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Sparse canonical correlation analysis relates network-level atrophy to multivariate cognitive measures in a neurodegenerative population

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ABSTRACT

This study establishes that sparse canonical correlation analysis (SCCAN) identifies generalizable, structural MRI-derived cortical networks that relate to five distinct categories of cognition. We obtain multivariate psychometrics from the domain-specific sub-scales of the Philadelphia Brief Assessment of Cognition (PBAC). By using a training and separate testing stage, we find that PBAC-defined cognitive domains of language, visuospatial functioning, episodic memory, executive control, and social functioning correlate with unique and distributed areas of gray matter (GM). In contrast, a parallel univariate framework fails to identify, from the training data, regions that are also significant in the left-out test dataset. The cohort includes164 patients with Alzheimer's disease, behavioral-variant frontotemporal dementia, semantic variant primary progressive aphasia, non-fluent/agrammatic primary progressive aphasia, or corticobasal syndrome. The analysis is implemented with open-source software for which we provide examples in the text. In conclusion, we show that multivariate techniques identify biologically-plausible brain regions supporting specific cognitive domains. The findings are identified in training data and confirmed in test data.

Introduction

Multivariate methods have advantages over univariate methods in genomics (Hibar et al., 2011; Le Floch et al., 2012; Parkhomenko et al., 2009), pattern recognition (Bishop, 1995; Roberts, 1997; Tipping, 2001) and neuroimaging (De Martino et al., 2008; Fan et al., 2008; McIntosh et al., 1996; Shamy et al., 2011; Tosun et al., 2012) due to the high dimensionality and latent structure within these types of datasets. Various forms of multivariate pattern analysis (MVPA) (Habeck et al., 2008; Hanke et al., 2009; Kloeppel et al., 2008; Norman et al., 2006; Stonnington et al., 2010) are frequently used in (often functional) magnetic resonance imaging (MRI) studies to increase detection power (McIntosh et al., 1996; Norman et al., 2006; O'Toole et al., 2007; Yamashita et al., 2008). Recently, multivariate analysis of structural MRI has gained more attention (Grosenick et al., 2013; Ryali et al., 2010; Sabuncu and Van Leemput, 2011). The large majority of these techniques relate a multivariate pattern to a univariate outcome.

Modern datasets allow the opportunity to relate two independent multivariate patterns. Neuroimaging and psychometric batteries describe cognition and the brain itself, respectively, with a matrix of quantitative measurements. These types of datasets may be analyzed with methods such as canonical correlation analysis (CCA) (Cherry, 1996) which is closely related to multivariate regression and partial least squares (Sun et al., 2009). Partial least squares (PLS), without sparseness, has been used for several years in multivariate brain mapping studies (Addis et al., 2004; Chen et al., 2009; Leibovitch et al., 1999; Lin et al., 2003; McIntosh et al., 1996). Ridge and related penalties allow these methods to be applied even when the number of subjects is far fewer than the number of measurements (Nestor et al., 2002b). However, a caveat of these approaches is that the resulting solution vectors have global extent i.e. cover the entire brain with basis vectors that are non-zero and may have both positive and negative values. Traditional approaches are more clearly directional: a long neurological history is founded on relating behavioral deficits (losses) associated with destruction of brain tissue by stroke or related disorders. Perhaps the most famous example is H.M. This epilepsy patient lacked the ability to form new memories after anterior temporal lobe resection. That is, loss of a specific part of the brain resulted in a specific deficit.

Tools such as independent component analysis and principal components analysis (PCA) (Borroni et al., 2012; Comon, 1994; Mansfield et al., 1977; Shamy et al., 2011; Yeung and Ruzzo, 2001) increase power by efficiently describing data. However, PCA solutions provide signed basis vectors with global support and therefore lose the specificity of classical region of interest approaches or lesion studies. Sparse multivariate methods have advantages of interpretability (Lee and Seung, 1999; Suykens et al., 2002) and, potentially, improved generalizability (Elad, 2006; Ryali et al., 2010; Yamashita et al., 2008; Zhang, 2008; Zibulevsky and Elad, 2010). In this paper, we use the cognitive variance induced by a spectrum of neurodegenerative conditions to examine how new, sparse multivariate analysis techniques more powerfully

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reveal relationships between brain and behavior. At the same time, sparse methods achieve a degree of specificity that cannot naturally be obtained by dimensionality reduction tools such as PCA (Lee and Seung, 1999). Here, we apply sparse multivariate methods to find cortical networks that vary with cognition in a mixed group composed of controls and phenotypes related to Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) pathology. An example of the difference between sparse solutions and more traditional approaches appears in Fig. 1.

Like AD, FTLD is a progressive neurodegenerative condition that is accompanied by changes in behavior. Unlike AD, which typically presents atrophy in the precuneus and temporal lobes, FTLD's pathology occurs more frequently in frontal and temporal lobes (Rabinovici et al., 2007; Whitwell et al., 2007). FTLD phenotypes include patients with a disorder of social comportment and executive functioning (bvFTD); a non-fluent/agrammatic variant of primary progressive aphasia (naPPA), also known as progressive non-fluent aphasia; a semantic variant of primary progressive aphasia (svPPA), also known as semantic dementia; and corticobasal syndrome (CBS). A common test for cognitive deficits in dementia is the Mini-Mental State Examination (Hill and Baeckman, 1995). However, the MMSE does not assess the behavioral and cognitive deficits associated with FTLD (Hutchinson and Mathias, 2007). Other tests have been developed to screen and compare patients with dementia syndromes, including the Frontal Assessment Battery (Dubois et al., 2000) (FAB); the Addenbrooke Cognitive Examination (Galton et al., 2005) (ACE); and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005).

The Philadelphia Brief Assessment of Cognition (Libon et al., 2007, 2011) (PBAC) provides an economical means to screen and assess important domains of cognitive and behavioral impairment associated with AD and FTLD spectrum phenotypes. The PBAC requires about 12 min for administration and scoring. An important component of the PBAC is the construction of sub-scales designed to assess specific cognitive and behavioral/comportment deficits that typify AD and FTLD syndromes, including executive/working memory, language, visuospatial/constructional skills, verbal/visual episodic memory, and behavior/social comportment. Dementia severity is assessed by summing all PBAC sub-scales. Recent research with the PBAC has demonstrated that AD and FTLD patients present with specific areas of impairment on sub-scales that correspond to phenotypic syndromes (Libon et al., 2011) i.e. clinical diagnosis.

The current study extends previous research with the PBAC (Libon et al., 2011) by examining the gray matter neuroimaging correlates of PBAC's cognitive and social measurements in a large number of AD and FTLD patients. From a neurological perspective, the purpose, here, is to use the variance within these patients to assess brain and behavior relationships across multiple behavioral loci, as opposed to diagnosis. From a technical perspective, the goal is to contrast univariate and multivariate techniques. To test the hypothesis that PBAC indirectly measures the integrity of different cortical networks (versus individual voxels), we employ a new data-driven machine learning technique, sparse canonical correlation analysis for neuroimaging (SCCAN), to associate high-dimensional imaging measurements with the full information provided by a multivariate psychometric battery such as PBAC. Specifically, this approach allows an optimal weighting of psychometric sub-scales (as opposed to averaging their values) such that the relationship with neuroimaging is maximized. At the same time, SCCAN optimizes and selects regions of gray matter (GM) to maximize correlation with psychometrics. This results in a set of gray matter regions that may be interpreted as the network most-associated with the given psychometric domain. SCCAN previously identified covariation between GM and diffusion tensor imaging white matter (WM) changes that optimally discriminate between CSF- and autopsy-defined patients with AD and FTLD (Avants et al., 2010b). The purpose of the current research is to test the hypothesis that SCCAN may employ individual PBAC sub-scales to extract GM networks that are reproducibly associated with variation in cognition. This would provide additional criterion validity for both the PBAC and multivariate techniques such as SCCAN, in contrast to univariate techniques, and establish a novel strategy for performing multivariate analyses of brain and behavior.

Methods

An overview of our study is in Fig. 2. We first discuss the core dataset and measurements. We then discuss the PBAC and SCCAN methods. We proceed with an evaluation framework, including a comparison against a univariate approach.

Patients

Individuals participating in the current research were drawn from a corpus of 270 patients, as previously described (Libon et al., 2011). Dementia patients were evaluated by experienced behavioral neurologists (AC, HBC, RGG, MG) and classified clinically on the basis of previously published criteria (Gorno-Tempini et al., 2011; McKhann et al., 2001; Rascovsky et al., 2011). A research diagnosis was made on the basis of an independent review of a semi-structured history obtained from patients and their families and a detailed neurologic examination. At least two trained reviewers from a consensus committee (inter-rater reliability, $r = 0.91$, $p < 0.001$) confirmed patients' clinical diagnosis and the presence of a specific dementia syndrome involving AD or FTLD. Discrepancies were resolved based on group discussion and follow-up assessment. The PBAC was not used for the initial diagnosis of research participants.

The clinical diagnosis of dementia was consistent with serum studies, clinical studies of cerebrospinal fluid (when available), clinical imaging studies such as MRI or CT, and functional neuroimaging studies such as SPECT or PET (these studies were not available to the consensus

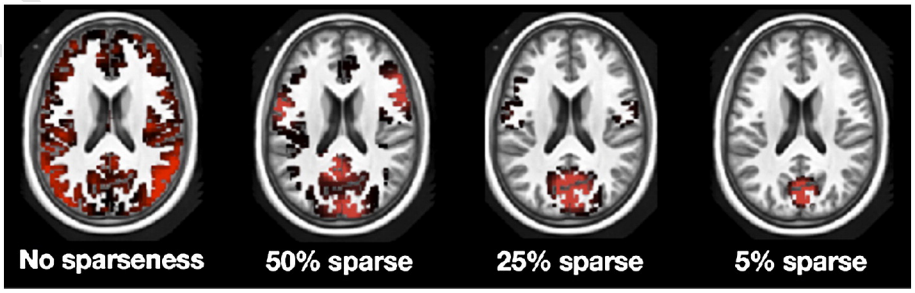

Fig. 1. Sparse canonical correlation analysis solution vectors are overlaid on a slice of the brain where the brightness of the red-hued overlay is related to the solution's weighting at the local voxel. A traditional canonical correlation analysis produces component vectors with global extent (to reader's far left). Sparse solutions (increasingly sparse to the reader's right) seek to extract controllably focal information thereby, in the context of this paper, isolating "networks" of voxels that collectively relate to cognition. This enables component vectors to be more easily interpreted in terms of traditional neuroscientific coordinate systems.

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