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Coordinatore: Prof. Bruno De Luca
Tutore: Prof. Gioacchino Tedeschi

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Non-inferential Exploration of Functional Magnetic Resonance Imaging Time-series with Independent Component Analysis. Methodological Advancements with Applications to Neuroscience.

SUMMARY

Functional Magnetic Resonance Imaging (fMRI) refers to an ensemble of techniques to study human and animal brain function “in-vivo” using the principles and the technology of nuclear magnetic resonance imaging (NMR-MRI). Nowadays, since it offers the most advantageous trade-off between spatial and temporal resolution of investigation among all the “in-vivo” and biologically non-invasive neuroimaging techniques, fMRI is acknowledged as a powerful tool to study brain functional phenomena in both research and clinical applications.

The most popular fMRI variant utilizes the blood oxygenation level dependent (BOLD) contrast, which is based on the differing magnetic properties of oxygenated and deoxygenated blood: when brain neurons change their state of activity, a corresponding change in regional blood flow and oxygenation occurs in the same location, which causes in its turn a net change in the proton NMR relaxation parameter T2*. This fundamental principle, thanks to the echo-planar imaging (EPI) technology of fast MRI acquisition, can be exploited to detect and measure localized signal changes in a given brain volume by simply acquiring repeatedly NMR data, in the form of “time-series” of T2*-sensitized images. In a typical fMRI experimental session, many thousands of different brain locations or “voxels” are sampled at hundreds of “time-points”.

The “raw” fMRI time-series consist of a complex multi-dimensional mixture of many interesting and useful, but also confound, signals, that occur at different brain locations with different weights, latencies and temporal profiles. After acquisition, the fMRI data are, thus, submitted to a chain of processing steps whose ultimate goal is to disentangle the orignal complexity of the time-series and to produce pairs of “purified” temporal signals and “synthetic” images or maps of brain activity. These pairs are often referred to as spatio-temporal patterns of brain activity: a successful analysis of fMRI data always produce one or more such patterns, depicting the spatial and temporal dynamics of neural processing that are relevant for the application.

The traditional way to translate BOLD-fMRI time-series into brain activity patterns consists in the direct specification by the researcher of one or more temporal waveforms for the expected BOLD signals in active voxels: “well-stylized” signals, conceptually associated to the sources (or factors) of their temporal variability, are, then, used as input functions for activity detection. The presence or the amount of influence of these sources is evaluated at each voxel through linear correlation or regression analysis techniques, followed by classical “null hypothesis” parametric tests, like t-, z- or F- tests, that assign confidence intervals to the readout. Thus, once provided the temporal part of the pattern, all the

required statistical tests generate a three-dimensional statistical parametric map (SPM). The application of a threshold to the SPM, according to an acceptable statistical significance, generates the activation map synthetising the spatial information of the pattern.

A valid and widely accepted alternative to the classical analysis framework is represented by the Independent Component Analysis (ICA).

ICA is a general purpose technique of multi-dimensional data transformation, that finds “statistically independent” sources of temporal variability (or “independent components”) in the recorded mixtures. Previous work has demonstrated the high neurophysiological plausibility of the information theoretic concept of statistical independence applied to neuroimaging time-series from different modalities: in fact, ICA, apart from fMRI, has been successfully applied also to electro- and magneto-encephalography (EEG, MEG).

The fundamental difference between ICA and the traditional methods is that, while the traditional approaches are hypothesis-driven (or inferential) and, thus, require the a priori specification of a temporal model for the effects of interest (in this sense being only “confirmatory”), ICA belongs to the class of exploratory data-driven approaches, that do not make assumptions about the time-profile or the location of the effects of interest but rather aim to characterize the intrinsic statistical distribution of the data by decomposing them automatically into spatio-temporal patterns, exclusively relying on the general constraint of statistical independence.

In the present work, an introduction to the general physiology and methodology of BOLD-fMRI is presented in chapter I. Then, ICA as a tool for BOLD-fMRI data analysis (chapter II) and a number of ICA methodological (chapter II and III) and application (chapter IV) contributions are organically presented.

In chapter II, the general ICA problem formulation is introduced and its neurophysiological plausibility is discussed. After the presentation of the mathematical and statistical foundations of the ICA data model for fMRI time-series, two technical issues, that are crucial for the practical and successful application of ICA to neuroimaging studies are considered in detail, namely the problem of the optimal choice of the ICA algorithm and the problem of the validation of the fMRI independent components. To this purpose, a description of “ad hoc” designed experimental methodology is provided and experimental results on simulated and real activation fMRI data are presented and discussed.

Another general issue, that is extremely relevant for the application of ICA to fMRI is the problem of the classification and selection (“rank ordering”) of the fMRI independent components. For the benefit of exposure, this issue is covered in chapter III, in the context of fMRI-oriented ICA advances.

The almost “free” registration of high-resolution anatomical information to the functional images is a general, and probably the most attractive, feature of fMRI over the other neuroimaging modalities. The use of this feature for display and representational purposes is addressed in chapter I, while the advantages provided by the “informative” combination of anatomical and functional data within the “cortex-based” ICA (cbICA) framework are discussed in chapter III. Experimental methodology and results are presented either for the comparison of the cbICA framework with the anatomically unconstrained “volume-based” ICA (vbICA) and for the “rank-ordering” of fMRI (cortical) independent components.

The challenging application of ICA to “real-time” fMRI (rtICA) is also presented in chapter III.

Real-time fMRI enables one to monitor a subject's brain activity during an ongoing experimental session, allowing the interactive development and refinement of stimulation paradigms in research and clinical trials and enabling fMRI-based neurofeedback applications. Experimental results are presented on simulated and real activation data that demonstrate the feasibility and the performances of rtICA as well as its ability to unravel transient unexpected neural activities in real-time with the acquisition, providing the fMRI researcher with a better understanding and control of subjects’ behaviors and performances.

Chapter IV is dedicated to the presentation and discussion of experimental results from three relevant neuroscience applications, where ICA has proven tremendously useful because of its exploratory nature.

First, the problem of separating complex linear and non-linear spatio-temporal dynamics of the auditory system under simple prolonged sound stimulation is presented, with the solution consisting in a totally ICA-generated spatio-temporal pattern of neural processing for the human auditory cortex.

Second, the ICA analysis of a visuo-spatial imagery fMRI experiment is presented, to show ICA capabilities in the context of mental chronometry, where the active neural processes systematically evoke region-by-region and trial-by-trial spatio-temporal variability in the BOLD responses, making intrinsicly more difficult and limited the use of the inferential approaches for activity pattern generation.

Third, a clinical fMRI application is presented, where not only the timing properties of the BOLD signal (like in previous two applications), but even the actual occurrence of the events (hallucinations) eliciting the BOLD responses are not predictable without explicit subject or patient cooperation, making extremely limited any classical hypothesis-driven analysis approach. ICA results on data from three schizophrenic patients, experiencing auditory verbal hallucinations are presented and discussed.