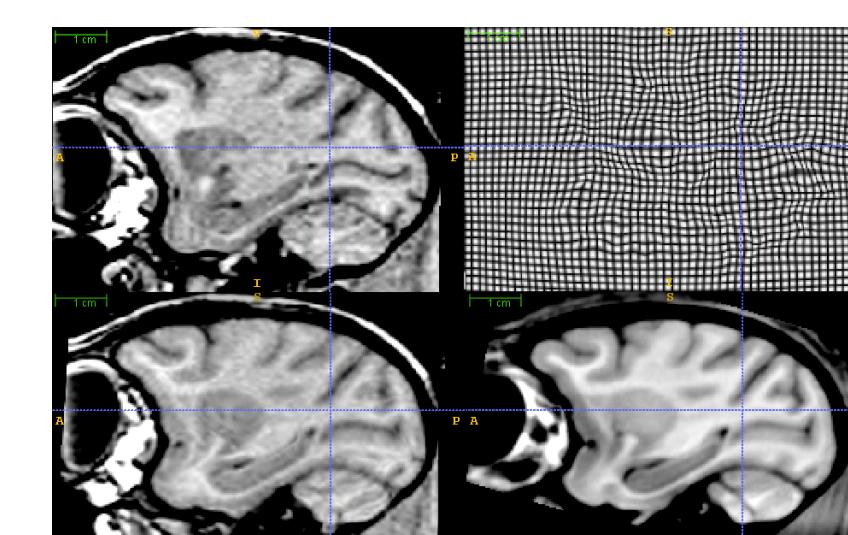
The TBI data used in this study is part of a larger effort investigating the relationship between various neuroimaging indices and cognitive and functional abilities in long-term survivors of TBI (principal investigator: John Whyte).

**Description of cohort:** 17 controls and 16 patients with TBI were used. Each patient had a history of non-penetrating traumatic brain injury of at least moderate severity defined by significant and well-documented loss or alteration of consciousness following injury in addition to meeting several other exclusionary criteria. The healthy volunteers were matched in terms of age, gender, ethnicity, handedness, and years of education.

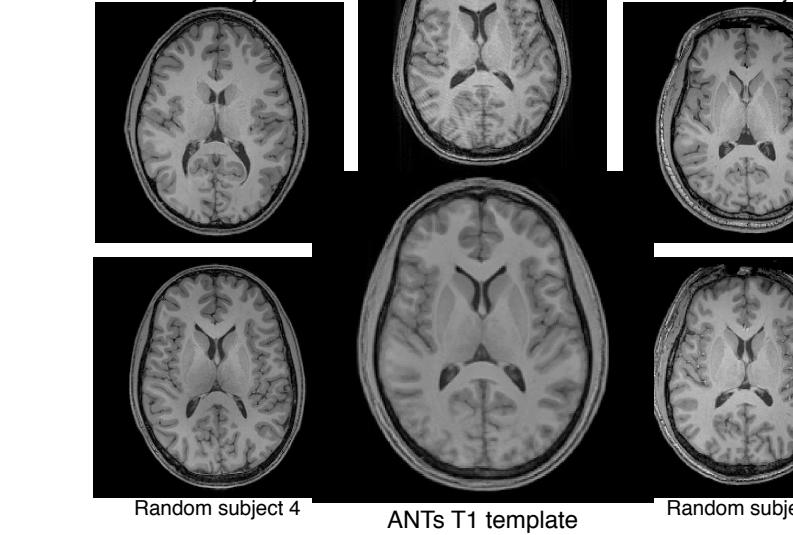
**Image acquisition:** High resolution T1-weighted anatomic images were obtained using a 3D MP-RAGE imaging sequence with the following acquisition parameters: TR = 1620 ms, TI = 950 ms, TE = 3 ms, flip angle = 15°, 160 contiguous slices of 1.0 mm thickness, FOV = 192 × 256 mm<sup>2</sup>, matrix = 192 × 256, 1NEX with a scan time of 6 minutes, and voxel size = 1 mm<sup>3</sup>. 30-directional DTI images were also obtained.

## Advanced Normalization Tools

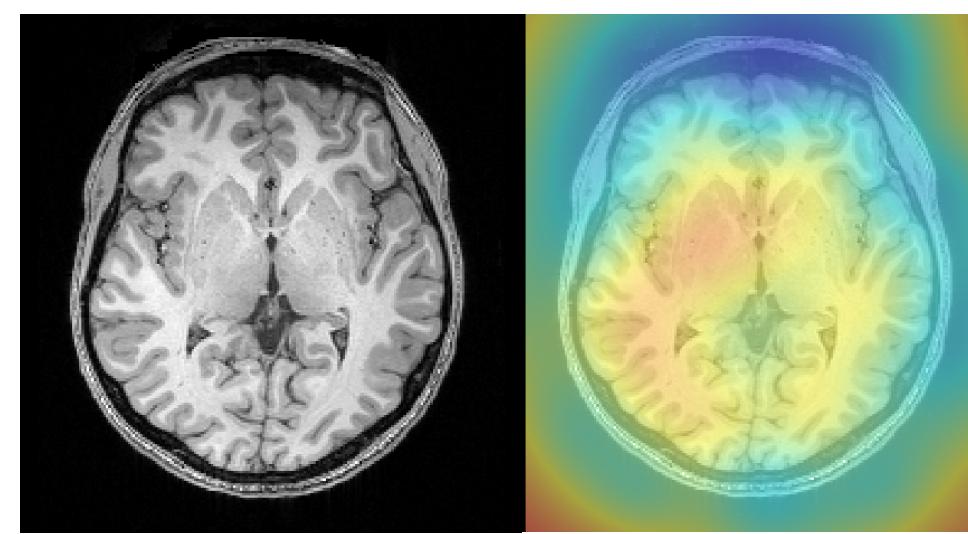
### Processing



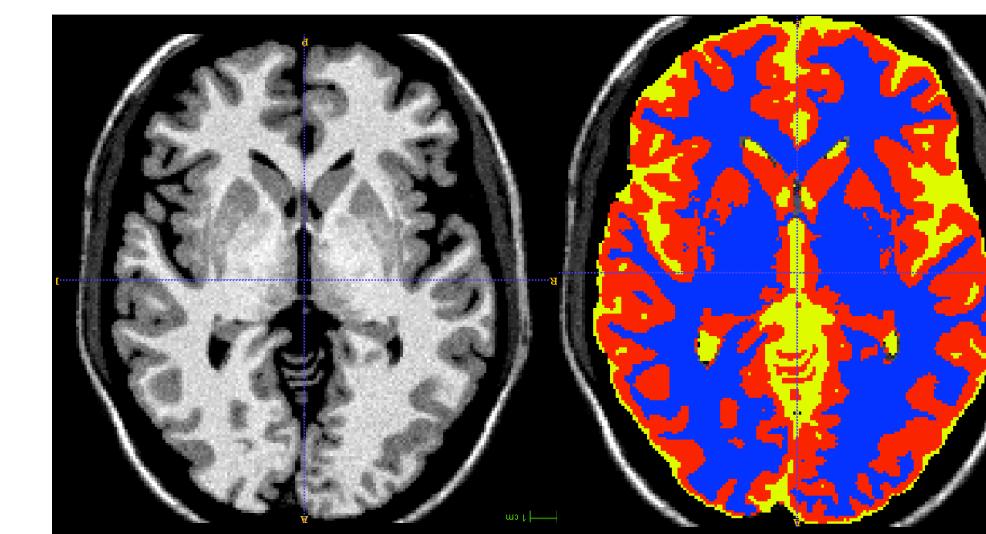
SyN normalization [2]



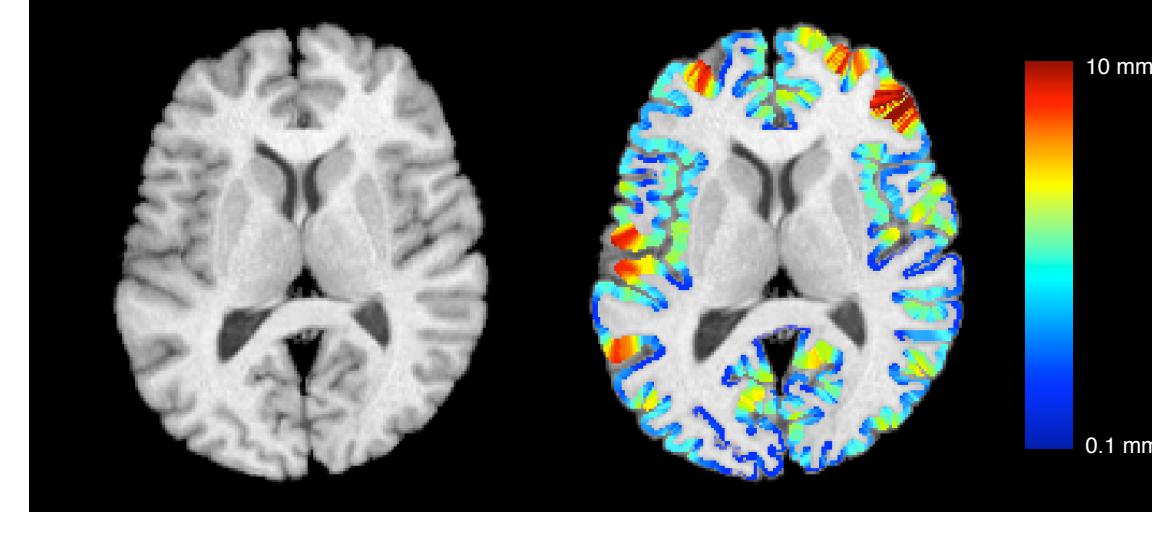
SyGN template building [4]



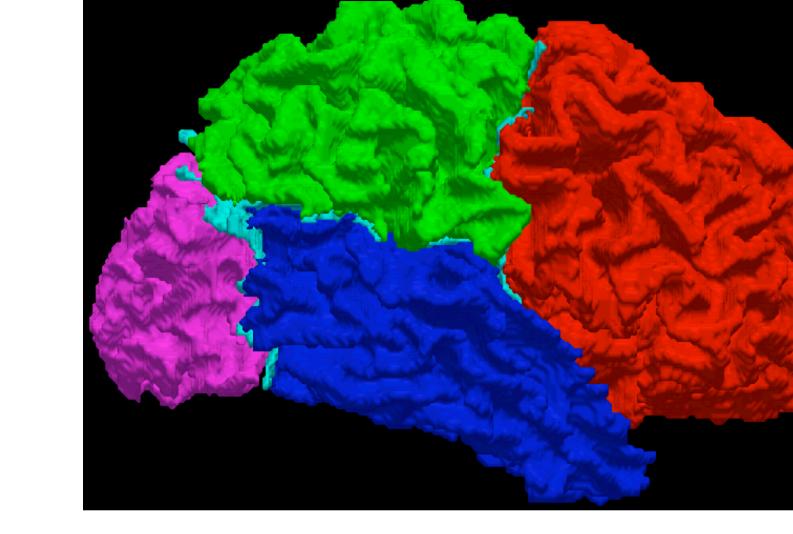
N4 bias correction [6]



Atropos n-tissue segmentation [3]



DiReCT cortical thickness [5]



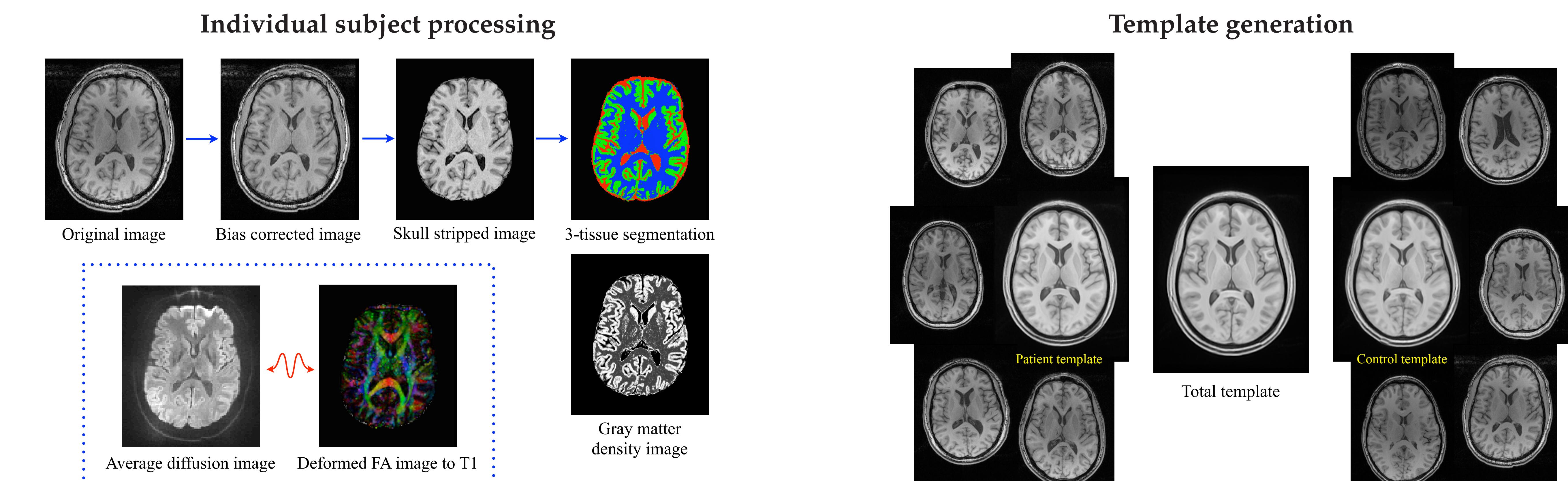
topological well-composedness [7]

### Multivariate analysis using SCCA

Sparse canonical correlation analysis (SCCA) adapts classical CCA to situations where the number of predictors is much greater than the number of subjects for inference of correlative relationships between different "views" of some underlying phenomenon. For gray matter density (G) and DTI-derived (F) views, SCCA solves the following criterion [1]:

$$\operatorname{argmax}_{\omega_G, \omega_F} \left\{ \omega_G^T F \omega_F - \lambda_G \sum_{v_G} |\omega_G|_1 - \lambda_F \sum_{v_F} |\omega_F|_1 \right\} : \|\omega_G\|, \|\omega_F\| \leq 1.$$

## Materials and methods: ANTs subject and template processing



Processing of each anatomical (T1-weighted) image consists of the following steps:

- bias correction,
- skull stripping using Atropos coupled with anatomical priors, and
- prior-based cerebrospinal fluid, white and gray matter segmentation. The latter yields the gray matter density (GMD) image for each subject.

DTI-derived fractional anisotropy (FA) images are mapped to each anatomical image using the transform obtained from registration of the average diffusion image to the corresponding T1.

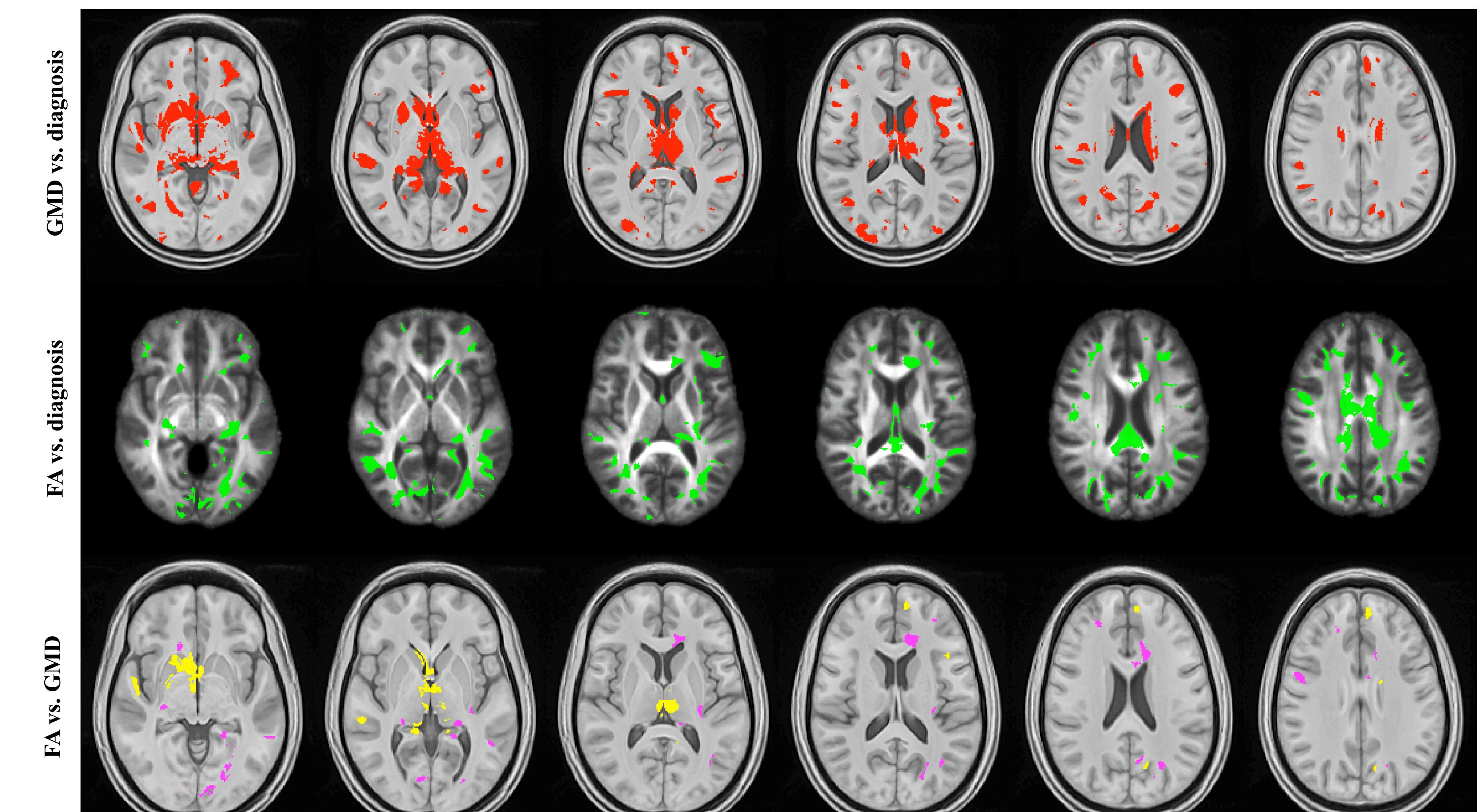
Statistical analysis requires normalization to a standard space provided by the total template. All 17 controls and all 16 TBI patients were used to generate their respective unbiased templates. These two templates were then used to generate the final/standard template. Thus the mapping from the individual GMD image to the total template is given by

$$GMD_{subject} \xrightarrow{\text{Id}} T1_{subject} \xrightarrow{\sim} \text{template}_{population} \xrightarrow{\sim} \text{template}_{total}.$$

Similarly, the mapping for each subject's FA image to the total template is given by the transform composition

$$FA_{subject} \xrightarrow{\sim} T1_{subject} \xrightarrow{\sim} \text{template}_{population} \xrightarrow{\sim} \text{template}_{total}.$$

## Multivariate analysis results



The significant correlations derived from the GMD/FA views vs. diagnostic view provide significant regions for finding correlations between GMD and FA.

## Conclusions

SCCA demonstrates significant differences between the control and patient groups in both the FA ( $p < 0.002$ ) and gray matter ( $p < 0.04$ ) that are widespread but largely focus on thalamocortical networks related to the limbic system. Specific regional differences included the medial thalamic nuclei, hypothalamus, amygdala, hippocampus, anterior cingulate cortex, orbitofrontal cortex and fornix. Using these SCCA-identified regions, we demonstrate a strong correlation ( $p < 0.01$ ) of the degree of injury in WM and GM within the patient group.

## Acknowledgments

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## Open source software



<http://www.picsl.upenn.edu/ANTs>



<http://www.itk.org/>