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Decoding post-stroke motor function from structural brain imaging

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ABSTRACT

Clinical research based on neuroimaging data has benefited from machine learning methods, which have the ability to provide individualized predictions and to account for the interaction among units of information in the brain. Application of machine learning in structural imaging to investigate diseases that involve brain injury presents an additional challenge, especially in conditions like stroke, due to the high variability across patients regarding characteristics of the lesions. Extracting data from anatomical images in a way that translates brain damage information into features to be used as input to learning algorithms is still an open question. One of the most common approaches to capture regional information from brain injury is to obtain the lesion load per region (i.e. the proportion of voxels in anatomical structures that are considered to be damaged). However, no systematic evaluation has yet been performed to compare this approach with using patterns of voxels (i.e. considering each voxel as a single feature). In this paper we compared both approaches applying Gaussian Process Regression to decode motor scores in 50 chronic stroke patients based solely on data derived from structural MRI. For both approaches we compared different ways to delimit anatomical areas: regions of interest from an anatomical atlas, the corticospinal tract, a mask obtained from fMRI analysis with a motor task in healthy controls and regions selected using lesion-symptom mapping. Our analysis showed that extracting features through patterns of voxels that represent lesion probability produced better results than quantifying the lesion load per region. In particular, from the different ways to delimit anatomical areas compared, the best performance was obtained with a combination of a range of cortical and subcortical motor areas as well as the corticospinal tract. These results will inform the appropriate methodology for predicting long term motor outcomes from early post-stroke structural brain imaging.

1. Introduction

The ability to predict long term outcome after stroke is urgently required in order to facilitate a stratified approach to clinical decision making (Ward, 2015). It has long been known that information encoded in brain lesions (e.g. extent and location) can explain variability in post-stroke outcomes (Bayona et al., 2005; Geva et al., 2011; Särkämö et al., 2009; Schiemanck et al., 2005; Yang et al., 2008; Zhu et al., 2010), but no approaches have been routinely incorporated into clinical practice.

Machine learning (ML) techniques are potentially useful for clinical applications, aiming to provide sensitive and specific diagnostic and prognostic indicators for individuals, as opposed to analysing statistical group differences (Wang et al., 2010). In neuroimaging, clinical applications of ML methods have initially focused mainly on binary classification of disease states (Davatzikos et al., 2005; Teipel et al., 2007; Fu et al., 2008; Klöppel et al., 2008; Vemuri et al., 2010). More recently, decoding of outcomes represented by continuous scales has also become increasingly common in several neurological and psychiatric conditions through predictive multivariate regression methods (Cohen et al., 2011).

The extraction of features from brain images in a way that is meaningfully related to the clinical condition being studied is a fundamental step in a predictive analysis framework. In the context of stroke, feature extraction from structural neuroimaging is additionally challenging due to the high variability in anatomical location and extension of brain injury. Although lesion characteristics can potentially contribute towards making accurate predictions of the likely level of impairment and recovery, there is currently no consensus on how to quantify these characteristics.

Progress has been made in predicting language outcomes using features derived from stroke lesions (Payabvash et al., 2010; Hope et al., 2013, 2015) but predicting motor outcomes is lagging behind. One of the most common approaches to quantify characteristics from lesions is summarizing the proportion of voxels in each region of interest (ROI) that are considered to be part of a lesion. This information is commonly referred to as *lesion load* and it is obtained using anatomical

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masks to define the ROIs and a method to segment the lesions, either manually (Kim et al., 2014) or automatically (Hope et al., 2013, 2015). Recently, voxel-based lesion symptom mapping (VLSM, (Bates et al., 2003)) has also been proposed as a way to extract features from stroke lesions to be used as input to machine learning models. Voxel-based lesion symptom values are obtained for each voxel through a statistical test on the continuous scores representing the symptom between two groups (which are defined according to the presence or absence of a lesion in that particular voxel). The voxelwise maps resulting from this method are used as a way to define a mask to restrict voxels (Munsch et al., 2015) or to build symptom or condition specific ROIs (Forkert et al., 2015).

In this paper we have directly compared a range of approaches for assessing the relationship between structural brain damage and long term motor outcome in chronic stroke patients. Using structural MRI images from 50 patients we derived lesion probability images (i.e., images where each voxel is assigned a value between 0 and 1 representing the likelihood of being part of injured tissue). We wanted to investigate which features have the highest power to decode the individual level of motor impairment. There are two key questions: firstly, what type of data should be extracted from the images? Secondly, which are the key brain regions from which data should be extracted? To investigate the first question, we used two strategies to extract information from images: *i*) patterns of voxels, where each feature corresponds to a single voxel representing lesion probability, and *ii*) anatomical summarization, where each feature corresponds to the lesion load in an ROI. To investigate the second question, we employed a number of different approaches to define anatomical regions: *i*) regions of interest (ROIs) from an anatomical atlas; *ii*) a mask delimiting the corticospinal tract (CST); *iii*) combination of all ROIs and the CST; *iv*) a subset of the ROIs expected to be related to motor function; *v*) combination of the subset of ROIs and the CST; *vi*) active voxels from fMRI acquired with a motor task in healthy controls; *vii*) a mask restricting voxels to lesions; *viii*) voxels selected through lesion-symptom mapping. Additionally, we performed a secondary analysis, applying multiple kernel learning techniques using kernels extracted from brain regions to investigate the possibility of assessing the relevance of each anatomical pattern.

2. Material and methods

2.1. Study population

Fifty patients that had their first stroke at least three months before the collection of the data (mean 29.1, std 31.1 months) participated in the study. The patients had mean age 54.2 years (std 12.6), Seventeen patients were female and in 18 patients the right hand was affected. Complete demographic and clinical characteristics of each patient can be found in the Supplementary material (Table S1). The extent and location of the lesions for each patient (Fig. S1) is also presented. A control group was composed by 23 age-matched healthy subjects who reported no history of neurological or psychiatric illness, vascular disease or hypertension. All subjects provided full written consent in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the UCL Institute of Neurology, The National Hospital for Neurology and Neurosurgery and UCL Hospitals NHS Foundation Trust.

2.1.1. Motor scores

Measures of motor impairment in the contralesional upper limb were obtained using four different assessment scales: Action Research Arm Test (ARAT) (Lyle, 1981), grip strength (GS) (Sunderland et al., 1989), Motricity Index (MI) (Bohannon, 1999) and Nine-Hole Peg Test (NHPT) (Mathiowetz et al., 1985).

As the different motor scores are correlated but also complementary, a single representative measure was calculated using principal component analysis (PCA). Considering Y as a matrix of 50 examples and 4 labels (corresponding to the number of patients and motor scores, respectively), the PCA was obtained using the following steps:

1. Calculate the mean of each score across patients and subtract it from Y (*zero mean Y*);
2. Obtain the covariance matrix from *zero mean Y (cov zero mean Y)*;
3. Find the eigenvalues of *cov zero mean Y*.

A vector $\mathbf{y} = [y_1, \ldots, y_m]$ where m is the number of subjects represents the first principal component (FPC) of the four scores, which accounts for the greatest possible variance across them. This approach has the advantage of avoiding floor and ceiling effects encountered with individual measures.

2.2. Images acquisition and pre-processing

T1-weighted high resolution magnetic resonance images were acquired using a 3 T Allegra system (Siemens AG, Erlangen, Germany) with the following protocol: number of slices = 176, slice thickness = 1 mm, matrix size = 224 × 256, in-plane resolution = 1 mm × 1 mm.

The origin of each image was set at the anterior commissure. Images from patients that had injury predominantly in the left hemisphere were flipped in relation to the mid-sagittal plane so that all scans presented lesion in the right hemisphere. Images from all subjects were segmented into grey matter, white matter, cerebrospinal fluid and then normalized using the New Segment routine in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/).

Lesion probability images were obtained from the high-resolution T1-weighted volumetric MRI scans using an automatic method for detection of outlier voxels (Seghier et al., 2008). This method is based on the assumption that lesions are characterized as atypical voxels regarding expected brain tissues (grey matter, white matter and cerebrospinal fluid). The characterization of tissues uses the unified segmentation-normalization approach (Ashburner and Friston, 2005) modified to include an extra tissue to account for the perturbation introduced by lesions. Grey and white matter segmented tissues from patients are compared with the corresponding tissues from healthy control subjects in a voxel by voxel way. As a result, each voxel is represented by a value between 0 and 1 that quantifies the likelihood of it being part of injured tissue.

2.3. Segmentation of lesions

Fig. 1 presents the steps that were performed to obtain binary images of the lesions. Images representing lesion probability were derived from T1 anatomical images according with the procedure described in the previous section. In order to segment the lesions we applied a threshold selecting the voxels with probability of being part of injured tissue >0.3, producing binary images. Finally we selected only contiguous clusters with 100 or more voxels. See (Seghier et al., 2008) for a detailed explanation regarding the rationale behind both parameters (threshold value and cluster size) and comparison with manually traced lesions. We also performed additional tests to check the adequacy of these parameters to segment lesions in our images (Supplementary material, item 2).

Fig. 2 shows examples of lesions segmented according to the described approach. The binary images corresponding to lesions (visualized in blue) were overlaid on the lesion probability images (visualized in grayscale).

Fig. 3 (panel a) presents a map illustrating the overlap of segmented lesions obtained using our approach across all patients. The colour map represents the incidence of lesions in each voxel, ranging from purple (lesion in 1 subject only) to red (lesion in 26 out of the 50 subjects). Fig. 3 (panel b) presents a plot showing the volume of the segmented lesion for each patient according to the procedure described above. This plot illustrates the variability of the sample regarding the extent of the lesions across the patients. In the Supplementary material, we provide