Neurobiology of Aging 36 (2015) S103–S112

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Network and connectivity

Seemingly unrelated regression empowers detection of network failure in dementia

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ARTICLE INFO

Article history:
Received 2 May 2013
Received in revised form 19 November 2013
Accepted 27 February 2014
Available online 27 August 2014

Keywords:
Brain connectivity
Neuroimaging genetics
HARDI tractography
Seemingly unrelated regression (SUR)
APOE4
Multivariate analysis

ABSTRACT

Brain connectivity is progressively disrupted in Alzheimer's disease (AD). Here, we used a seemingly unrelated regression (SUR) model to enhance the power to identify structural connections related to cognitive scores. We simultaneously solved regression equations with different predictors and used correlated errors among the equations to boost power for associations with brain networks. Connectivity maps were computed to represent the brain's fiber networks from diffusion-weighted magnetic resonance imaging scans of 200 subjects from the Alzheimer's Disease Neuroimaging Initiative. We first identified a pattern of brain connections related to clinical decline using standard regressions powered by this large sample size. As AD studies with a large number of diffusion tensor imaging scans are rare, it is important to detect effects in smaller samples using simultaneous regression modeling like SUR. Diagnosis of mild cognitive impairment or AD is well known to be associated with ApoE genotype and educational level. In a subsample with no apparent associations using the general linear model, power was boosted with our SUR model—combining genotype, educational level, and clinical diagnosis.

1. Introduction

Brain connectivity is progressively disrupted in Alzheimer's disease (AD). Several new technologies can recover patterns of brain connectivity from scans performed in a clinical setting, such as diffusion-weighted magnetic resonance imaging (MRI). Connectivity maps are of interest from a neuroscientific point of view, but there is also practical interest in whether connectivity measures are useful biomarkers for identifying factors that affect the brain in epidemiologic studies or for monitoring brain decline in clinical trials.

Connectivity maps reveal organizational features of the brain not detectable on standard anatomical MRI. There is some interest in determining whether connectivity measures might help in predicting patient diagnosis or prognosis, either alone or when combined with other biomarkers. Connectivity measures may also provide insight into disease beyond what can be inferred from

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[1] Many investigators within the Alzheimer's Disease Neuroimaging Initiative (ADNI) contributed to the design and implementation of ADNI and/or provided data, but most of them did not participate in analysis or writing of this report. A complete list of ADNI investigators may be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.032

other imaging measures or from clinical or cognitive assessments. In particular, diffusion tensor imaging (DTI) and its mathematical extensions (such as high angular resolution diffusion-weighted imaging or q-space imaging) can reveal disease-related changes in white matter integrity (Nir et al., 2013), and depict how various cortical regions are connected to each other. Using diffusion MRI, structural connectivity can be defined in terms of the density or integrity of reconstructed fiber tracts connecting various regions of the brain. Often, cortical regions are identified automatically on T1-weighted structural MRI scans. Based on coregistered diffusion-imaging data, we can then study the trajectories and densities of white matter tracts interconnecting the cortical regions.

Clinical studies of brain connectivity are highly informative. Brain connectivity changes profoundly during development (Dennis et al., 2013; Hagmann et al., 2008, 2010) in normal aging (Brown et al., 2011), in elderly people with HIV (Jahanshad et al., 2012), AD (Daianu et al., 2013a; Nir et al., 2012), and other neurodegenerative diseases (Toga and Thompson, 2013), and in disorders such as epilepsy (Engel et al., 2013). Such work reveals how diseases disrupt connections and networks, offering insights into neurobiological mechanisms and disease consequences.

Large-scale efforts, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), have led to analyses of neuroimaging data in large cohorts of patients. ADNI recently launched a second phase (ADNI-2) of longitudinal data collection to include diffusion-weighted scans, with the goal of studying microstructural integrity and anatomical connectivity (among other measures) in elderly individuals. ADNI-2 is still in its early stages, and data are still being collected from AD, mild cognitive impairment, and normal elderly subjects with varying degrees of cognitive impairment. Of the projected 1000 additional subjects in its second phase, ADNI will scan around 300 subjects with DTI. Yet, even in the early stages of data acquisition, connectivity disruptions in AD have been shown using ADNI-DTI (Daianu et al., 2013a, 2013b; Hasan et al., 2012; Nir et al., 2012; Prasad et al., 2013). As with the more common MRI, DTI can therefore also detect changes associated with dementia. Even so, some factors that affect brain-imaging measures require tens of thousands of subjects to detect (Hibar et al., 2013; Stein et al., 2012); efforts are needed to maximize power for discovering factors that predict network decline. Fortunately, combining predictors from all clinical categories can significantly enhance power to predict brain integrity and decline, or in other words, combining information from multiple sources can reduce the sample size needed to detect statistical associations (Kohannim et al., 2010; Xiang et al., 2013; Yuan et al., 2012).

To identify clinically relevant changes in the brain's networks, one typical approach is to fit multiple general linear regression models to identify connections whose integrity is statistically associated with clinical or cognitive scores or with ratings of dementia severity. Detecting connections whose strength are associated with cognitive decline may help to delineate compromised brain regions and subnetworks. This may focus attention on regions where medication effects may be monitored more specifically. Ideally, one would prefer to analyze a very large cohort of subjects to have enough statistical power to identify all connections associated with changes in cognition. However, as with other measures, the power to relate brain connectivity to clinical parameters is limited by the available sample size. This makes it vital to examine new ways to optimize power to detect clinical associations with images.

In this study, we have 2 goals. First, we identify a pattern of connections in the brain whose density is associated with clinical decline. To do this, we use a standard regression model where the elements of the connectivity matrix are predicted using widely used cognitive test scores including the global clinical dementia rating (CDR) and Mini-Mental State Examination (MMSE) scores. The classical approach to find brain measures related to disease burden is to fit a large regression model that includes as many relevant predictors as possible. These predictors may include measures of dementia severity (such as the CDR or MMSE) or other predictors known to be associated with AD, such as ApoE4 genotype (Reiman et al., 1996), age, and educational level (Stern et al., 1994). In other words, the connectivity matrix is treated as a 2D image, and all relevant predictors are fitted to the data at each matrix element, leading to a statistical parametric map of connections that decline in AD.

However, as a second goal, we propose a different and more powerful tactic to pick up connectivity patterns that decline in disease, based on a method known as seemingly unrelated regression (SUR), adapted from econometrics (Zellner, 1962). SUR is more common in the financial literature but perhaps less so in brain imaging, so we explain it briefly here. In the standard statistical model, we could insert all the predictors we have (MMSE, CDR, educational level, ApoE genotype, etc.) into a single multiple regression equation to predict the values of connectivity matrix elements, C(x,y). If that is done, then as long as there is sufficient power to find an effect, a pattern of connections would be found that relates to clinical decline. With SUR, we instead have a set of simultaneous regression equations where each equation in the set does not necessarily have to predict the same outcome measure. Some of the regression equations may predict a different dependent variable, and some predictors may be present or absent in each equation. If the predictors depend on each other statistically, we are then able to use the fact that the errors are correlated among the larger set of equations to solve them more accurately. We essentially use the correlated errors among equations to boost power to find brain connections that decline in AD.

As SUR can be more powerful than a standard regression, we used both SUR and a standard linear regression to identify brain connections related to clinical decline. We hypothesized that SUR would detect associations too weak to detect with the standard model. Our goal was to boost the effect sizes of associations between brain connectivity measures and clinical scores to "revive" significance for tests that would have failed using the standard regression model. The overall goal of our work is to enhance the power to pick up patterns of brain connections that decline in AD. This is particularly useful when the available sample size is limited but should always be beneficial even in large samples.

2. Methods

2.1. Subject information and image acquisition

Data collection for the second phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI2) includes diffusion MRI, but, at the time of writing (April 2013), this is still in its early stages. Here, we performed an initial cross-sectional analysis of the ADNI DTI data from 200 adults whose DTI scans passed a quality control procedure; the QC process involved checking each scan for cropping or incomplete coverage of the brain, slice or gradient dropout, stripes or other artifacts, and excessive distortion or excessive rotational or translational motion during the scan. Scans that failed QC were excluded. Table 1 shows a summary of relevant demographic information for these 200 participants. Age, sex, and educational level (in years) were ascertained for all subjects. Clinical assessments of dementia severity include the MMSE (Folstein et al., 1975) (lower scores denote greater impairment), and the Clinical Dementia Rating