Multimodal neuroimaging reveals gray and white matter associations with language deficits in frontotemporal degeneration

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Introduction: Language deficits are widely reported in frontotemporal dementia (FTD), including non-fluent primary progressive aphasia (naPPA), semantic-variant primary progressive aphasia (svPPA) behavioral variant FTD (bvFTD). We hypothesize that these deficits are due to disruption of a large-scale neural network involving both language and executive resources. Here we use multi-modal MRI and sparse statistical methods to evaluate whether imaging of white matter (WM) with diffusion MRI enhances prediction of the neuroanatomic basis for their deficit when combined with cortical thickness derived from T1 MRI.

Data acquisition: A total of 69 subjects participated in the study, including 54 patients with naPPA, bvFTD or svPPA from the Penn FTD Center who were diagnosed with an FTD-spectrum disease according to published consensus criteria, and 15 healthy seniors matched to the patient group in age and education. Verbal fluency was assessed with a one-minute administration of a category (Animals) fluency test. Naming was assessed with the Boston Naming Test. MR images were acquired on a 3T Siemens scanner and consisted of an MPRAGE T1 sequence with 1mm isotropic voxels, and a diffusion-weighted sequence consisting of 4 images with b = 0 s/mm2, followed by 30 images at b = 1000 s / mm^2, 2.2 mm isotropic voxels. The MRI images are processed with the PipeDream neuroimaging toolkit http://picsl.upenn.edu/ANTS/pipedream.php, which implements multi-modal spatial normalization pipelines powered by ANTs [1] and Camino [2]. To compute cortical thickness, the T1 brain image is first segmented into three tissues using Atropos. The gray and white matter probability maps are then input to DiReCT [3]. The diffusion images are skull-stripped and diffusion tensors are calculated using Camino. Both the tensor and the T1 images are normalized to a common template space.

Table 1: R^2 for different models

Test	GM	WM	Combined
Animals	0.51	0.48	0.59
BNT	0.67	0.52	0.69

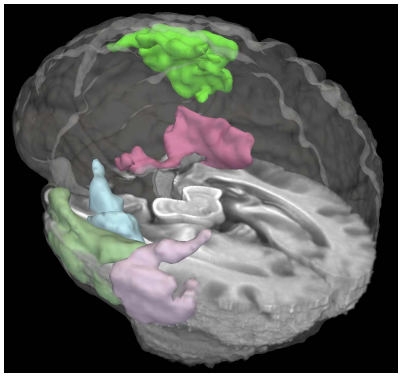

Fig 1: regions correlated with naming and fluency.

Eigenanatomy brain parcellation: We use Eigenanatomy [4] to parcellate the cerebrum into regions of interest based upon the variation in the subject population. Like Principal Component Analysis (PCA), Eigenanatomy finds a low-dimensional representation of the very high-dimensional data matrix containing all voxel data for all subjects. An innovation of Eigenanatomy is that the components are sparse, unsigned and spatially clustered, resulting in linearly weighted regions of interest (ROIs) that capture variance in the data but are also spatially specific. We compute independent Eigenanatomy for cortex (GM, excluding occipital lobe, where segmentation is less reliable) and WM. We set the number of regions to 30 for both gray and white matter. The sparsity is set to 1/30 for approximate whole-brain coverage, no ROI can exceed that fraction of the total volume of the GM or WM. The algorithm maximizes the variance in the data set that is explained by the Eigenanatomy, approximately 85% for both the GM and WM images. The variance explained is stable as we increase the number of components.

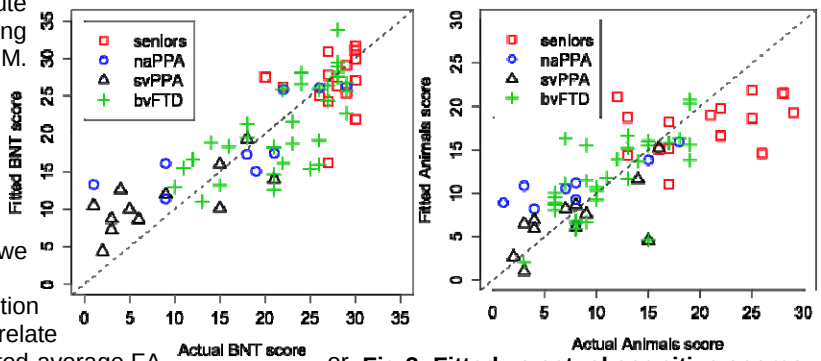

Fig 2: Fitted vs actual cognitive scores

Correlation with cognition: We apply model selection techniques to search for a subset of the ROIs that best correlate with language performance. Specifically, we use the weighted-average FA or cortical thickness over each ROI as predictors of language in a linear regression model. The *leaps* package in R [5] provides a method to test and rank subsets of a linear regression model according to the Bayesian Information Criterion (BIC). The complexity of a subset search increases exponentially with the number predictors; we search for models with 8 or fewer predictor. Separately, we run *leaps* using only GM or only WM regions.

Results: The BIC and R^2 for the GM, WM, and combined models with 3 predictors are shown in table 1. Combined models are not forced to include GM and WM, but the best models returned by *leaps* feature both kinds of predictors, and fit the data better (evidenced by lower BIC and higher R^2) than unimodal models. The relative performance of GM, WM and combined models is similar with more than 3 predictors. For BNT, GM predictors can produce a model that is almost as efficient as the combined model. For Animals, the difference in R^2 is larger when using a both modalities. The same WM ROI (fig. 1, blue), in the left inferior longitudinal fasciculus, is selected for both models. For BNT, the green cortical regions are selected, one in the left anterior temporal lobe, the other in the right frontal lobe. For Animals, the pink cortical regions include the left temporal lobe and the right insula / orbitofrontal cortex. The performance of the combined model using the regions shown in fig. 1 is shown in the plots in fig. 2.

Conclusions: Eigenanatomy, combined with linear regression, provides a powerful, data-driven method for integrating GM and WM modalities to identify large-scale neural networks supporting language and executive resources during performance of language tests in FTD. Eigenanatomy is available in ANTs (http://picsl.upenn.edu/ANTS).

References: 1. Avants et al, *Medical image analysis* 12:26-413, 2008. 2. Cook et al, *Proc ISMRM* p. 2759, 2006. 3. Das et al, *Neuroimage* 45:867-879, 2009. 4. Avants et al, *MICCAI* 2012 p. 206-213. 5. Lumley and Miller, R package *leaps* version 2.9.