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Dementia induces correlated reductions in white matter integrity and cortical thickness: A multivariate neuroimaging study with sparse canonical correlation analysis

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ABSTRACT

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). This process is based on a novel computational model derived from sparse canonical correlation analysis (SCCA) that allows us to automatically identify mutually predictive, distributed neuroanatomical regions from different imaging modalities. We apply the SCCA model to a dataset that includes 23 control subjects that are demographically matched to 49 subjects with autopsy or CSF-biomarker-diagnosed AD ($n=24$) and FTD ($n=25$) with both DTI and T1-weighted structural imaging. SCCA 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 SCCA is a potentially valuable approach in image analysis that can be applied productively to distinguishing between neurodegenerative conditions.

Introduction

Neuroimaging studies suggest that frontotemporal dementia (FTD) leads to decreases in cortical thickness and white matter integrity, and these may reflect degraded cortical and white matter neural networks underlying language, social and executive functioning. Alzheimer's disease (AD) also induces large-scale neurodegeneration that, in contrast to FTD, may reflect episodic memory loss. However, the distinguishing, integrated effects of these diseases on the cortical and white matter networks underlying these behavioral changes have not been established.

FTD is an early-onset neurodegenerative condition with an average age of onset in the sixth decade of life (Hodges et al., 2003; Neary and Snowden, 1996; Grossman, 2006). The disease is due to a disorder of tau metabolism (Lee et al., 2001) or the accumulation of a ubiquinated protein known as TDP-43 (Neumann et al., 2006). The condition is almost as common as AD in individuals less than 65 years of age (Rosso et al., 2003; Knopman et al., 2004; Cairns et al., 2006). Survival is typically 8 years from onset (Hodges et al., 2003; Cairns et al., 2006; Xie et al., 2008). Developing biomarkers for early detection of disease and assessment of treatment is of great significance because of the development of therapies specifically for this condition.

One common, inexpensive, non-invasive tool in diagnosis of FTD is clinical measurement of cognitive abilities and behavior. Diagnosis of FTD consequently includes observation of syndromes such as primary progressive aphasia (PPA) and/or a disorder of social comportment and personality together with limited executive resources (McKhann et al., 2001; Neary et al., 1998). Recent studies have begun to demonstrate longitudinal decline on language and cognitive measures in clinical (Blair et al., 2007; Libon et al., 2009b) and pathologically defined (Grossman et al., 2008) populations. However, when validated against autopsy defined series, clinical diagnostic assessment may be inaccurate in up to 30% of cases (Forman et al., 2006). Most of the missed diagnoses are uncommon, young-onset presentations of AD. Thus, comparative studies of patients with neurodegenerative conditions are needed to demonstrate the specificity of a method for accurate diagnosis.

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One potential source of additional diagnostic information involves biofluids such as cerebrospinal fluid (CSF). In a series of patients with known pathology, the ratio of CSF-tau to CSF beta-amyloid achieved an overall diagnostic accuracy of 93%, with excellent sensitivity and specificity (Bian et al., 2008). However, CSF ratio measures require an invasive lumbar puncture and their levels may not change enough over time to be useful for monitoring treatment response (Buchhave et al., 2009).

Magnetic resonance imaging is a non-invasive alternative to characterize the disease process in terms of objective, quantitative measurements of brain function and anatomy. Many studies have analyzed the spatial pattern of atrophy (Jack et al., 1992; Laakso et al., 2000; Chan et al., 2001; Galton et al., 2001; Frisoni et al., 2002; Thompson et al., 2003; Ballmaier et al., 2004; Studholme et al., 2004, 2006) by contrasting control and neurodegenerative populations. These studies show atrophy in several frontal and temporal regions in FTD. Attempts to validate these findings include examining cortical atrophy in patients with autopsy-defined disease (Whitwell and Jack, 2005) and relating cortical atrophy in autopsy-defined cases directly to the clinical phenotype through regression studies (Grossman et al., 2007a). Cross-sectional studies have related language deficits to neuroanatomic substrates using MRI in clinical (Grossman et al., 2004) and pathologically defined (Josephs et al., 2006a; Grossman et al., 2007b) populations.

However, there have been few comparative studies assessing MRI changes in FTD relative to AD. MRI assessments of gray matter atrophy in AD show significant changes in the hippocampus as well as neocortical areas of the posterior temporal, parietal and lateral frontal lobes (Bocti et al., 2006; Rabinovici et al., 2007). However, direct contrasts of autopsy-proven cases of AD and FTD show only subtle differences (Grossman et al., 2007a; Whitwell et al., 2008a), perhaps because subgroups of patients with FTD can have changes in these same areas. For example, patients with semantic dementia tend to have relatively more hippocampal and temporal neocortical disease, and patients with behavioral-variant FTD have disease focused more in frontal brain regions.

Most studies analyze progressive cortical atrophy during the course of FTD with T1-weighted MRI (Whitwell and Jack, 2005; Brambati et al., 2007). However, additional insight into the anatomic consequences of dementia may be provided by diffusion tensor imaging (DTI) (Larsson et al., 2004; Yoshiura et al., 2006; Borroni et al., 2007). This modality provides a surrogate measure of white matter integrity. There is considerable evidence that the pathologies associated with FTD cause significant white matter disease (Forman et al., 2002; Neumann et al., 2006). DTI studies in FTD are rare. One study (Zhang et al., 2009) suggested that DTI-derived white matter degeneration is more prominent in FTD compared to AD. However, there is some concern about these results because the participating patients were diagnosed clinically and there was no independent validation of the diagnosis with autopsy or CSF biomarker data. Thus, the first contribution of our study is to use DTI and T1 imaging simultaneously to help describe large-scale patterns of difference in patients with autopsy or CSF biomarker-diagnosed diseases.

The second innovation in the current study concerns the manner in which we combine these two imaging modalities. While T1-weighted and DTI modalities provide complementary windows into disease, the degree to which the appearance of gray matter and white matter disease are correlated across modalities is unknown. Multivariate relationships between cortical and white matter signals such as this have been challenging to address due to their essentially disjoint nature and the tremendous number of multiple comparisons required to directly assess such correlations. While research performed on separate modalities in non-overlapping groups provides compelling evidence that both FTD and AD affect white and gray matter tissue, no study has yet been performed to assess the reciprocity provided by these modalities or to quantify the extent to which white matter and cortex change together, as measured by MRI. To achieve this, new multiple modality techniques must be adopted that enable us to determine whether neurodegeneration occurs across cortical and white matter networks.

Few studies have investigated the extent to which cortical atrophy and white matter integrity are quantitatively related. Most studies perform separate analyses for T1 structural and DTI modalities, where voxel-based morphometry is used separately for cortical and white matter analysis (Thivard et al., 2007; Ibrahim et al., 2009) and avoid explicit investigation into correlated DTI and T1 effects. In contrast, Sydykova et al. (2007) used a single region of interest (ROI) to show that, in AD, the average fractional anisotropy (FA) in anterior and posterior corpus callosum correlated with anterior and posterior cortical atrophy, where atrophy was measured by voxel-based morphometry. Kochunov et al. (2007) also used ROIs in white matter to show correlations, in normal aging, between average brain and corpus callosum FA and cortical thickness averaged across the whole brain and across hemispheres. Here, we use recent advances in a well-established statistical technique to provide a new method for correlating multiple imaging modalities.

Canonical correlation analysis (CCA) (Hotelling, 1936) is an established method for estimating the linear relationship between two sets of measurements taken across subjects. Hotelling proposed CCA in 1936 and it remains a method that is ideally suited to investigating multi-view problems, that is, datasets with two different real-world measurements of some "hidden" underlying phenomenon. CCA, a multiview extension of principal component analysis (PCA), finds canonical variates that allow an estimation of the extent to which one view correlates with the other, via a projection. Its output is the correlation value itself and the projection vectors, which provide a set of *canonical weights* on the original data that give the best projection, when combined across all subjects, of one view onto the other. CCA has been used in medical imaging to investigate anatomical correlations (Rao et al., 2008) where one may assess the degree to which, for example, left hemisphere caudate volume predicts right hemisphere caudate volume. CCA is also used in pre/post-processing for fMRI studies (Ragnehed et al., 2009; Bruguier et al., 2008). These studies use designs where the number of subjects is greater than or equal to the number of multiview measurements, a primary numerical prerequisite for application of CCA. While extremely powerful, traditional CCA has been severely limited by this condition, as most imaging datasets contain a number of measurements (e.g. voxels), p, that is much larger than the number of subjects in the dataset, n.

Recent advances in sparse statistical methods, spurred by the gene expression analysis community, have resolved some of these issues. In particular, *Sparse CCA (SCCA)* was recently proposed by a number of different researchers (Witten and Tibshirani, 2009; Witten et al., 2009; Parkhomenko et al., 2009; Cao et al., 2009). SCCA makes CCA computationally feasible and applicable in the case when only a fraction of the p measurements is likely to be important for the problem at hand. Sparse CCA can be used to find which subsets of voxels, genes, or other measurements in each modality best predict the other modality.

In our application, SCCA enabled the computation of the significance of correlations between the most predictive subsets of fractional anisotropy and cortical thickness voxels. The size of these subsets is a controllable parameter that corresponds to the "sparseness" of the computation. Sparse CCA has advantages over other integrative approaches that rely on spatially overlapping signals (Avants et al., 2007, 2008) as SCCA is ideal for computing spatially disjoint multivariate associations.

Here, we use SCCA to elucidate cortical thickness and fractional anisotropy relationships in both AD and FTD. Moreover, we hypothesize that the regions identified by SCCA correspond to tissue regions affected by disease. To test this hypothesis, and ensure the