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Predicting intrinsic brain activity

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ABSTRACT

Multivariate supervised learning methods exhibit a remarkable ability to decode externally driven sensory, behavioral, and cognitive states from functional neuroimaging data. Although they are typically applied to task-based analyses, supervised learning methods are equally applicable to intrinsic effective and functional connectivity analyses. The obtained models of connectivity incorporate the multivariate interactions between all brain regions simultaneously, which will result in a more accurate representation of the connectome than the ones available with standard bivariate methods. Additionally the models can be applied to decode or predict the time series of intrinsic brain activity of a region from an independent dataset. The obtained prediction accuracy provides a measure of the integration between a brain region and other regions in its network, as well as a method for evaluating acquisition and preprocessing pipelines for resting state fMRI data. This article describes a method for learning multivariate models of connectivity. The method is applied in the non-parametric prediction accuracy, influence, and reproducibility–resampling (NPAIRS) framework, to study the regional variation of prediction accuracy and reproducibility (Strother et al., 2002). The resulting spatial distribution of these metrics is consistent with the functional hierarchy proposed by Mesulam (1998). Additionally we illustrate the utility of the multivariate regression connectivity modeling method for optimizing experimental parameters and assessing the quality of functional neuroimaging data.

Introduction

Multivariate supervised learning methods, commonly referred to as multi-voxel pattern analysis (MVPA), have shown a remarkable ability to decode externally driven sensory, behavioral, and cognitive states from functional neuroimaging data (Chu et al., 2011a; Cox and Savoy, 2003; Haxby et al., 2001; Haynes and Rees, 2006; Kamitani and Tong, 2005; LaConte et al., 2005; Mitchell et al., 2004; Mourão-Miranda et al., 2005; Polyn et al., 2005; Strother et al., 2002). Although these techniques are typically applied to task-based experimental parameters, they can also be used to model intrinsic brain activity (Chu et al., 2011b; Friston, 1994; Friston and Frith, 1993). In this setting, a connectivity model is learned from distributed statistical relationships, and thus is capable of decoding (predicting) the intrinsic activity of a brain region.

A multivariate regression connectivity (MRC) model relates the activity measured in a brain region to a linear (or non-linear) combination of the activity measured in every other region of the brain (Friston, 1994; Friston and Frith, 1993). Typically, the number of brain regions to be modeled is much greater than the number of observations, resulting in an underdetermined system of linear equations that cannot be solved uniquely. Methods for dealing with this include dimensionality reduction (Friston, 1994; Friston and Frith, 1993), feature selection, regularization based algorithms (Ryali et al., 2011; Varoquaux et al., 2010), or frameworks such as statistical learning theory (Chu et al., 2011b). The result is a network model of connectivity that accounts for the complex interactions between all modeled brain regions simultaneously, which is a more accurate representation of the connectome than achieved with standard bivariate connectivity measures (Varoquaux et al., 2010). Further, the learned models can be applied to independently acquired data to decode a region's intrinsic activity from these new data (Chu et al., 2011b; Varoquaux et al., 2010).

Although the reproducibility of intrinsic functional connectivity (iFC) has been examined (Braun et al., 2012; Shehzad et al., 2009; Wang et al., 2011; Zuo et al., 2010a, 2010b), the ability of iFC models to *predict* intrinsic brain activity has been largely overlooked (notable exceptions include Chu et al. (2011b) and Varoquaux et al. (2010)). The ability to make accurate predictions is a fundamental criterion for scientific models. Poor prediction accuracy might indicate that a model is missing an important source of information about the

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phenomena being modeled (i.e. unmodeled variance), makes invalid assumptions, or is inconsistent over time. In the case of connectivity models of brain architecture, unmodeled variance would indicate that there is a component of local intrinsic activity that is not present in other regions of the brain, and the modeled brain region exhibits a degree of segregation from the rest of the brain. As such, prediction accuracy provides a means to evaluate the amount of information that exists in the brain about a specific brain region, and quantifies the degree to which a brain region is integrated with its iFC network (Kjems et al., 2002; Marrelec et al., 2008; Tononi, 1998). This is in contrast to centrality measures, which assess functional integration of a brain region based on its number of connections with other regions (Zuo et al., 2011). Similarly prediction accuracy can be used as a quantitative metric to evaluate the degree to which iFC models differ over time, between subjects, and with experimental paradigms (i.e. task vs. rest). Poor prediction accuracy may also reflect the validity of the modeling framework, and as such when combined with reproducibility provides a data driven approach that can be used to compare the modeling frameworks as well as acquisition and analysis parameters (Chu et al., 2011b; Kjems et al., 2002; LaConte et al., 2003; Shaw et al., 2003; Strother et al., 2002). Additionally the predictive quality of models of iFC provides a mechanism for real-time tracking of iFC for neurofeedback and brain–computer-interface applications (LaConte, 2011; LaConte et al., 2007).

This article describes multivariate prediction analysis of intrinsic brain activity measured from functional magnetic resonance imaging (fMRI) data. We have used support vector regression (SVR) (Drucker et al., 1997; Müller et al., 1997; Vapnik et al., 1996), but other multivariate regression methods, such as PLS, ridge regression, Lasso, and elastic-net, could also be used. We discuss the links between prediction accuracy and integration (Kjems et al., 2002; Marrelec et al., 2008; Tononi, 1998), as well as between reproducibility and signal-to-noise ratio (SNR) of the regression models (Strother et al., 2002). Regional variations in prediction accuracy and reproducibility were investigated across anatomical and functional subdivisions of the brain. The impacts of subject age, sex and head motion on these metrics were also evaluated. Additionally, we evaluated the impact of scan length on model performance. This paper is methodologically related to previous work (Chu et al., 2011a; Friston, 1994; Friston and Frith, 1993). Here, we provide an extensive characterization of regional variation in predictive modeling of intrinsic brain activity using the NPAIRS framework. In addition, we demonstrate the utility of parcellation to reduce the number of regression models required to perform these analyses and facilitate the anatomical interpretability of results.

Methods

Subjects and scanning

Thirty-three healthy volunteers (age: 19–48, mean 27.2, std. dev. 7.9, 16 females) participated in accordance with Baylor College of Medicine Institutional Review Board policy. To qualify for inclusion, subjects were required to be between the ages of 18 and 65, have no contraindications for MRI, to be medication free, and have no current or past neurological or psychiatric conditions.

Subjects were scanned on a 3 T Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions USA; Malvern PA, USA) using a 12-channel head matrix coil. The scanning procedure began with a high-resolution anatomic scan followed by two separate 10-minute resting state fMRI runs (Rest 1 and Rest 2). Anatomic images were acquired at $1 \times 1 \times 1$ mm^3 resolution with a 3D T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (Mugler and Brookman, 1990) using: field of view (FOV) $256 \times 256 \times 176$ mm^3, repetition time (TR) 2600 ms, echo time (TE) 3.02 ms, inversion recovery time (TI) 900 ms, flip angle (FA) 8°, phase partial Fourier 6/8, slice partial Fourier 7/8, GRAPPA factor of 2 with 24 reference lines, and bandwidth 130 Hz/pixel. Resting state fMRI data were acquired with a blood oxygenation level dependent (BOLD) contrast weighted gradient-recalled echo-planar-imaging sequence (EPI). Twenty-nine 3.6-mm thick interleaved oblique slices were acquired with a 10% slice gap and the parameters: TR 1750 ms, TE 30 ms, FA 90°, 64×64 matrix, 220-mm FOV, in-plane resolution 3.45×3.45 mm^2, anterior-to-posterior phase encoding and bandwidth 2442 Hz/pixel. Each resting-state scan consisted of 343 functional volumes, lasting approximately 10 min. For resting state functional scans, subjects were instructed to passively view a fixation cross while clearing their minds of any specific thoughts.

This dataset has been made available for non-commercial use through the International Neuroimaging Data-Sharing Initiative (http://fcon_1000.projects.nitrc.org/).

Data preprocessing

Data preprocessing was accomplished using a combination of tools from AFNI (Cox, 1996) and FSL (Smith et al., 2004). Anatomical images were skull stripped, segmented, and then registered to MNI152 space using a two-step procedure, which first calculates a linear registration (FLIRT; Jenkinson et al., 2002) that is subsequently refined using a non-linear registration (FNIRT). Conservative white matter (WM) and cerebrospinal fluid (CSF) masks were derived from the results of segmentation (Zhang et al., 2001) by applying probability ≥ 0.99 thresholds to WM and CSF probability maps. These maps were down sampled to 4 mm isotropic resolution and subsequently dilated by 1 voxel to further prevent overlap with gray matter.

Functional image preprocessing began with slice timing correction and then motion correction. The mean image from each scan was calculated and used to co-register each functional scan to the corresponding anatomic image. Next nuisance variable regression was performed by regressing out WM and CSF time series, the six motion parameters calculated from motion correction, and a 4th order polynomial to account for baseline drifts (Friston et al., 1996; Lund et al., 2006). The functional to anatomical and anatomical to MNI152 transformations calculated for each dataset were concatenated to construct a functional to MNI152 transform. This transform was applied to the corresponding functional images to write them into MNI space at 4 mm isotropic resolution. The resulting images were smoothed using a 6-mm full width at half maximum (FWHM) Gaussian kernel.

ROI generation

This analysis used 179 ROIs specified by a 2-level temporal correlation based whole brain functional parcellation (Craddock et al., 2012) of resting state data from 198 subjects from the Cambridge dataset publically available from the 1000 functional connectome project (Biswal et al., 2010). The independent dataset was used to exclude any bias that might be introduced by generating ROIs from the same data that were analyzed. The Cambridge dataset was preprocessed identically to our experimental data, except that it was band-pass filtered ($0.001 \text{ Hz} < f < 0.08 \text{ Hz}$) after nuisance variable regression as in Craddock et al. (2012). The parcellation procedure produced 196 ROIs, which were reduced to 179 ROIs after excluding regions in the cerebellum and brain stem (Fig. 1A).

Multivariate model of intrinsic brain function

The application of support vector regression to model intrinsic brain function follows the analysis of task-based fMRI experiments, in which the goal is to learn the relationship between a vector of *features* (from each brain image) and scalar *labels* (of the task conditions) (Cox and Savoy, 2003; LaConte et al., 2005; Mourão-Miranda et al., 2005). The crux of the approach used here is that the labels