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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 includes 164 patients with Alzheimer's disease, behavioral-variant frontotemporal dementia, semantic variant primary progressive aphasia, nonfluent/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.

Keywords

Alzheimer disease; Frontotemporal lobar degeneration; Philadelphia Brief Assessment of Cognition; PBAC; MRI; Sparse canonical correlation analysis

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

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Conflict of interest

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analysis (MVPA) (Habeck et al., 2008; Hanke et al., 2009; Kloppel 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 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 compartment and executive functioning (bvFTD); a non-fluent/agrammatic variant of primary progressive aphasia (naPPA), also known as progressive nonfluent 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 FTLN 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/compartment deficits that typify AD and FTLN syndromes, including executive/working memory, language, visuospatial/constructional skills, verbal/visual episodic memory, and behavior/social compartment. Dementia severity is assessed by summing all PBAC sub-scales. Recent research with the PBAC has demonstrated that AD and FTLN 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 FTLN 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 FTLN (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 FTL. 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 committee). Exclusion criteria included the presence of other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorders (e.g., major depression, psychosis), or a systemic illness that can interfere with cognitive functioning. Some patients were taking a cholinesterase inhibitor (e.g. donepezil, galantamine), memantine, or a non-sedating anti-depressant (e.g., serotonin-specific re-uptake inhibitors such as sertraline), or an atypical neuroleptic agent (e.g., quetiapine) consistent with clinical care; however, no patient demonstrated evidence of sedation. The current research examined patients with AD (n=17), behavioral variant-FTD (bvFTD; n = 41), semantic variant-primary progressive aphasia (svPPA; n = 14), non-fluent/agrammatic-primary progressive aphasia (nfaPPA; n = 15) and corticobasal syndrome (CBS; n = 24). The imaging analysis also included elderly controls (n=56) who were living independently in the community and not taking psychoactive medications. Normal control participants presented with no cognitive complaints or impaired instrumental activities of daily living. Table 1 summarizes participant demographic features. This research was approved by the University of Pennsylvania Institutional Review Board and informed consent was obtained consistent with the Declaration of Helsinki.

The Philadelphia Brief Assessment of Cognition (PBAC)

Full details regarding the rationale and construction of the PBAC can be found elsewhere (Libon et al., 2011). The PBAC consists of 20 variables grouped into 5 domain-specific rating scales. These variables are grouped into five sub-scales measuring: working memory/executive control, language, visuospatial/constructional ability, verbal/visual episodic memory, and behavior/social comportment. The total PBAC score ranges between 0 and 93. The executive scale includes measurements of fluency, digits backward and digits forward. The language scale measures naming, speech, reading, writing and semantic ability. The memory scale quantifies delayed free recall, recognition and Rey recall. The visuo-spatial scale measures judgment of line orientation (JOLO) and the Rey copy test. The behavioral scale includes subjective measurements of apathy, disinhibition, social comportment, agitation, empathy and ritual. The correlations between these different sub-scales are shown in Fig. 3.

Image acquisition

All images were acquired with a Siemens Trio 3.0Tesla MRI scanner. Following a rapid sagittal T1-weighted scan to determine patient position, a T1-weighted structural image was acquired with TR = 1620 ms, TE = 3 ms, slice thickness = 1 mm, in-plane resolution = 0.9766 mm × 0.9766 mm, and FOV = 256 × 192.

Image processing

The imaging analysis is based on the publicly available and open-source Advanced Normalization Tools (ANTs, <http://stnava.github.io/ANTs/>) and the associated pipelining framework PipeDream (<http://neuropipedream.sourceforge.net>). PipeDream automates and quality-assures ANTs processing via a single parameter file and data organization hierarchy.

Each patient's T1 imaging data are inhomogeneity corrected via the N4 bias correction algorithm (Tustison et al., 2010). PipeDream then performs diffeomorphic normalization via the top-performing symmetric normalization methodology available in ANTs (Avants et al., 2008, 2011a, 2012; Tustison et al., in press) to map each subject to a population-specific template built from the same scanner and imaging parameters. The template contains prior labeling and probability maps that are used to guide both brain extraction and neuroanatomical segmentation. Segmentation is performed with a Markov Random Field approach (Avants et al., 2011b) implemented in the ANTs toolkit which has been validated on publicly-available datasets. GM probability maps are then smoothed by a 2 mm Gaussian kernel, mapped to the template space, and down-sampled to 2mm resolution. These normalized GM probability maps are used for subsequent multivariate correlation with PBAC.

Dimensionality reduction/statistical analysis

There are two primary reasons that univariate approaches lack power. First, power is compromised because the same test is repeated at each measurement site leading to an often severe multiple comparisons problem. Second, univariate methods do not exploit the latent signal in the data that is spread across measurement sites. In this study, rather than perform voxel-wise testing, we employ a dimensionality reduction method implemented in SCCAN. Briefly, this is an imaging-specific extension of sparse canonical correlation analysis (Avants et al., 2010a; Cao et al., 2009; Witten and Tibshirani, 2009; Witten et al., 2009) that is itself a sparse extension to Hotelling's seminal canonical correlation analysis (CCA) (Hotelling, 1935, 1936). CCA, in turn, is a multi-modality extension to principal component analysis.

Classical CCA may be used to compute a multivariate association between two different views of a dataset. One of Hotelling's original examples associated measurements of height and weight to measurements of cognition. More recently, sparse versions of CCA have been developed to increase the interpretability of the output where we take motivation for sparse methods from our introductory material. Sparse CCA methods, like classical CCA, compute eigenvectors (in actuality, *pseudo*-eigenvectors) that maximize the Pearson correlation between the input modalities.¹ In this work, we use sparse CCA in a similar way to Hotelling's classic study, i.e. to associate two different types of measurements, one anatomical and one psychometric, in a population.

We employed the SCCAN implementation of sparse CCA to directly associate the five PBAC sub-scales described above with GM measures taken from T1-weighted MR images. In general, SCCAN elucidates the relationship between two sets of measurements taken across a population and is thus well-suited to multivariate neuroimaging data. The input to SCCAN is two matrices X and Y . The size of X is $n \times p$ where n is the number of subjects and p is the number of voxels from the cortical gray matter. The matrix thus collects all cortical imaging data for each subject. The size of Y is $n \times q$ where there are q psychometric measurements in the given PBAC sub-scale i.e. $q=3$ for executive, 5 for language, 3 for memory, 2 for visuospatial and 6 for behavioral scales.² SCCAN maximizes the Pearson correlation, in a rotated space, between nonnegatively weighted columns of these matrices. More formally, SCCAN, like classic CCA, introduces new unknown solution vectors, x ($p \times 1$) and y ($q \times 1$) that act as weight functions on columns of X and Y . The SCCAN optimization criterion is:

¹Pseudo-eigenvectors are based on optimizing an objective function that is related to the eigenvalue problem but may not strictly satisfy the eigenvalue problem and related constraints.

²One column of the behavioral scales (self insight) was excluded due to lack of variance.

$$x^*, y^* = \arg \max_{x, y} \frac{x X^T Y y}{\|Xx\| \|Yy\|} \quad \text{subject to} \quad \sum_j \|x^j\|_1 \leq s, x^j \geq 0, \quad (1)$$

where x^* and y^* are the optimal solution vectors, x^j denotes the j th entry of x , s determines the sparseness level and $\|\cdot\|_1$ denotes the ℓ_1 norm. The ℓ_1 norm forces the solution x to be sparse i.e. have zero value over the majority of the brain. In this application, we do not enforce sparseness on the y vector as it is relatively small, i.e. $q \ll n$. SCCAN's objective function can be optimized even when the matrices are fat i.e. $p \gg n$, often the case in neuroimaging studies. Due to the non-linear (even np-hard) nature of subset selection (sparse optimization) from a large matrix, optimizing for a single canonical variate pair, x , y , involves a nonlinear gradient descent on the objective function above. The analytical gradient of the objective function (ignoring the ℓ_1 and positivity constraints) w.r.t. x is:

$$X^T Y y - \frac{1}{2} X^T X x \|Xx\| \|Yy\|. \quad (2)$$

Following this gradient will cause the candidate solution x to leave the permissible solution space and, as such, we follow the gradient update step with a projection step as in Polak (1997) and Schwartz and Polak (1997). The projection step involves a standard soft-thresholding operation used in ℓ_1 optimization which is easily modified to include positivity constraints (Donoho, 1995; Elad, 2006; Tibshirani, 1996; Witten and Tibshirani, 2009). The gradient for y is obtained at the same time as that for x with a simple switching of variables. Following, we refer to x^* as x and y^* as y interchangeably.

SCCAN therefore produces a sparse projection vector acting on GM voxels that, taken as a set, maximally correlate with the user-selected PBAC domain of interest. Here we use the working memory/executive, language, visuospatial, memory, and social/behavioral PBAC sub-scales, thus requiring only five direct multivariate tests, i.e., one for each cognitive domain. The sparse eigenvectors that emerge from SCCAN identify the brain regions supporting the specific PBAC domain that was passed to the algorithm as the second view. In this study, we restrict the SCCAN eigenvectors to be positive. Thus, each eigenvector can be reinterpreted as a weighted average of values over a restricted region of GM, like a region of interest (Chen et al., 2010; Poldrack, 2007; Rasmussen et al., 2012; Zhou et al., 2011). This may be achieved in a post-processing step that sets the sum of the solution vector, x or y , to equal one. The implementation details are available in the Advanced Normalization Toolkit's `sccan.cxx` program which contains the SCCAN source code. The significance of SCCAN results may be tested by permuting one of the two views over many different simulations. One then compares the correlation value produced by the original ordering of the data to the correlations produced over the N permutations. Large N (typically >1000) is needed to provide a reasonable sampling of the empirical null distribution. In this analysis, we use a training and testing paradigm³ to avoid permutation testing and to allow us to perform parameter selection (for s) on the training dataset in a manner that is independent of the test dataset. Finally, we note that ANTsR example code for SCCAN section highlights a few of the key steps in this analysis as implemented with a pre-release of the ANTsR software.

³As recommended by reviewers.

Parameter selection

Image processing—Our studies used reproducible research practices by employing open methods, standardized parameter sets and version control of both parameters and code via git. We employed standard parameters in PipeDream and ANTs for template construction, normalization, segmentation and GM estimation. These analysis protocols are described elsewhere (Avants et al., 2011a, b; Tustison et al., 2010, in press).

Statistical parameters—SCCAN was used to extract the single most dominant features associating GM and a PBAC sub-scale in a training dataset. Our study design involves setting only a single parameter, s , which controls the sparseness of the imaging space solution vector, x . We chose to restrict x to also be nonnegative such that the solutions can be interpreted with clear directionality i.e. as a weighted average. To identify the parameter s , we run SCCAN with a range of $s^{\text{candidate}}$ values ($s = 0.005, 0.01, \dots, 0.5$) and store the resulting SCCAN correlation for each trial. We then fit a model, SCCAN-correlation $\approx \beta_1 s^{\text{candidate}} + \beta_2 (s^{\text{candidate}})^2 + \beta_3 (s^{\text{candidate}})^3 + \beta_4 (s^{\text{candidate}})^4$, to the function mapping $s \rightarrow$ SCCAN-correlation. We set the final parameter s to correspond to the value of our model that maximizes the dependent SCCAN-correlation value. If there are ties, we take the first from the left (maximally sparse) solution. We then compute the final solutions x^*, y^* that will be evaluated for reproducibility in our test dataset. We did not employ sparseness on the 2nd view (the PBAC sub-scale scores). We need only to perform 5 tests in total as opposed to $5p$ tests required by a univariate setting. Here, $p = 90,084$ and $5p = 450,420$. Parameter selection results are in Fig. 4.

Comparison of univariate to multivariate feature selection

This study employs a training and testing paradigm. Therefore, SCCAN may be viewed as a tool that generates “feature vectors” (x, y) that are optimized in a multivariate manner to associate GM and PBAC. Using our existing terminology, these maximize $\text{Corr}(Xx, Yy)$ where Corr denotes Pearson correlation and X and Y correspond to the training dataset matrices. These feature vectors may be used as “hypotheses” and applied to a new testing dataset, X_{test} and Y_{test} , to determine if the patterns extracted from training data are reliable in test data. In this analysis, we use the correlation in test data as our outcome measurement which is computed as $\text{Outcome}_{\text{Multivariate}} = \text{Corr}(X_{\text{test}}x, Y_{\text{test}}y)$ where x and y are derived from training data.

We can also compute a parallel univariate outcome, $\text{Outcome}_{\text{univariate}}$, via a similar methodology based on univariate feature selection. We use Occam’s razor to decide upon a univariate feature selector i.e. we do something simple-minded yet akin to several other studies (Chen et al., 2010; Dickerson and Wolk, 2012). We compute the univariate p -values of a model associating the PBAC sub-scale summary measurement (an average of the Z transformations of the individual measurements within the sub-scale) with each voxel in the cortex. This univariate model may be written as PBAC-sub-scale $\approx v_i$ where v_i is a vector containing the subject GM values at a given voxel (so i takes values $1 \dots p$). The p -value associated with v_i is then denoted as p_i . Now, define u as a p -length weight vector similar to the weight vector x . However, the entry at u_i is zero if p_i is > 0.01 (unadjusted) and 1 otherwise. This finally allows us to define the univariate outcome as $\text{Outcome}_{\text{univariate}} = \text{Corr}(X_{\text{test}}u, \text{PBAC-sub-scale}_{\text{test}})$.

This protocol allows us to compare a joint multivariate feature selector that identifies weights on PBAC sub-scale values (y) and the brain (x) with a univariate feature selector acting only on the brain (u). While the univariate approach does not weight the PBAC-sub-scale, it does use a standard average of the sub-scales commonly used in PBAC assessment. Thus, we compare a new, fully multivariate approach, to an existing standard approach. One

may argue that the threshold selected to binarize the u vector is arbitrary. However, this is a common/standard style of analysis employed in univariate methods, i.e. select a significance threshold and accept the results as the truth. The univariate solutions do not survive multiple comparison correction so we had no choice but to use uncorrected p -values as feature selectors.

Results

Univariate: PBAC sub-scales and GM density

No univariate outcome measurement achieves significance when relating brain and behavior in the test data. That is, the correlation between PBAC-sub-scale_{test} with $X_{test}u$ is weak in each of the five PBAC sub-scales (p -values: exec 0.93, language 0.078, memory 0.85, visuospatial 0.66, behavioral 0.78). However, the relationship between PBAC-sub-scale_{train} with $X_{train}u$ is strong, as expected (all p -value <0.01). This indicates that, at least in this dataset, naive univariate feature selection overfits to the training data.

Multivariate: PBAC sub-scales and GM density

Based on training data, we found, in testing data, significant associations between GM density and each of the five PBAC sub-scales consistent with putative neuroanatomical substrates at the Bonferroni-corrected $p < 0.01$ level. Scatterplots are in Fig. 6 where raw p -values are also reported (rounded below 0.0001 to 0). Fig. 5 shows the x function for each sub-scale plotted on the brain. Note these are *sparse* functions i.e. no additional thresholding is performed to generate these overlays. Fig. 6 shows the test data relationship between brain and behavior, as well as a visualization (in heatmap form) of each PBAC sub-scale.

Reporting multivariate results

We display SCCAN *pseudo*-eigenvectors on the brain in a manner that is similar to traditional voxel-based analysis, as in Fig. 5. As mentioned in Methods section, these weight vectors are similar to weighted averages in that the difference between these vectors and a traditional weighted average is only a scalar multiplication. Therefore, the effect on a correlation is null. We also tabulate results in Talairach coordinates similar to traditional methods (e.g. Table 2). However, instead of plotting coordinates of peak p -values, we annotate the Talairach coordinate of each spatial component of the *pseudo*-eigenvector such that we gain a degree of spatial resolution in the interpretation of SCCAN results. Despite using a familiar reporting system, the key point is that p -values are assessed over the relationships computed from the entire operation on the multivariate dataset (e.g. $Corr(X_{test}x^*, y^*)$). Thus, we are reporting the collection of neuroanatomical data points that contribute to the relationship with cognition as opposed to a single point. We estimate Brodmann areas and AAL labels from the label sets included with mricron (Rorden et al., 2007). Fig. 6 displays results in a glass brain where we draw connections between the major sub-regions of the pseudo-eigenvectors. We also show, via a heatmap, the distribution of cognitive scores for each PBAC sub-scale. Most importantly, we display the distribution of the test dataset gray matter against cognition.

As summarized in Fig. 6 and Table 2, PBAC-defined behavior/social compartment focuses on medial and inferior prefrontal cortex. The memory sub-scales (Table 5) relates to precuneus, hippocampus, and bilateral posterior temporal atrophy more prominently on the left than the right. Significant visuospatial/constructional impairment (Table 6) relates to bilateral posterior temporal–occipital and bilateral parietal–occipital lobe. The language sub-scale (Table 4) was related to left temporal and left temporal–parietal gray matter. The executive network involves a distributed temporal and frontal network and is described in Table 3.

Discussion

This study establishes, for the first time, that sparse canonical correlation analysis finds repeatable relationships between multivariate psychometric batteries and network level gray matter density measurements. Our analysis restricts the signs of the gray matter density solution vector, x^* , to be sparse and positive enabling directional relationships to be established (i.e. low gray matter, low cognitive score). The SCCAN multivariate analysis framework shows improved generalizability and power over the univariate method against which it is compared.

This study also represents the first comparison of PBAC sub-scales to structural neuroimaging. The PBAC was designed as a screening instrument to assess overall dementia severity and to differentiate between neurodegenerative syndromes within the AD and FTLN spectrum. Previous research with the PBAC found a significant correlation between the total PBAC score and the MMSE (Libon et al., 2007, 2011), thus demonstrating that performance on the instrument reasonably captures overall dementia severity. The psychometric qualities of the PBAC include good internal consistency among the tests within each PBAC sub-scale and highly significant intra-class correlations between PBAC sub-scales and standard neuropsychological tests tetlibon-Philadelphia-2011. PBAC sub-scales also show good clinical utility in distinguishing between AD and FTLN, and between FTLN-related phenotypes using sub-scale cut scores, although diagnosis is not the focus here.

The current research used novel imaging methods to provide further evidence for the criterion validity of the PBAC by associating PBAC sub-scale test performance with corresponding areas of GM atrophy. The heterogeneity of this population (which includes controls and five different clinical phenotypes) drives these relationships. For instance, patients with AD are known to present with striking memory impairment as well as atrophy involving the hippocampus, precuneus and related anatomic structures. In the current research, the PBAC memory sub-scale was associated with GM involving left hippocampus mid-body, anterior hippocampus and precuneus. Bilateral inferior temporal cortex and right parahippocampal gyrus are also involved. Hippocampal and precuneus involvement in clinically-defined patients with anterograde amnesia and AD is well known (Nestor et al., 2002a; Pengas et al., 2010). Moreover, prior research with AD and amnesic mild cognitive impairment suggests that these areas are part of a neurocognitive network for memory (Delano-Wood et al., 2012; Gardini et al., 2011). Table 5 shows all regions associated by SCCAN to the verbal and visual episodic memory sub-scale.

The behavioral variant of FTLN induces variance in the behavioral sub-scale. bvFTLN presents with alterations in social comportment (Rascovsky et al., 2011; Shany-Ur and Rankin, 2011), including apathy, disinhibition, and lack of empathy. In the current study, the PBAC-behavior/social scale is related to striking bilateral medial and ventral frontal GM, perhaps with greater right-sided involvement. Previous research has associated these behavioral abnormalities with bilateral ventral and medial frontal atrophy (Massimo et al., 2009; Rosen et al., 2010).

Similarly, CBS is associated with significant impairment in visuospatial and visuoconstructional tests, as well as some executive deficits (Libon et al., 2007, 2009). The current research associates the PBAC-visuospatial/constructional sub-scale with right posterior GM atrophy including parietal and occipital lobes. Prior neuroimaging research with CBS patients is controversial, with some researchers suggesting both parietal and frontal atrophy (Grossman and Ash, 2004) and others only frontal involvement (Hassan et al., 2011). In the present study, atrophy in primarily right visual association cortex was

related to the visuospatial/constructional sub-scale which, in turn, was designed to identify individuals with the clinical diagnosis of CBS. Table 6 highlights the visuospatial network defined by SCCAN.

In contrast to other domains, the executive/working memory sub-scale is not typically associated with a single diagnosis but instead is associated with several diagnostic subgroups, including CBS, bvFTLD and AD. Prior research with the PBAC has shown that patients with naPPA score lower on the PBAC-working memory/executive sub-scale (Libon et al., 2007, 2011) confirming executive and working memory deficits in these patients and reflecting that their disease centered primarily in the frontal lobe (Gunawardena et al., 2010; Rogalski et al., 2011). The executive network highlights diverse regions (see Table 3) including superior frontal and middle frontal gyrus (a classic working memory region) and superior temporal gyrus which has been previously implicated as a neural substrate for the digits backward test (Li et al., 2012). Inspecting Fig. 5 shows the executive scale extracts several brain regions that form key points in the default mode network such as precuneus, superior prefrontal cortex, lateral temporal lobe and lateral superior parietal cortex (Buckner et al., 2008). The PBAC-working memory/executive sub-scale consists of verbally-mediated tests and, as such, several language regions are involved as well.

The PBAC language sub-scale is strongly related to left temporal GM density, primarily with prominent posterior and inferior temporal GM. These data are consistent with prior research demonstrating left temporal atrophy in patients with svPPA who have language-related cognitive impairment (Bonner et al., 2009; Williams et al., 2005). The measures on the PBAC language sub-scale focus mostly on object comprehension, single word expression, reading and writing, with little emphasis on the characteristics important for identifying naPPA (Gorno-Tempini et al., 2011). Future modifications of the PBAC may include measures to improve detection of regions that would be specifically impaired in the naPPA subgroup. Such focused tests are not currently included in PBAC.

Taken together, these data extend past research to show that PBAC sub-scales are associated with MRI-defined anatomical substrates. The identified relationships between neurocognitive GM networks and psychometrics underscore the power of SCCAN over traditional univariate approaches to imaging analysis. By using SCCAN, we obtain massive dimensionality reduction which significantly enhances the empirical ability to detect these behavioral and neuroimaging relationships in both training and testing data. Prior work demonstrated the advantages of SCCAN in combining GM and diffusion tensor imaging data to distinguish between autopsy- and CSF-defined cases of AD and FTLD (Avants et al., 2010b). The results of the current study reveal that SCCAN is capable of associating multi-dimensional psychometric and neuroimaging data to reveal the large-scale neural networks that are degraded when cognition is compromised in neurodegenerative conditions like AD and FTLD.

There are several caveats to this study. A primary technical issue is whether the network structure (i.e. distributed sets of voxels) that SCCAN extracts is either a minimal or maximal reliable network supporting the selected cognitive domain. Indeed, it is likely that subsets of the voxels added to or subtracted from the SCCAN solutions may not alter predictive accuracy to a strong degree. This hypothesis is strengthened by the fact that our sparseness versus correlation curves (Fig. 4) is relatively smooth. However, identifying an optimally predictive set of high-dimensional variables across arbitrary subsets of a population is a generally unsolved problem. We elected to address this by defining our networks based on a tractable parameter search strategy that maximizes the SCCAN correlation in training data. A secondary issue is that our comparison with the univariate strategy may not be ideal. There are several alternative approaches for univariate feature selection that may be

employed with better results, for instance optimizing the recently proposed cluster-level FDR (Chumbley and Friston, 2009). We leave this question to future work by ourselves or others and also note that this approach would remain univariate in the dependent variable. SCCAN, on the other hand, uses a multivariate treatment of both datasets, cognition and neuroimaging.

The clinical aspects of this research also have limitations. First, the PBAC was not designed nor should it be used as a substitute for a comprehensive neuropsychological evaluation. This is reflected most clearly in the fact that PBAC sub-scales appear to extract primarily posterior temporal regions, medial frontal regions, medial posterior regions and parietal lobe. There is little representation of motor regions and anterior temporal regions. Second, the sample size for several groups was relatively modest which makes evaluating diagnostic power very challenging due to the large number of diverse phenotypes, i.e. 5 neurodegenerative and one control group. The results of the present study will require confirmation with larger groups of patients. Further evaluation of SCCAN as a tool to aid diagnosis and prognosis is also required. Third, virtually all work with the PBAC has been confined to differentiating AD from FTLD and to distinguishing between FTLD phenotypes. The utility of the PBAC in other populations such as Parkinson's disease, amyotrophic lateral sclerosis, and Mild Cognitive Impairment requires further examination. Finally, SCCAN associated some unexpected brain regions with a specific cognitive domain. Additional work is needed to understand the basis for these associations and whether these additional voxels are part of a minimal or maximal predictive network. With these limitations in mind, the current study suggests the power of a multivariate analytic approach such as SCCAN to interrogate multivariate brain and behavior relationships.

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Appendix A. ANTsR example code for SCCAN

We first load the relevant libraries for this analysis.

```
suppressPackageStartupMessages(library(ANTsR))
library(xtable)
library(abind)
library(grDevices)
library(visreg)
library(vegan)
```

Several organizational steps are not included. The key steps of univariate and multivariate feature selection, along with assessment on testing data, are shown below.

```

# do the univariate test to get the sparseness param
print("UNIVARIATE")
voxside <- "~ vox"
if (nam == "exec")
myform <- as.formula(paste(unames[1], voxside))
if (nam == "lang")
myform <- as.formula(paste(unames[2], voxside))
if (nam == "vs")
myform <- as.formula(paste(unames[3], voxside))
if (nam == "mem")
myform <- as.formula(paste(unames[5], voxside))
if (nam == "behav")
myform <- as.formula(paste(unames[6], voxside))
print(myform)
bynum <- 1
ss <- seq(1, ncol(trainmat), by = bynum)
ntests <- length(ss)
progress <- txtProgressBar(min = 0, max = ntests, style = 3)
upvs <- rep(1, ncol(trainmat))
for (i in ss) {
vox <- trainmat[, i]
fit <- lm(myform, data = demog[permutesubs, ])
upvs[i] <- coefficients(summary(fit))[2, 4]
if (i%%1000 == 0) {
setTxtProgressBar(progress, i)
}
}
sigthresh <- 0.01
upvs[is.na(upvs)] <- 1
qvsm <- upvs
qvsm[upvs < sigthresh] <- 1
qvsm[upvs >= sigthresh] <- 0
qvsm <- qvsm/sum(qvsm)
qvsm <- matrix(qvsm, nrow = 1)
vox <- testmat %*% t(qvsm)
fit <- lm(myform, data = demog[permutesubs2, ])
print(summary(fit))
uvmg <- antsImageClone(maskimg)
uvmg[mask] <- (1 - upvs)
antsImageWrite(uvmg, paste(DIR, nam, "_uv.nii.gz", sep = " "))
resUV <- lappend(resUV, c(nam, coefficients(summary(fit))[2, 4]))
# now do the multi-variate equivalent
print(paste("MULTIVARIATE"))
if (length(sparMV) < 5) {
sparlist <- (seq(1, 50, by = 4)/100)
corrlist <- list()
for (sigfrac in sparlist) {
print (paste("SEARCH:", sigfrac))
ff <- sparseDecom2(inmatrix = list(trainmat, cogmat[permutesubs, nw]),

```

```

inmask = c(maskimg, NA), sparseness = c(sigfrac, -1), nvecs = 1,
its = 15)
myprojla <- trainmat %*% t(imageListToMatrix(ff$eigl, maskimg))
myprojlb <- cogmat [permutesubs, nw] %*% as.matrix(ff$eig2)
corrlist <- lappend (corrlist, cor.test(myprojla, myprojlb)$est)
}
corrlist <- unlist(unlist(corrlist))
fit <- lmCcorrlist ~ sparlist + I(sparlist^2) + I(sparlist^3) +
I(sparlist^4)
pdf(paste("figs/sccan_param_", nam, ".pdf", sep = " "))
mytitle <- paste("Correlation v. Sparseness", nam, sep = " ")
visreg(fit, main = mytitle, xlab = "Sparseness", ylab = "SCCAN correlation",
cex.main = 2, cex.lab = 2)
dev.off()
sigfrac <- sparlist[which(corrlist == max(corrlist))]
sp <- data.frame(sparlist = (c(1:200)/1000))
pc <- predict(fit, newdata = sp)
sigfrac <- sp$sparlist[which.max(pc)]
sparMV <- lappend(sparMV, sigfrac)
} else sigfrac <- sparMV[[opt]]
ff <- sparseDecom2(inmatrix = list(trainmat, cogmat[permutesubs, nw]),
inmask = c(maskimg, NA), sparseness = cCsigfrac, -1),
nvecs = 1, its = 15)
myprojla <- trainmat %*% t(imageListToMatrix(ff$eigl, maskimg))
myprojlb <- cogmat [permutesubs, nw] %*% as.matrix(ff$eig2)
myproj2a <- testmat %*% t(imageListToMatrix(ff$eigl, maskimg))
myproj2b <- cogmat[permutesubs2, nw] %*% as.matrix(ff$eig2)
cogweights <- c(round(ff$eig2 * 1000)/1000)
print(cogweights)
imaging <- myproj2a[, 1]
cognition <- myproj2b[, 1]
myform <- as.formula("cognition ~ imaging")
fit <- lm(myform, data = demog[permutesubs2, ])
mypv <- coefficients(summary(fit))[2, 4]
print(summary(fit))

```

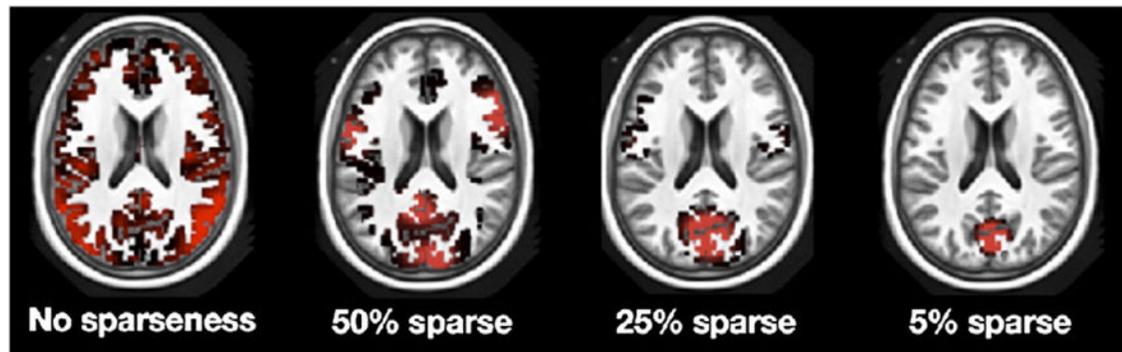


Fig. 1.

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.

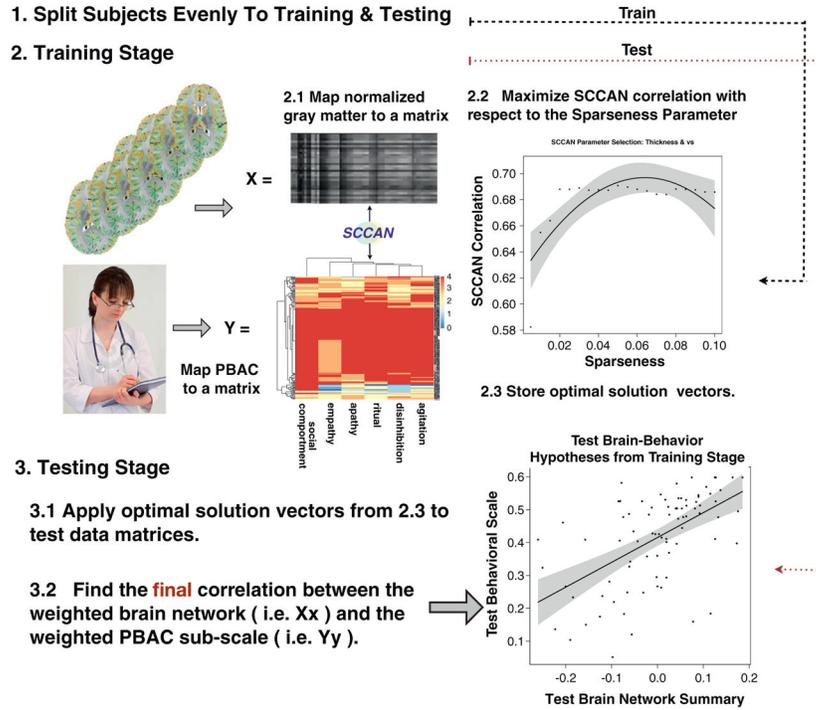


Fig. 2. Diagram of the study. The data splitting in step 1 happens only once. We perform stages 2 and 3 for each of the five PBAC sub-scales.

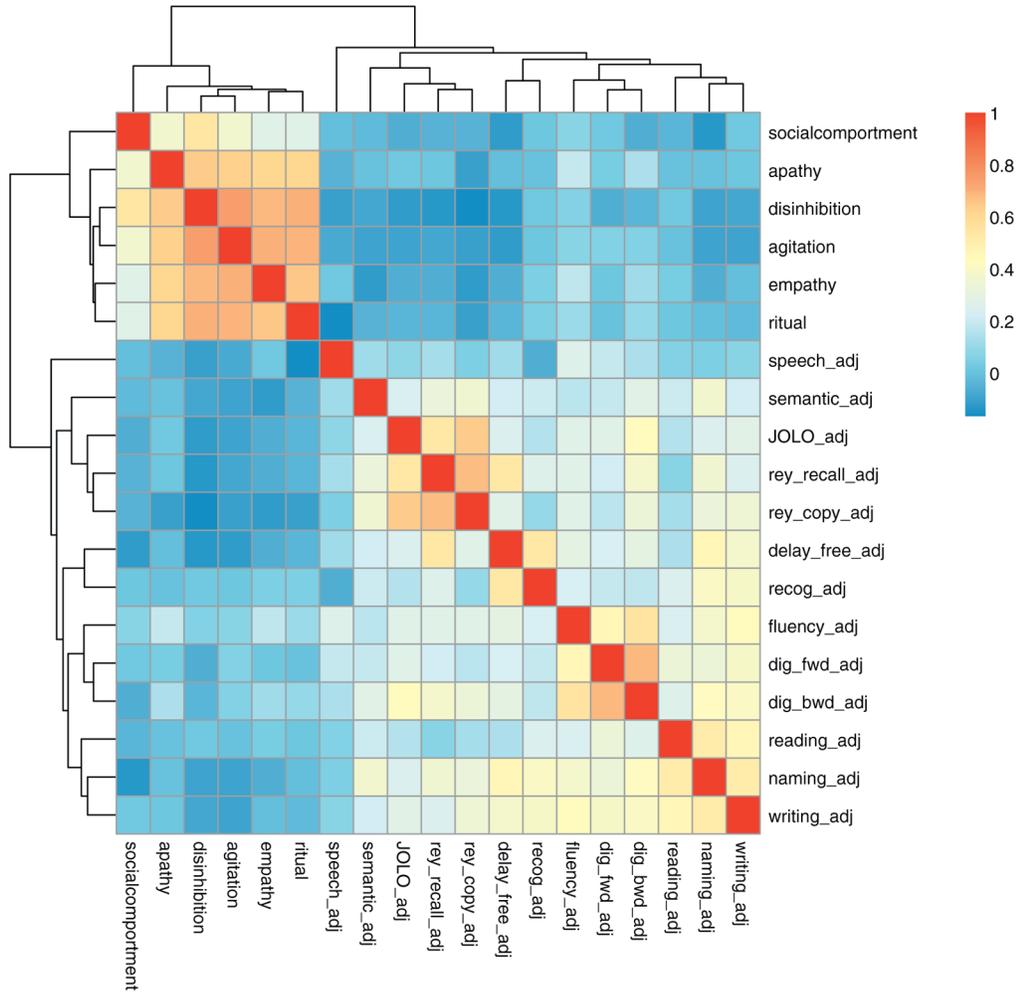


Fig. 3. We visualize, with a heatmap, the correlations between the different PBAC individual scales which are clustered together to form the sub-scales studied here. The total PBAC is an average of the 5 sub-scale scores. The sub-scales provide a reasonable separation of measurements.

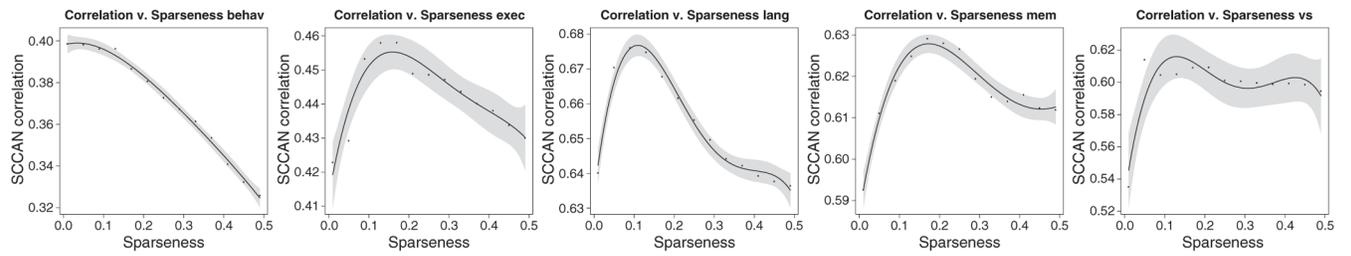


Fig. 4.

A one parameter search over sparseness, in the training dataset, allows us to identify the optimal sparseness parameter for each cognitive domain. The network variables x^* and y^* that arise from SCCAN computed at the optimal sparseness level will be evaluated in the test dataset for reproducibility.

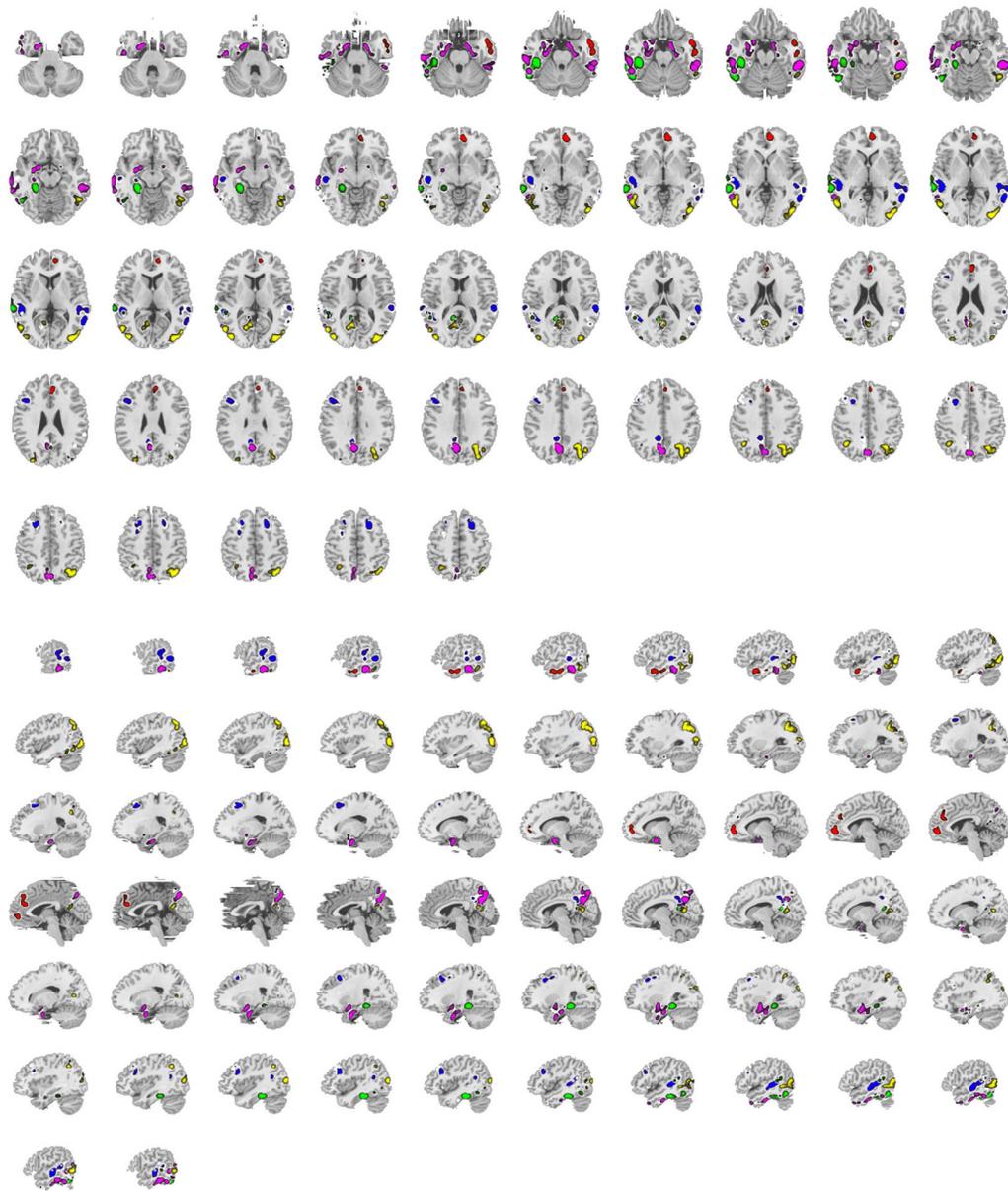


Fig. 5. All of the x^* solution vectors are combined in axial and sagittal views of the brain. Red is behavior, blue executive, green language, magenta episodic memory and yellow visuospatial. The left hemisphere of the brain is on the reader's left in the axial view.

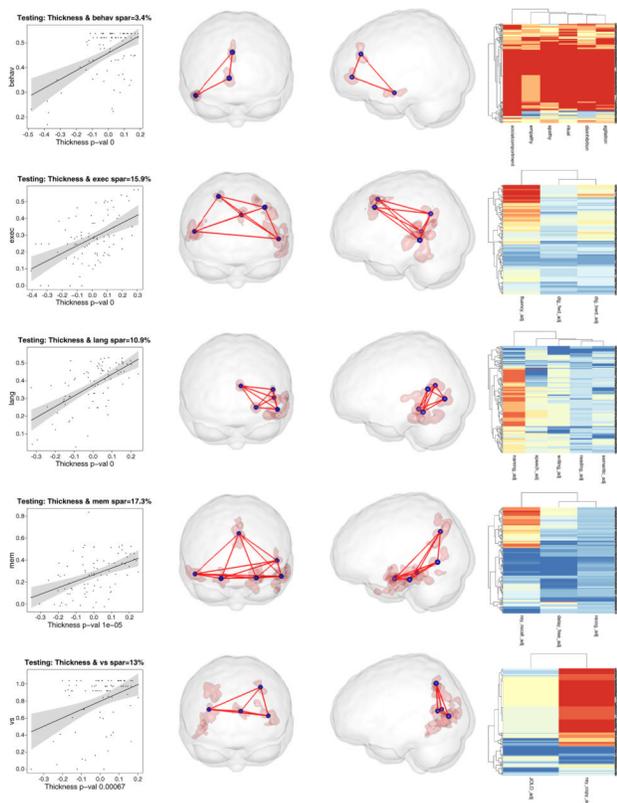


Fig. 6. We visualize the correlation between $X_{\text{test}}x^*$ and $Y_{\text{test}}y^*$ for each of the five PBAC sub-scales. We also show the PBAC sub-scales and their corresponding putative support regions in the cortex, as identified by SCCAN and verified in testing data. Each row, from the top, contains the results for the behavioral/social compartment scale, the executive/working memory scale, the language scale, the episodic memory scale and the visuospatial scale.

Table 1

The demographics for this study of 164 subjects are listed as mean/standard deviation in each column. For the testing and training split, subjects are matched on age, education and MMSE. MMSE = Mini-Mental State Examination, AD = Alzheimer's disease, bvFTD=behavioral variant of frontotemporal dementia, nfaPPA=non-fluent agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia, CBS = corticobasal syndrome, NC = normal control.

DX	N	Age	Education	MMSE
1 AD	17.00	70.88/7.79	14.82/3.17	21.94/4.75
2 bvFTD	41.00	61.51/9.55	16.05/3.66	25.44/4.85
3 nfaPPA	15.00	66.2/10.64	14.27/2.25	20.73/7.94
4 svPPA	14.00	63.21/5.85	17.64/2.34	19.14/10.16
5 CBS	24.00	62.42/8.52	14.33/2.46	22.29/3.94
6 NC	56.00	64.88/8.86	15.38/2.76	20.55/8.33

Table 2

The approximate Talairach coordinates and AAL labels for network behavior with significance $1.31e-06$ and sparseness 0.034 . Weights on the multivariate PBAC sub-scale (the y) are 0.029 , 0.027 , 0.028 , 0.017 , 0.017 , and 0.016 .

	x	y	z	t	Label	Brodman	AAL
1	52.00	-6.00	-21.00	0	1	21	Temporal_Mid_R
2	8.00	50.00	-5.00	0	2	10	Frontal_Med_Orb_R
3	4.00	39.00	23.00	0	3	32	Cingulum_Ant_R

Table 3

The approximate Talairach coordinates and AAL labels for network exec with significance 9.31e-07 and sparseness 0.159. Weights on the multivariate PBAC sub-scale (the y) are 0.031, 0.054, and 0.038.

	x	y	z	t	Label	Brodman	AAL
1	-51.00	-35.00	3.00	0	1	22	Temporal_Mid_L
2	-64.00	-41.00	-15.00	0	2	20	Temporal_Inf_L
3	60.00	-54.00	4.00	0	3	37	Temporal_Mid_R
4	20.00	19.00	46.00	0	4	0	Frontal_Sup_R
5	61.00	-32.00	15.00	0	5	42	Temporal_Sup_R
6	-43.00	19.00	24.00	0	6	48	Frontal_Inf_Tri_L
7	-25.00	19.00	39.00	0	7	0	Frontal_Mid_L
8	-7.00	-54.00	27.00	0	8	0	Precuneus_L
9	51.00	-33.00	2.00	0	9	21	Temporal_Mid_R
10	65.00	-37.00	4.00	0	10	22	Temporal_Mid_R
11	-9.00	-45.00	35.00	0	11	0	Cingulum_Mid_L

Table 4

The approximate Talairach coordinates and AAL labels for network lang with significance 3.26e-10 and sparseness 0.109. Weights on the multivariate PBAC sub-scale (the y) are 0.051, 0.006, 0.035, 0.03, and 0.013.

	x	y	z	t	Label	Brodman	AAL
1	-56.00	-39.00	-13.00	0	1	20	Temporal_Inf_L
2	-26.00	-38.00	-11.00	0	2	30	ParaHippocampal_L
3	-55.00	-67.00	1.00	0	3	37	Temporal_Mid_L
4	-6.00	-58.00	18.00	0	4	23	Precuneus_L
5	-54.00	-60.00	-16.00	0	5	37	Temporal_Inf_L

Table 5

The approximate Talairach coordinates and AAL labels for the memory network with significance 1.03e-05 and sparseness 0.173. Weights on the multivariate PBAC sub-scale (the y) are 0.064, 0.061, and -0.004. Left hippocampus is clustered together with parahippocampal gyrus.

	x	y	z	t	Label	Brodman	AAL
1	-3.00	-65.00	34.00	0	1	0	Precuneus_L
2	57.00	-38.00	-16.00	0	2	20	Temporal_Inf_R
3	-57.00	-30.00	-21.00	0	3	20	Temporal_Inf_L
4	-22.00	-11.00	-27.00	0	4	36	ParaHippocampal_L
5	-26.00	-5.00	-16.00	0	5	34	Amygdala_L
6	16.00	-9.00	-22.00	0	6	28	ParaHippocampal_R
7	-68.00	-28.00	-11.00	0	7	21	Temporal_Mid_L
8	-57.00	-54.00	-0.00	0	8	37	Temporal_Mid_L
9	-56.00	-50.00	-19.00	0	9	37	Temporal_Inf_L
10	-66.00	-14.00	-17.00	0	10	21	Temporal_Mid_L
11	-4.00	-59.00	47.00	0	11	7	Precuneus_L
12	-57.00	-66.00	10.00	0	12	37	Temporal_Mid_L
13	-66.00	-44.00	-11.00	0	13	20	

Table 6

The approximate Talairach coordinates and AAL labels for network vs with significance 0.0007 and sparseness 0.13. Weights on the multivariate PBAC sub-scale (the y) are 0.065 and 0.054.

	x	y	z	t	Label	Brodman	AAL
1	34.00	-64.00	39.00	0	1	7	Angular_R
2	41.00	-81.00	8.00	0	2	19	Occipital_Mid_R
3	-52.00	-65.00	3.00	0	3	37	Temporal_Mid_L
4	-40.00	-83.00	11.00	0	4	19	Occipital_Mid_L
5	50.00	-55.00	-10.00	0	5	37	Temporal_Inf_R
6	-10.00	-64.00	11.00	0	6	17	Calcarine_L
7	-37.00	-55.00	39.00	0	7	39	Angular_L
8	46.00	-65.00	-7.00	0	8	37	Temporal_Inf_R
9	-29.00	-56.00	49.00	0	9	7	Parietal_Sup_L
10	2.00	-60.00	19.00	0	10	23	Calcarine_R
11	-30.00	-86.00	26.00	0	11	19	Occipital_Mid_L