Dementia Induces Correlated Reductions in White Matter Integrity and Cortical Thickness: A Multivariate Neuroimaging Study with Sparse Canonical Correlation Analysis

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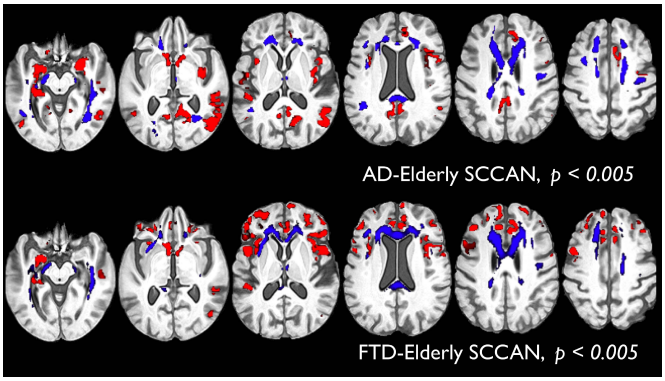
Introduction: We use a new, unsupervised multivariate imaging and analysis strategy to identify related patterns of reduced white matter integrity, measured with the fractional anisotropy (FA) derived from diffusion tensor imaging (DTI), and decreases in cortical thickness, measured by high resolution T1 weighted imaging, in Alzheimer's disease (AD) and frontotemporal dementia (FTD) [4]. This process is based on a novel computational model derived from sparse canonical correlation analysis for neuroimaging (SCCAN) that allows us to automatically identify mutually predictive, distributed neuroanatomical regions from different imaging modalities. We apply the SCCAN model to a dataset that includes 23 control subjects that are demographically-matched to 49 subjects with autopsy or CSF-biomarker diagnosed [2] AD (n=24) and FTD (n=25) with both DTI and T1 structural imaging. SCCAN shows that the FTD-related frontal and temporal degeneration pattern is correlated across modalities with permutation corrected $p < 0.0005$. In AD, we find significant association between cortical thinning and reduction in white matter integrity within a distributed parietal and temporal network ($p < 0.0005$). Furthermore, we show that—within SCCA identified regions—significant differences exist between FTD and AD cortical-connective degeneration patterns. We validate these distinct, multimodal imaging patterns by showing unique relationships with cognitive measures in AD and FTD. We conclude that SCCAN is a potentially valuable approach in image analysis that can be applied productively to distinguishing between neurodegenerative conditions and as a preprocessing method to optimally reduce the dimensionality of imaging datasets.

Methods: *Image Acquisition:* All images were acquired with a Siemens Trio 3.0 Tesla MRI scanner. Each study began with a rapid sagittal T1-weighted scan to determine patient position. A T1 structural acquisition was then acquired with .9766mm x .9766mm and 1mm slice thickness. The diffusion tensor imaging sequence was acquired last with a 30 direction sequence with 3 averages and 72 2 mm thickness slices with in-plane resolution: 2mm x 2mm.
Multivariate Assessment of Cortical Thickness and White Matter Integrity: The overall image analysis experimental design is as follows: *1*. Spatially normalize DTI and T1 imaging data from healthy controls and patients with FTD and AD diagnoses. *2*. Define a white matter region of interest in the DTI template and a cortical region of interest in the T1 template. In this study, the whole cortex and all white matter with FA > 0.2 were used. *3*. Apply SCCAN within a collection of controls and AD or FTD subjects to compute the subset of voxels within each ROI that are most strongly correlated with the alternate modality. *4*. Perform permutation testing of one of the two modalities to assess the significance of the correlation. *3*. Leverage the SCCAN projections to summarize DTI and T1 relationships across all selected voxels and/or to constrain further testing such as computing imaging relationships with neuropsychological evaluations or group tests. Here, we use diffeomorphic normalization of the T1 and diffusion tensor modalities as a pre-processing step that will cluster the image-based features before down-stream SCCAN. The DTI and T1 modalities are processed separately due to the presence of inter-modality distortion and because SCCA does not require the two views of the patient to be spatially aligned. The analysis of T1 imaging is based on the publicly available and open-source Advanced Normalization Tools (ANTS, http://www.picsl.upenn.edu/ANTS/) and the associated pipelining framework PipeDream (http://sourceforge.net/projects/neuropipedream/). PipeDream automates and quality assures ANTS processing via a single parameter file and data organization hierarchy. Each subject's T1 imaging data are inhomogeneity corrected via the Insight Journal implementation of N3. The brain is then segmented via ANTS tools [1] to generate cortical and white matter probability maps, in the individual space, which are input to Diffeomorphic Registration-Based Cortical Thickness (DiReCT), a robust tool for image-based thickness estimation that respects sulcal boundaries and prevents over-estimation of thickness via prior-based restrictions [3]. The resulting thickness images are then mapped---via diffeomorphism---back to the space of the T1 imaging template and smoothed with a 2mm standard deviation Gaussian kernel. The diffusion-tensor normalization and template was computed using the DTITK software [6] (http://www.nitrc.org/projects/dtitk/). We also generate a T1 template to DT template mapping for visualization of our results in a single space, as in Figure 1 below.



Sparse Canonical Correlation for Neuroimaging: We use sparse canonical correlation analysis [5] to empirically assess the extent to which white matter disease and cortical disease are predictive of each other in the FTD plus control and AD plus control grouping of our data. SCCAN achieves this by computing a reduced, optimal ``weighted average'' of the voxels in each modality's ROI that maximizes the correlation between modalities. This ``sparse'' selection process serves to control the influence of outliers on the computed correlations and automatically locates the most reliable, but spatially distributed voxels from the ROI. Standard methods of assessing correlation require a more detailed definition of an ROI by hand wherein all voxels are weighted equally. In contrast, SCCAN increases power over this traditional strategy by using a variational approach to define the sets of voxels in one modality that are most informative about the other. See XXX for details. Fig. 1, at left, shows the spatially varying SCCAN weights that reveal, in blue for each disease, the white matter regions that are mutually informative with the cortical thickness regions shown in red at $p<0.005$, permutation tested.

Results: The key results of this study show that unique, syndrome-specific patterns of degeneration are revealed by SCCAN and that these identified regions relate uniquely---via a double dissociation---to MMSE in AD and verbal fluency in FTD. In terms of neuroanatomy, SCCAN automatically identified subsets of the brain in FTD where cortical thickness showed significant and widespread differences from controls including: bilateral insula, left middle frontal gyrus, bilateral inferior frontal gyrus, bilateral orbitofrontal gyrus and left precentral gyrus, as well as left and right cingulate gyrus. Likewise, in white matter, the uncinate, inferior-frontal-occipital and anterior corpus callosum projections are densely involved in FTD. In AD, we found effects in superior/inferior temporal gyrus, left and right parahippocampal/hippocampal regions, right inferior parietal lobe and left and right precuneus. Correlated white matter tracts that are significantly compromised in AD include the superior longitudinal fasciculus, inferior frontal-occipital fasciculus, descending corticospinal fibers and the corpus callosum.

Conclusions: To our knowledge, this is the first demonstration of a consistent and integrated analysis of DTI and cortical thickness in an autopsy-confirmed and biomarker-diagnosed imaging population. We established the validity of this new approach by associating its findings with both neuropsychological testing and known patterns of anatomical effects in well-studied disorders. Our findings suggest that FTD and AD induce correlated white matter and cortex degeneration and that these diseases act through unique pathways. This multivariate imaging analysis and integration with SCCAN demonstrates a powerful new paradigm of investigation that may be extended to other populations and experimental designs and may be adapted to both *a priori* and exploratory studies. Future work will focus not only on assessment of the weights---and potential inclusion of more variates in the analysis---but also on extending these analyses to tri-variate studies.

References: [**1**] Avants et al, *MEDIA*, vol. 12, 2008. [**2**] Bian, et al., *Neurology*, vol. 70, 2008. [**3**] Das et al., *Neuroimage*, vol. 45, 2009. [**4**] Grossman et al, *Brain*., vol. 127, 2004. [**5**] Witten et al., *Biostatistics*, vol. 10 2009. [**6**] Zhang, et al., *IEEE-TMI,* vol. 26, 2007.

Acknowledgement: We thank the National Institutes of Health for funding this work through AG17586, AG15116, NS44266, and NS53488.