WDS'10 Proceedings of Contributed Papers, Part I, 94–98, 2010. ISBN 978-80-7378-139-2 © MATFYZPRESS

When Informatics Meets Neuroscience: Software and Statistics for Human Brain Imaging

J. Straková

Charles University, Faculty of Mathematics and Physics, Prague, Czech Republic.

Abstract. Human language as one of the most complex systems has fascinated scientists from various fields for decades. Whether we consider language from a point of view of a classical linguistics, psychology, computational linguistics, medicine or neurolinguistics, it keeps bringing up questions such as "How do we actually comprehend language in our brain?"

The most interesting achievements often result from a joined effort of multiple scientific fields. In this paper, we will explore how statistics and informatics contributed to human brain neuroimaging and how this answered some of the linguistic questions about human brain.

The purpose of this paper is not to survey these achievements in detail, but rather to offer a comprehensive coverage of methods and techniques on the border of neuroimaging and informatics. To achieve this, we will touch on some of the basic and advanced methods for neuroimaging techniques, ranging from fundamental statistical analysis with the General Linear Model, Bayesian analysis methods to multivariate pattern classification, in the light of neurolinguistic research.

Introduction

Our understanding of neural mechanisms underlying language production and comprehension has made considerable progress in the past few decades. Starting from the very first neurolinguistic attempts to describe the correlation between language impairment and brain lesions by Paul Broca in 19th century, the wide accessibility and improvement of brain imaging methods, such as functional magnetic resonance and electroencephalography, have allowed scientists to hugely change and redevelop our perception of language-brain relationship.

The goal of this paper is to briefly survey the mathematic and informatic basics for human brain data analysis, which enabled the recent psycho- and neurolinguistic achievements. This paper will particularly focus on Statistical Parametric Mapping (SPM) as a means of performing statistical analysis of functional neuroimaging data (fMRI experiments). For the sake of briefness, event-related potential (ERP) experiments will only be mentioned shortly.

Brain imaging

Hemodynamics

Functional magnetic resonance imaging (fMRI) allows researchers to measure changes in blood flow, usually by recording the changes in blood oxygenated level dependent (BOLD) signal (Huettel et al. (2004)) while the participants perform certain cognitive tasks, such as reading or listening to words. This method offers quite detailed space resolution (scaled in milimeters), on the other hand, the human blood response is usually delayed by seconds (5-10s), thus resolving in rather poor temporal resolution, especially for linguistic purposes.

Furthermore, the sensitivity of BOLD response increases with sustainability of brain event in question, putting block-designed experiments, where the brain is influenced by a certain condition for a longer period of time (e.g. 30s), in great advantage to event-designed experiments, where the analysis of single events is more complicated.

The most consistent linguistic findings have been those focusing in localisation of certain language abilities, be it syntax processing (associated with left inferior frontal cortex, e.g. "syntactic specialisation of Broca's area" described in Embick et al. (2000)) or semantic processing (Binder and Price (2001)).

Event-related potentials

Event-related potential (ERP) is an averaged measurable electrophysiological response as a result of a thought or perception (reaction to stimuli). ERPs are measured by electroencephalography (EEG) or magnetoencephalography (MEG).

Electroencephalography benefits from the fact that when a group of neurons in the brain fire together, they create an electric dipole or current, which is then directly measured through the scalp as event-related potential (that is, electrical activity time-locked to the presented stimuli). Unlike fMRI, event-related potentials have time-resolution directly corresponding to the real-time cognitive task performance. On the other hand, the detection of activity source is rather difficult in EEG.

The linguistic research through ERP involves more real-time featured experiments. For example, Schlesewsky and Bornkessel (2006) answer the question how we response to conflict in a sentence meaning ("conflict resolution"), especially for subject-object ambiguities. Molinaro et al. (2008) analysed anomalous sentences containing multiple anomalies and how the processing of an early anomaly affected processing of the later.

Having briefly touched the ERP experiments, we will now focus on functional neuroimaging data analysis – Statistical Parametric Mapping.

Statistical Parametric Mapping

Statistical Parametric Mapping (SPM, Friston et al. (2006), Friston et al. (1994)) is a statistical technique for analyzing recorded brain activity and making statistically significant distinction between activated and deactivated regions of the brain.

In the scanner, the brain is scanned in "volumes", each volume being a planar map of certain slice of the brain, which results in a three dimensional representation of the brain space with coordinates x, y, z. Each unit in the space occupying such coordinates, and also a basic unit of measurement, is called a "voxel"[1].

The key idea behind SPM is a voxel-by-voxel modelling and statistical inference. For each voxel, a model describing its behaviour depending on the experiment design (i.e. presence of the stimuli) is estimated and then for each voxel a significance test (i.e. whether the particular voxel is activated or deactivated) is made.

SPM also refers to a free MATLAB package, a statistical software developed by Wellcome Department of Imaging Neuroscience at University of London (SPM, Friston et al. (2006)). This software implements all methods further explained in this paper.

Preprocessing

After acquiring the raw data, the workflow starts by preprocessing steps. The preprocessing phase description is not the aim of this paper, but to provide the reader with a rough idea, the images need to be realigned (motion corrected), unwarped, time corrected (to account for time difference in volumes acquisition), coregistered with anatomical images[2], spatially normalized to a standard template (i.e. selected brain template) and smoothed. For an overview, see Huettel et al. (2004), for a detailed description of these procedures, see Friston et al. (1995), Ashburner (2007), Ashburner and Friston (2005) or Klein et al. (2009)).

General Linear Model

The General Linear Model (Friston et al. (1994)) has the form

$$y = X\beta + \epsilon$$

[1] A typical voxel size is $3 \times 3 \times 3mm$.

[2] Image registration or image alignment is a method to transfer multiple images to one coordinate system, that is, to align them to be able to compare and view data obtained from multiple measurements.

where y is the measured voxel data in time (a column vector $1 \times$ scans), X is the design matrix (scans $\times$ design variables) and β are the unknown parameters to be estimated and tested (design variables $\times$ 1). The residuals (error terms) ϵ are assumed independent, identically distributed and usually Gaussian.

The columns of design matrix X explain all accessible knowledge about the experiment, such as presence or absence of the stimuli at the present time, parameters modeling the participant's movement or low frequency noise. Thus the model is specified by explanatory variables X and a well behaved error term ϵ.

The unknown parameters β are estimated using the ordinary least squares method.

Statistical Inference

Having estimated parameters β, we are now able to model our measured data, that is to predict the measured value y given the input X. Our marginal question, however, is whether a certain region of the brain or a group of voxels is statistically significantly activated during a certain experiment condition. To arrive to such a decision, we postulate a null hypothesis describing an effect we wish to reject ("zero activation"), while the alternative summarises evidence against the null hypothesis. Using a simple T-test and given a certain significance level α, observing a p-value more extreme than the selected threshold then indicates rejecting the null hypothesis in favour of the alternative.

Because numerous statistical tests are being conducted and because of the large number of independent voxels, corrections for false positives have to be made, such as family-wise error (FWE) correction or alternatively, less strict false discovery rate (FDR, Genovese et al. (2002)) correction. For each voxel-wise "uncorrected" p-value a new criterion ("corrected" p-value) is adjusted to minimize error of falsely identifying the noise as signal (activation).

Group analysis

A classical statistical test performed on one subject data proceeds by generalising over a group[3] (Holmes and Friston (1999)), thus introducing a new type of variance – inter-subject variance besides intra-subject variance. To be able to infer any conclusions from a group results, random-effect analysis (Holmes and Friston (1999), Penny et al. (2003b)) must be made.

The per subject analysis is sometimes called 1st level analysis, the statistical inference at a group level 2nd level analysis. Generally, in classical statistical inference, more general levels of statistical analysis take the parameters and infer from lower levels, thus creating what is known as hierarchical models (Penny et al. (2003a)).

Bayesian analysis

Besides a conventional statistical inference in a hierarchical model, another arrangement can be considered using the Bayesian statistics (Friston et al. (2002)). Where a classical statistical inference outputs a p-value as a measure of likelihood of observed effect given no activation, we would like to see the probability distribution of the activation given the data, which in Bayesian approach is the posterior probability. Instead of inferring measured data Y from design variables X and therefore obtaining the probability of observed effect given no activation ($p(t|\textit{null hypothesis})$), bayesian statistics infers the unknown parameters θ and their probability given the measured data ($p(\theta|y)$, "inverted model"). Knowing such a distribution implies knowing the probability of the voxel being activated, which brings advantages such as being able to reject the alternate hypothesis and to avoid the false positives problems.

[3] A typical fMRI experiment involves about 12-25 participants.

Pattern classification

General Linear Model analysis is based on independent voxel-by-voxel analysis, where each voxel is treated independently. Pattern classification analyses multiple voxel patterns across space, taking advantage from information contained in activity patterns. Using this information and through standard classifiers (Pereira et al. (2008)), we can predict the stimuli observed from the decoded brain activity (Mitchell et al. (2004)). For example, Haynes and Rees (2005) used pattern classification to decode the orientation of visual stimuli from brain activity in participants. The methodology for this approach is a standard pattern recognition (classification), starting from acquiring the fMRI data, through feature selection, labeling the patterns, training the classifier and applying it to independent test data and finally a cross-validation evaluation. However, reliable pattern classification is a challenge due to large sparsity and high dimensionality of functional data. Also, such applications as decoding the observed stimuli from the measured brain image or even predicting participant's cognitive state ("mind-reading" if you will) raise ethical questions which need to be further concerned.

Conclusions

In this brief overview, we have surveyed the basic mathematical principles and applications in human brain (functional) imaging. Starting with linguistic motivation and a few examples of recent neurolinguistic findings, we have explained the principles of two major neuroimaging techniques, functional magnetic resonance and event-related potentials and briefly sketched the statistical analysis methods for functional data. Finally, we have concluded with a short description of advanced methods of analysis of functional data, briefly sketching the potential ethical concerns of the most recent techniques.

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