INDEPENDENT COMPONENT ANALYSIS OF AUDITORY FMRI RESPONSES

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ABSTRACT

The basic principles used by the auditory cortex to decipher the sensory streams are less understood than those used by the visual cortex. Based on previous research on animals, functional Magnetic Resonance Imaging (fMRI) responses in the human auditory cortex to simple streams of colored acoustic noise are expected to follow both linear (sustained) and non-linear (transient) spatio-temporal patterns. Analysis employed in previous fMRI studies only allows the detection of linear responses. Here we present a data analysis strategy, that allows the detection and separation of both linear and non-linear responses. This strategy is based on the hierarchical combination of two "transposed" variants of the independent component analysis (ICA), operating in the space and in the time domain.

1. INTRODUCTION

The processes to be accomplished to explore the world of sounds are basically different from those needed to perceive images. This is due to the intimate and very peculiar nature of auditory information, which is received in temporal series. As a consequence, one major operation that the auditory system carries out to decode acoustic information is the temporal analysis of sound features. This is accomplished through a suitable translation of these features into specific neural discharge patterns. In fact, decomposition in the time domain is used for the qualitative and quantitative perceptual analysis of sound information [1, 2].

In animals, the neurons of the auditory cortex have been broadly classified according to their temporal dynamics of discharge during sound stimulation. At a first level of analysis, the complex neural response pattern can be unfolded into transient and sustained neural responses and has been suggested as a fundamental mechanism in auditory perception [3, 4].

In the human auditory cortex, however, temporal principles of encoding sound information are not yet fully understood and only recently evidences of multiple sources of neural processing have been produced [5].

To address these questions we employed a spatio-temporal signal decomposition using a hierarchy of techniques based on independent component analysis (ICA) that allowed us to blindly extract and characterize the main constituent signal sources of the evoked blood oxygen level dependent (BOLD) responses. The ICA techniques were applied on functional magnetic resonance data that were collected during one minute of sound immediately after a baseline of silence.

Functional MRI data sets contain many different brain activities. These are recognizable by 'inferential' statistical approaches such as, for example, regression analyses only if a suitable temporal model of each activity pattern is provided [6]. However, if a certain model of neural activity is not available and thus a suitable temporal profile at least for activities of interest cannot be formulated *a priori*, then a decomposition that is 'blind' to *a priori* assumptions on the nature of neural activity is a favorable choice. ICA appears to be the method of choice when such blind decompositions of fMRI data, are required [7,8].

Applied to fMRI data, the ICA problem can be formulated in two different ways [9], called spatial ICA and temporal ICA. In the spatial ICA, it is assumed that the hemodynamic sources are "independent" in their spatial locations while in the temporal ICA, the hemodynamic sources are assumed to be "independent" as regards to their temporal observations, in analogy to ICA applied to electro- or magneto-encephalographic data, the channels corresponding to the voxels from which the mixed signals are picked up.

Here we used a hierarchical combination of these two variants to study cortical auditory processing in humans.

2. MATERIALS AND METHODS

2.1 Auditory stimulation and data acquisition

High-speed fMRI is inevitably associated with considerable ambient noise produced by the scanner, and thus with unpredictable entangling with the neural responses evoked by the experimental stimuli. Therefore, we used the sounds generated periodically by the rapid gradient switches during functional image acquisition for auditory stimulation. Eight healthy subjects (N = 4 females/4 males; mean age and standard deviation, 36.4 $\pm$ 8.9 years) were examined and instructed to attend to the auditory stimulation but not to perform any output task.
To achieve auditory stimulation after a baseline period of silence, we employed a silent preparation of the echoplanar imaging sequence with radiofrequency excitation and soft slice selection gradient pulses that produced magnetization steady state at the initiation of image acquisition and auditory stimulation [10]. This is in contrast to conventional fMRI, where the T_2*-weighted signal drops during the first 5-10 s when magnetization steady state is being approached. For functional studies of the auditory system, this coincides with the time constant of neural excitation and obscures its detection [11]. Images were collected on a 3 T Medspec Avance whole body system equipped with a BGA38 head gradient system (gradient strength, 28 mT/m; slew rate, 280 T/m/s on all three axes) and a circularly polarized head coil. After anatomical imaging, functional volumes consisting of ten gradient recalled echoplanar images (slice thickness, 4 mm; matrix, 64 x 64 pixels; field of view, 240 x 240 mm^2; flip angle, 60º; echo time, 30 ms; slice acquisition time, 100 ms, repetition time, 1000 ms) positioned along the lateral sulcus to cover the superior temporal gyrus including primary and secondary auditory cortices were acquired. After collecting a first set of 60 conventional echoplanar volumes, 60 silent dummy repetitions consisting of radiofrequency and slice selection gradient pulses with long sinusoidal ramps were carried out to obtain magnetization steady state for the second set of 60 echoplanar volumes. Each trial was repeated five times in each subject during one experimental session.

2.2 Data analysis

The functional images were warped into the standard Talairach space, resampled into 3-mm isotropic voxels, rescaled in intensity to account for receiver sensitivity run-to-run differences, corrected for slice acquisition time, head motion, and intra-session between-run differences using BrainVoyager 4.6 (*www.brainvoyager.com*). Afterwards, they underwent a combination of ICA-based analysis steps as synthesized in Fig. 1.

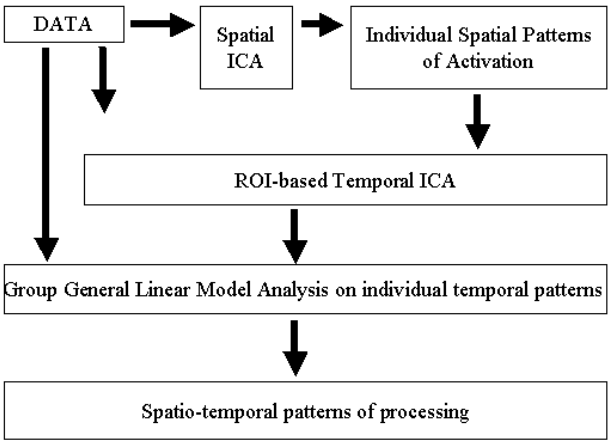

Figure 1. Basic Diagram of the data analysis

An in-depth study of the two varieties of spatial and temporal ICA (sICA and tICA) has been presented in [9].
The basic definition of the sICA model is that P time-course vectors (each corresponding to one out of P selected voxels in a reference anatomical image) in a T-dimensional space of time-courses (T being the number of time-points) are linearly mapped to P vectors in a K-dimensional space (i.e. the space of the Independent Components or ICs), K being less or equal than T:

$$\mathbf{x}_{sICA}(p) = \mathbf{A} \cdot \mathbf{s}_{sICA}(p) \qquad p = 1,...,P \qquad (1)$$

where, $\mathbf{x}_{\mathbf{sICA}}(p)=[x_{sICA1}(p),\ldots,x_{sICAT}(p)]^T$ is the observed time-course for voxel p and $\mathbf{s}_{\mathbf{sICA}}(p)=[s_{sICA1}(p), \ldots,s_{sICAK}(p)]^T$ is a K-fold set of statistically independent variables, observed at each voxel p, defining the spatially independent maps (ICs).
The TxK unknown matrix **A** in (1), is the "mixing" matrix. **A** is assumed to be invertible, and each of its columns, that corresponds to a basis vector of the new space of the ICs, represents a "time-course of activation" (TC).
Any ICA algorithm will assess the model (1) by seeking for an "unmixing" KxT matrix **W** so that the vector:

$$\mathbf{y}_{sICA}(p) = \mathbf{W} \cdot \mathbf{x}_{sICA}(p) \qquad (2)$$

is an estimate of the hidden variables $\mathbf{s}_{\mathbf{sICA}}(p)$, except for permutation, signs and amplitudes. Matrix **A** will be computed as the pseudo-inverse of **W**.
In order to neglect inter-trial variability of the responses and to find out those regions that, most consistently across trials, were involved in auditory processing, a full brain sICA decomposition was carried out on individual averaged single trials time series (T=60). After removing the spatial mean of the data, the infomax algorithm [12] was applied with a principal component analysis (PCA)

based 'prewhitening' step that, while retaining the 99% of individual eigenvalue variance, diminished the target components from 60 to 40. The ICA decomposition was computed for each fMRI session using the *runica* routine (*www.cnl.salk.edu*) in Matlab. Then we selected a unique spatially independent component for each subject by applying the conjunction of two criteria [13]:

a) the majority (> 95%) of the active voxels ($|z| \geq 2$) in the spatial ICA map were located in the primary and/or secondary auditory cortices (segmented Heschl's gyri, temporal and polar planes [14] based on individual anatomies);

b) the associated time courses were compatible with the hemodynamic response pattern upon persistent auditory stimulation starting from a silent baseline [15].

After employing a descriptive threshold of $|z| \geq 2$ to these 'auditory' components [8], individual 'pattern-driven' masks were generated to segment "functionally" the original forty data sets (corresponding to the five single trials of the eight subjects). These approach yielded forty data matrices with a highly reduced number of voxels that enabled a temporal ICA decomposition [9] of the measured single-trial fMRI auditory responses.

The tICA data model is the transposed of the sICA data model. The number P of time-course vectors included in the analysis corresponds to the dimension of the input space. The number T of time-points corresponds to the actual number of observations used in the learning process of the model:

$$\mathbf{x}_{tICA}(t) = \mathbf{B} \cdot \mathbf{s}_{tICA}(t) \qquad t = 1, \ldots, T \qquad (3)$$

where, $\mathbf{x_{tICA}}(t)=[x_{tICA1}(t),\ldots,x_{tICAP}(t)]^T$ is an observed P-fold map at scan t and $\mathbf{s_{tICA}}(t)=[s_{tICA1}(t),\ldots,s_{tICAK}(t)]^T$ is a K-fold set of statistically independent variables, defining the temporally independent signal sources.

The PxK unknown matrix **B** in (3), is the "mixing" matrix. As for sICA, the ICA algorithm will estimate the target sources by computing an "un-mixing" matrix:

$$\mathbf{y}_{tICA}(t) = \mathbf{U} \cdot \mathbf{x}_{tICA}(t) \quad (4)$$

Matrix **U** defines the spatial filter separating the recorded BOLD activity from the region-of-interest into distinct, temporally independent component processes.

Again, the infomax algorithm was applied after a temporal mean removal and a principal component analysis based 'prewhitening step'. While retaining the 95% of the original eigenvalue variance, this dimension reduction step diminished the target components to 15. The temporal ICA decomposition was computed for each fMRI session separately using *runica*. Because of the small number of observations (scans) as compared to the number of channels (voxels) selected in the spatial ICA step and in order to prevent overlearning [16], we applied a greater dimension reduction of the single-trial individual multivariate data-sets. Eventually, to determine which of the temporal components were common across trials and subjects, we performed an inter-subject crosscorrelation analysis: among all sets of the 15 temporally independent sources extracted from the single trial auditory responses, a component was selected based on the conjunction of two criteria:

a) the component time course of each decomposition showed a crosscorrelation coefficient $|r| > .38$ ($p < .001$) with one and only one component time course present in each of the other decompositions ('intertrial' and 'intersubject' consistency);

b) the component's contribution to the magnitude of the original data (root mean square of the data set obtained solely from that component signal [7]) was among the greatest five out of 15.

The selected temporally independent signals were normalized and made consistent for the sign on the basis of the corresponding region of activity time course [17] in the associated map.

As the region-of-interests for temporal ICA decompositions were different across subjects, group spatial maps were determined by means of a multi-subject general linear model analysis [6]. This way, it was possible to map specific classes of responses to a standard cortical space while preserving the individual hemodynamic response properties as blindly extracted in the temporal ICA step. This was practically achieved by using the individual means of the temporally independent components' time-courses as subject specific regressors. By averaging the single-trial responses on a subject-by-subject basis, we intended to lower the effects of the residual noise in the components, while preserving the individual temporal dynamics. These maps were then projected onto a standard brain template (*www.bic.mni.mcgill.ca*).

3. RESULTS AND DISCUSSION

Spatial ICA extracted a unique map related to auditory activity and a unique associated time course for each subject (Fig. 2). The activity maps covered, consistently across subjects, the supposed primary and secondary auditory cortices. The time course of activation was characterized by an initial post-stimulation peak at about six seconds that was followed by a plateau with persistent and irregularly oscillating signal effects superimposed. This irregularity was also reflected in a greater inter-subject variance observed in the temporal patterns during the latter compared to the initial segments of the spatial ICA representative time courses of activation. These same temporal patterns suggested the presence of at least two concurrent - possibly temporally independent - processes,

a transient and a sustained response type. However, these two presumptive effects concurred in the same components identified by spatial ICA and were mixed with other less consistent oscillatory phenomena. Assuming single cellular assemblies and microscopic vascular sources for the independent BOLD signal components and imaging voxels in the order of magnitude of millimeters, each will contain a mixture of different tissue and different temporal behaviors. Consistent with this position, the spatial ICA decomposition was not able to produce spatially segregated maps representing specific temporal response types.

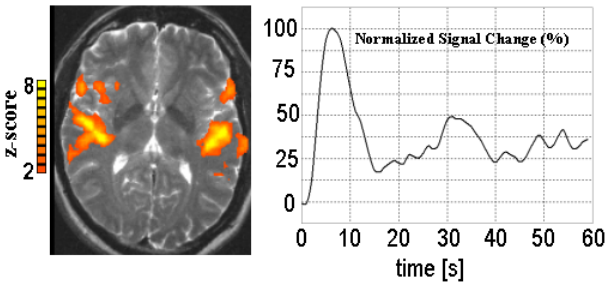

Figure 2*. Spatial ICA map and associated time-course of activation.

Assuming the presence of more than one (spatially overlapping) temporally independent signal source, we further decomposed the recorded signals from the anatomical regions of interest identified with spatial ICA into maximally temporally independent components.

Here we assumed implicitly that no signal contribution was to be expected from target auditory signal sources in the voxel recordings located outside the spatial patterns provided by spatial ICA on individual anatomies.

As far as the hypothesis of temporal independence between the target processes holds true to a certain degree of approximation, we should be able to identify different sources responsive of the different response behaviors revealed by the spatial ICA time-courses of activation.

Among all the signal sources extracted by temporal ICA, two of them, namely a “transient” and a “sustained” component (fig. 3) were found to be highly reproducible across different trials and subjects.

At this point, it is of note that these two prototypical components were concurrently present in the data mixture and were blended within the signal mixtures arising from all fields of the primary and secondary auditory cortices. To segregate those portions of the auditory cortex in which the transient or the sustained temporal response patterns predominated in relative terms in all our subjects, we mapped them to the standard cortical space using a group general linear model analysis. We identified a specific pattern of activation with spatially varying relative contributions in which one of the two temporal response types were more prevalent (Fig. 4). This pattern was characterized by a central stripe-like area predominated by the sustained response type and a surrounding area predominated by the transient response type. Anatomically, the central portion corresponds to Heschl's gyri whereas the adjacent portions correspond dorsally to the temporal planes and ventrally to the planar planes and the temporal opercula.

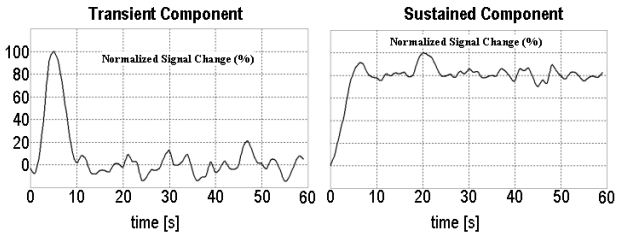

Figure 3. Time-courses of transient and sustained signal sources extracted by temporal ICA.

These findings may be viewed as an indication that the brain may use different temporal codes even to process a single uniform (yet complex) stimulus type.

More importantly, our findings suggest that on a microscopic (subvoxel) level, the BOLD signal observed within an imaging voxel arose from tissue that was composed of one or of different nearby sources that emit transient and sustained signals. Consecutive superposition of varying phasic events with different time constants, possibly reflecting individual neurons' habituation and adaptation processes, could be a possible explanation of the irregular oscillations that we have observed during the sustained phase. Additionally, this finding is also consistent with the existence of two neuron populations in the monkey auditory cortex, one exhibiting stimulus-synchronized and the other non-synchronized discharge patterns and thus use 'temporal' or 'rate' codes to decipher sound information [4]. On the macroscopic level, the relative predominance of transient and sustained signal sources was unevenly distributed and spatially segregated. This parcellation is reminiscent of the cytoarchitectonical [18] and functional [19] distinction into *core* and *belt* areas of the monkey auditory cortex. In humans, a similar distinction has been observed in functional neuroimaging studies that contrasted the cortical response to at least two different types of auditory stimulation.

At this point we may tentatively hypothesize that the transient response in the belt areas may be related to event detection and the sustained response in the core to sound source identification, their relative predominance tending to be segregated into the core and belt areas.

Independent component analysis (ICA) has been successfully applied in the exploratory analysis of functional magnetic resonance imaging (fMRI) data.

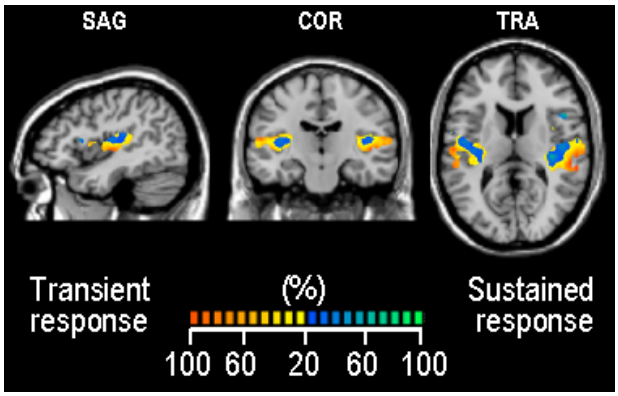

Figure 4*. Relative contribution map of transient and sustained signal sources to the group data.

The general appeal of ICA for fMRI data analysis is that it often reveals brain activation phenomena that - because they do not follow regularly external stimulation events - cannot be predicted by a "bottom-up" approach. These phenomena are therefore neglected by standard analysis approaches.

In the case presented here, detection and separation of transient responses in the human auditory cortex would have been pursued using a non-linear model of the hemodynamic filter. However, the nature of the filter was unknown.

More in general, this and other recent neuroimaging studies (see for example [20]) show that ICA is a convenient alternative to conventional methods, especially when the neurophysiological phenomena to be investigated are not known in detail. In these cases, ICA methods can be used to dissect and clarify the underlying basic biophysical and neurophysiological mechanisms and ICA results can be used to generate new hypotheses to be tested in new experiments.

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