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Relating brain anatomy and cognitive ability using a multivariate multimodal framework

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ABSTRACT

Linking structural neuroimaging data from multiple modalities to cognitive performance is an important challenge for cognitive neuroscience. In this study we examined the relationship between verbal fluency performance and neuroanatomy in 54 patients with frontotemporal degeneration (FTD) and 15 age-matched controls, all of whom had T1- and diffusion-weighted imaging. Our goal was to incorporate measures of both gray matter (voxel-based cortical thickness) and white matter (fractional anisotropy) into a single statistical model that relates to behavioral performance. We first used eigenanatomy to define data-driven regions of interest (DD-ROIs) for both gray matter and white matter. Eigenanatomy is a multivariate dimensionality reduction approach that identifies spatially smooth, unsigned principal components that explain the maximal amount of variance across subjects. We then used a statistical model selection procedure to see which of these DD-ROIs best modeled performance on verbal fluency tasks hypothesized to rely on distinct components of a large-scale neural network that support language: category fluency requires a semantic-guided search and is hypothesized to rely primarily on temporal cortices that support lexical-semantic representations; letter-guided fluency requires a strategic mental search and is hypothesized to require executive resources to support a more demanding search process, which depends on prefrontal cortex in addition to temporal network components that support lexical representations. We observed that both types of verbal fluency performance are best described by a network that includes a combination of gray matter and white matter. For category fluency, the identified regions included bilateral temporal cortex and a white matter region including left inferior longitudinal fasciculus and frontal–occipital fasciculus. For letter fluency, a left temporal lobe region was also selected, and also regions of frontal cortex. These results are consistent with our hypothesized neuroanatomical models of language processing and its breakdown in FTD. We conclude that clustering the data with eigenanatomy before performing linear regression is a promising tool for multimodal data analysis.

Introduction

One of the fundamental challenges of cognitive neuroscience is relating brain anatomy to cognitive processes. Most neuroimaging studies linking brain structure to behavior use mass univariate approaches, relying on a whole-brain regression framework in which the relationship between a dependent variable (e.g. gray matter density or fractional anisotropy; FA) and a behavioral measure is assessed at every voxel in the brain.[1] An advantage of this traditional approach is that it makes few a priori assumptions about the location of the relationship, or the spatial extent of the brain region(s) relating to behavior. However, there are also some challenges. An obvious limitation is that, without some sort of prior narrowing of focus, voxelwise methods result in a large number of statistical tests that need correction for multiple comparisons. A common strategy to address multiple comparisons is to accumulate voxel data into larger regions of interest (ROIs). However, ROIs are often difficult and labor-intensive to define for each application. For example, the cytoarchitectonic boundaries of Broca's area involved in language are both structurally (Amunts et al., 1999) and functionally (Clos et al., 2013) heterogeneous across individuals. The anatomical boundaries of a particular label set may not align with

Abbreviations: AIC, Aikake Information Criterion; AICc, corrected AIC; bvFTD, behavioral-variant FTD; CVMSE, cross-validation mean squared error; FTD, frontotemporal degeneration; naPPA, non-fluent/agrammatic variant PPA; PPA, primary progressive aphasia; svPPA, semantic variant PPA.

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[1] For parsimony we refer to "voxelwise" analyses, but this also applies to mass-univariate surface-based analyses.

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functionally relevant areas or the concentration of pathological change in a disease under study. These issues motivate the use of data-driven ROIs (DD-ROIs) that can be defined automatically on different populations of images, have soft boundaries instead of the hard labeling of most manual label sets, and can be optimized based on criteria other than visual anatomical boundaries. Such approaches have been used for automated diagnosis of Alzheimer's disease (Klöppel et al., 2008) and the classification of primary progressive aphasia variants (Wilson et al., 2009). Variability of white matter across individuals has also been suggested to impact language performance (Berthier et al., 2012; Flöel et al., 2009). Another important issue with ROI studies of white matter is the lack of available labels: while there are several dense parcellations of cortical gray matter available to researchers, there are few white matter atlases and those that are available focus on major tracts that can be delineated using diffusion tensor imaging.

In this report, we use a multivariate approach that aims to integrate neuroimaging measures of gray matter and white matter in order to define a large-scale neural network that accounts for linguistic performance. This approach relies on "eigenanatomy" (Avants et al., 2012a; McMillan et al., 2013b, 2014), which is a recently proposed algorithm for generating DD-ROIs. These soft ROIs are defined automatically by maximizing the covariance of voxel-wise measurements normalized to template space and collected into a matrix representation. There is no need for prior manual labeling of the subject images and one only needs to define an anatomical domain of interest in the template, for example cortical gray matter for cortical thickness and white matter for diffusion-tensor statistics. Eigenanatomy also addresses the need to take into account spatial smoothness in the ROIs. Voxelwise approaches do this in a post-hoc manner by considering clusters of contiguous results. More recent multivariate approaches take spatial dependency as a given, and seek to capitalize on this from the outset. We view this as a sensible assumption, given the continuous nature of the neural tissue, and the fact that processes such as neural development, age-related cortical thinning, and gray matter loss due to neurodegenerative disease all show a significant degree of spatial localization. By capitalizing on these dependencies, we should be able to better characterize variations in brain shape and tissue structure. Further, theoretical arguments suggest that exploiting prior knowledge when solving challenging optimization problems fundamentally improves results in terms of performance, stability and interpretability (Wolpert and Macready, 1997).

In combination with eigenanatomy dimensionality reduction, we apply a model selection procedure to determine which DD-ROIs in gray matter and white matter form the most efficient regression models of behavioral measures. This approach combines information from multiple imaging modalities in a principled manner within a single regression framework while maintaining the interpretability of classic regression models. Although in theory researchers certainly appreciate the joint contribution of gray matter and white matter integrity to behavioral performance, in practice it has proven difficult to study these at the same time in the same set of subjects. In particular, it has been challenging to quantitatively evaluate the relative contribution of gray matter and white matter to behavior: if a patient has damage to both, which is the better predictor of performance?

To demonstrate the utility of our multivariate approach, we focus on the neural basis of language limitations in patients with frontotemporal degeneration (FTD). The two most common forms of FTD yield either a language disorder, primary progressive aphasia (PPA) (Gorno-Tempini et al., 2011), or a disorder of personality, social comportment, and executive dysfunction, behavioral-variant FTD (bvFTD) (Rascovsky et al., 2011). Within PPA there is a semantic variant (svPPA) that is characterized by difficulty with naming, word meaning, and object knowledge. This variant has been associated with considerable atrophy in the anterior and ventral temporal lobe, more prominently on the left than the right, as well as disease in uncinate and inferior longitudinal fasciculi projections (Mahoney et al., 2013; Whitwell et al., 2010). There is also a non-fluent/agrammatic variant (naPPA), involving slowed, effortful speech with grammatical difficulty and this has been associated with left-lateralized frontal and anterior–superior temporal cortical regions and prominent white matter disease in corpus callosum and inferior frontal–occipital fasciculus (Grossman, 2012; Grossman et al., 2012; Mahoney et al., 2013). bvFTD is not associated with an obvious aphasia, though executive-social limitations can have consequences on language processing (McMillan et al., 2013a), and these patients have gray matter frontal atrophy that is most prominent in ventral and medial frontal regions and extends into dorsolateral frontal areas, with associated disease in white matter projections from these areas (Lillo et al., 2012; Zhang et al., 2013).

Given the distributed localization of disease within the FTD variants we hypothesize that distinct large-scale neural networks contribute to patients' language limitations. Specifically, we focus on verbal fluency. This is a complex task that involves mental search through the lexicon of words that meet the criteria of a category. This process requires conceptual knowledge of word meanings, lexical retrieval, and executive resources involving a flexible mental search strategy. Verbal fluency tasks are common neuropsychological measures that can be adjusted to stress different cognitive processes and thus place different demands on a large-scale neuroanatomical network. For example, a category fluency task ("Name as many animals as you can") emphasizes knowledge of lexical and conceptual information. By contrast, a letter fluency task ("Name as many words as you can that begin with the letter F") requires lexical information and additionally requires an advanced executive search strategy to search through all words that begin with a specific letter. In the context of FTD patients, svPPA patients have more difficulty with category fluency than letter fluency and this has been associated with temporal cortex disease (Libon et al., 2009a). However, letter fluency appears to be more associated with frontal cortex disease in FTD and is compromised in bvFTD and nvPPA (Libon et al., 2009a). Assessments of gray matter regions contributing to verbal fluency tasks have been performed using a priori regions of interest (Amunts et al., 2004) or regression analyses using voxel-based morphometry (Libon et al., 2009b). We are unaware of investigations evaluating the relative contributions of gray matter and white matter disease to verbal fluency deficits in FTD.

Together, we hypothesize that our novel multivariate approach and model selection procedure will reveal a large-scale neural network that supports verbal fluency, including fronto-temporal gray matter regions as well as white matter projections between these brain regions, and that the cortical-white matter network implicated in performance will be tailored to the specific task. We test this in a multimodal imaging study of FTD. These observations would provide proof-of-concept evidence for utilizing this approach to better understand the relative contributions of gray matter and white matter in the context of cognitive neuroscience, and would improve our understanding of brain–behavior relationships in neurodegenerative conditions like FTD.

Materials and methods

Participants

We recruited 54 patients from the Penn Frontotemporal Degeneration Center and Hospital of the University of Pennsylvania Cognitive Neurology Clinic who were native-English speakers and clinically-diagnosed with FTD by a board-certified neurologist using published criteria of either PPA (Gorno-Tempini et al., 2011) or bvFTD (Rascovsky et al., 2011). Other causes of dementia were excluded by clinical exam, blood and neuroimaging tests. Exclusion criteria included other neurologic, psychiatric or medical conditions that can result in cognitive change. Some patients may have been on a small, stable dose of a non-sedating neuroleptic or anti-depressant medication. We also recruited 15 healthy older adults who were demographically comparable in age and education relative to the patient cohort. All subjects had T1- and diffusion-weighted structural MRI scans. Thirty-eight subjects

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