COMBINING ICA AND CORTICAL SURFACE RECONSTRUCTION IN FUNCTIONAL MRI INVESTIGATIONS OF HUMAN BRAIN FUNCTIONS

Elia Formisano[1], Fabrizio Esposito[2], Francesco Di Salle[3], Rainer Goebel[1]

[1]Department of Cognitive Neruoscience, Faculty of Psychology, University of Maastricht, The Netherlands
[2]Second Division of Neurology, Second University of Naples, Italy
[3]Department of Neurological Sciences, University of Naples "Federico II", Italy

ABSTRACT

The cerebral cortex is the main target of analysis in many functional magnetic resonance imaging (fMRI) studies. Since only about 20% of the voxels of a typical functional data set lie within the cortex, statistical analysis can be restricted to a subset of the voxels obtained after cortex segmentation. Here, we describe a novel approach for data-driven analysis of single-subject fMRI time-series that combines techniques for reconstruction of the cortical surface of the subject's brain and spatial independent component analysis (ICA) of functional time-courses (cortex-based ICA or cbICA).
Compared to conventional, anatomically unconstrained ICA, besides reducing computational demand (20,000 vs 100,000 voxels time-courses), our approach improves detection of cortical components and estimation of their time-courses, particularly in the case of event-related designs.

1. INTRODUCTION

One of the major advantages of functional magnetic resonance imaging (fMRI) over the other brain mapping techniques is the potentiality to look at the relationships between brain anatomy and function non-invasively and on an individual basis. This unique feature of fMRI is fully exploited when the functional topography of the brain areas is analyzed in relation to an explicit representation of the subject's cortex. In such cases, maps of brain activation, as obtained from the statistical analysis of the functional time-series, are visualized on a folded or morphed (inflated, flattened) computerized reconstruction of the subject's cortical surface (see e.g. [1-3]).

In this type of approach, anatomical and functional information is merged together at the final stage of the analysis and only for visualization purposes. Recently, individual anatomical information has been used at an earlier stage, as an additional constraint for the statistical detection of functional activation [4-6]. In all the cases methods employed for the functional analysis were hypothesis-driven (*univariate*, [4, 5]; or *multivariate* [6]) statistical methods that require an *a priori* specification of a temporal model of the effects of interest. Exploratory *data-driven* approaches that do not make assumptions about the time-profile of the effects of interest offer a complementary perspective to the conventional analysis of fMRI time-series. This might be especially useful in those cases in which the event of interest is not predictable (hallucinations, epileptic seizures) and when the hemodynamic response is difficult to model, such as in event-related designs with complex cognitive tasks or in experiments with ambiguous stimuli (e.g., [7]).

Among data-driven methods, independent component analysis (ICA, [8]) appears to be particularly promising for the analysis of fMRI data. In the first applications of ICA to fMRI data-analysis [9-11], the ICA-variant used is *spatial* in that the observed 4D fMRI-signals are modelled as linear "mixtures" of unknown spatially inde pendent processes (e.g. BOLD signal changes related to the cognitive task, physiological pulsations, head movements, artifacts, etc.), each contributing to the data set with an unknown time profile. An adaptive ICA algorithm [12] was adopted to decompose the time series into spatial components (ICs), each having a unique time course (TC). The decomposition process maximizes the spatial statistical independence of the components, the idea being that the new representation of the data (ICs/TCs) reflects the "unmixed" configuration of the original spatial processes. More recently, a temporal ICA-variant has been also adopted and compared to the sICA [13].

In the sICA, as proposed in [9], the entire matrix of the fMRI time-series is blindly decomposed. This matrix includes signals not only from the cerebral cortex, but also from other parts of the brain, including subcortical structures, the white matter and the ventricles. The resulting decomposition, thus, also models the dynamics of the signal in these other structures. As the maximal number of spatial components is fixed (it equals the number of time samples, i.e functional scans), restricting the analysis to a

subregion of the matrix can enhance anatomical specificity of the spatial observations.

Here, we exploit this possibility by combining the sICA of fMRI time-series with the cortex-based approach. We use the mesh of the white matter/grey matter boundary, automatically reconstructed from T1-weighted MR-images [14] to limit the spatial ICA only to those voxels of the T2*-weighted functional time-series which are within a specified region with respect to the cortical sheet (cortex-based ICA or cbICA). Besides reducing computational demands and speeding up the convergence of ICA decomposition, this cortex-based approach promises to improve the separation of the cortical sources. Exclusion of extracortical contributions to the signal data-set, indeed, allows using the same number of components, otherwise used to separate non-interesting processes (e.g. signal changes in the ventricles, near the eyes, imaging artefacts) only for potentially interesting neural processes occurring on the cortical surface.

In the present paper, we illustrate the cbICA framework in the context of whole-brain fMRI blocked- and event-related experimental designs. FMRI time-series are decomposed blindly into *cortical surface components* (CSC) that can be directly visualized on the folded or morphed representation of the cortex. Results are compared to the results of conventional methods of linear multiple regression, principal component analysis (PCA), as well as to anatomically unconstrained spatial ICA [9].

2. MATERIALS AND METHODS

2.1 General description of the cortex-based ICA approach

The steps of the cbICA as implemented in the BrainVoyager 2000 software (www.brainvoyager.com) are schematically illustrated in Figure 1.

Input data-sets consist of a high spatial resolution 3D anatomical volume and a functional time-series of the same subject (volume time-courses or VTC) that has been previously co-registered to it (see below).

The initial steps of the cbICA approach is the generation of a cortical mask of each subject and the selection of a restricted functional data set consisting of the time-courses corresponding to the cortical voxels in the functional time-series. First, a polygonal mesh representing the white/gray matter border is obtained from the 3D recording of the subject (see **2.2**). This mesh is then projected into the functional VTC and those voxels that lie within a specified range with respect of the white/gray matter border are tagged as "gray matter" voxels (see **2.3**). Finally, the data set consisting of these cortical time-courses is decomposed using ICA in spatially independent components each having an associated time-course (see **2.4**). The components consist of voxel values at locations linked to the cortical surface and therefore can be directly visualized on the folded, inflated, and flattened representation of the cortex (cortical surface components or CSC, Figure 2) [15].

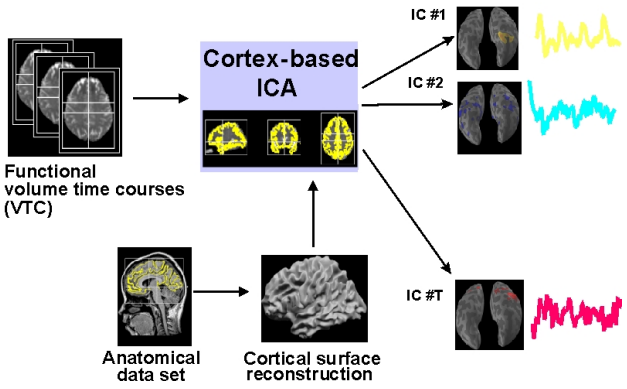

Figure 1* Schematic representation of the cortex-based ICA approach.

2.2 Generation of a cortical mesh

A polygonal mesh reconstruction of both cortical hemispheres of each subject is generated from high-resolution 3D anatomical MR volumes collected during the fMRI sessions (see below). The white/gray matter border is segmented with a region-growing method preceded by inhomogeneity correction of signal intensity across space. The border of the resulting segmented subvolumes istessellated to produce a polygon mesh representation of each cortical hemisphere. The tessellation of the white/gray matter boundary of a single hemisphere yields a polygon mesh typically consisting of approximately 250,000 triangles. Then, an iterative 3D morphing algorithm is used to move all surface vertices outward along their normals, such that the surface came to represent the spatial structure of the cortical gray matter. Through visual inspection, this process is halted when the surface reached the middle of the gray matter corresponding approximately to layer 4 of the cortex. The resulting surface is used to create the cortical mask (see **2.3**) and as spatial reference in projecting functional data onto inflated representations of the cortex.

2.3 Co-registration of functional and anatomical data and selection of cortical time courses.

In order to select the functional time-courses that correspond to "gray-matter" voxels functional slices need to be co-registered accurately to the 3D anatomical volumes.

Since the functional and 3D structural measurements are usually performed within the same recording session, co-

registration of the respective data sets could be obtained directly based on the slice position parameters of the T2*-weighted measurement (number of slices, slice thickness, distance factor, angles, field of view, shift mean, off-center read, off-center phase, in plane resolution) and on parameters of the T1-weighted 3D T1 measurement (number of sagittal partitions, shift mean, off-center read, off-center phase, resolution) with respect to the initial overview measurement (scout). For confirmation of co-registration accuracy a 2D anatomical data set can be obtained by reslicing the 3D data set using the slice position parameters and compared visually to the EPI data sets. Based on the parameters for importing the 2D functional slices into the 3D data sets and on the parameters for transforming the 3D data sets into Talairach space, the complete functional data of each subject are interpolated to 3mm x 3mm x 3mm resolution (using trilinear interpolation) and transformed into Talairach space. This yields a normalized 4D data representation (volume time course or VTC) for each functional data set.

Since VTCs are co-registered to 3D anatomy, they are also co-registered to the polygon mesh representing the cortical sheet, which thus can be dirctly used to tag the cortical voxels of the functional data. The cortical mesh is projected into the functional data set and the voxels that were within a specified range were tagged as "cortex". This range is defined in mm along the direction of the normal vector of each vertex. A normal vector points outward, i.e. into the grey matter. Its direction is orthogonal to the local surface patch surrounding a vertex. The corresponding set of functional time courses form the reduced matrix of the cortical time courses used in cbICA.

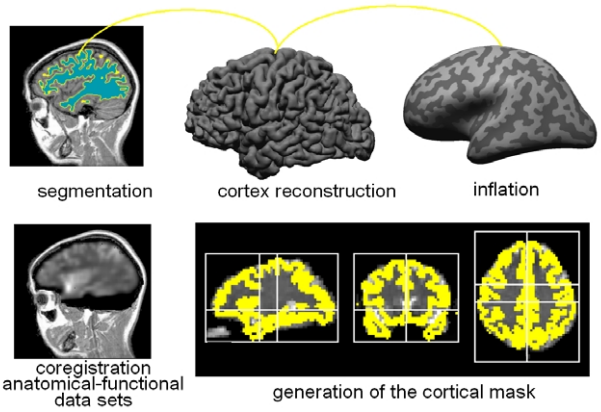

Figure 2*: The use of individual subject cortex reconstruction for visualization on an inflated representation (upper row) and for tagging of *cortical* voxels in the 4D matrix obtained by functional magnetic resonance imaging (lower row).

Figure 2 shows the voxels in a $1mm^3$ T1-weighted data set indexed by the reconstructed cortical sheet of a subject and the spatial correspondence mapping between anatomical volume, folded and inflated cortex reconstruction (upper row). The yellow contours are the result of projecting the reconstructed and slightly smoothed surface into the T1-weighted data set. Lower row shows the voxels of a $3mm^3$ T2*-weighted functional data set indexed by the same cortex reconstruction.

2.4 Spatial ICA decomposition.

Let $\mathbf{X_c}$ be the T x M_c (T = number of scans, M_c = number of cortical time-courses) matrix of the observed cortical time courses (as defined in step 2), $\mathbf{C}$ the N x M_c matrix whose rows C_i (i=1,...,N) contain the spatial processes ($N \leq T$ = number of processes) and $\mathbf{A}$ the T x N mixing matrix whose columns Aj (j=1,...,N) contain the time courses of the N processes. The problem for of the ICA-decomposition of fMRI time series can be formulated as the estimation of both matrices of the right side of the following equation:

$$\mathbf{X}_c = \mathbf{A} \cdot \mathbf{C} \qquad (1)$$

under the constraint that the processes C_i are spatially independent. No a priori assumption is made about the mixing matrix A, i.e. about the time courses of the processes.

Different ICA algorithms solve this problem using different strategies. Here, we decompose $\mathbf{X_c}$ with a fixed-point ICA algorithm (FastICA, [16] as implemented in http://www.cis.hut.fi/projects/ica/fastica/). The FastICA algorithm minimizes the mutual information of the components using a robust approximation of the negentropy as a contrast function and a fast, iterative (non-adaptive) algorithm for its maximization (for a detailed description of the FastICA algorithm, see [16]). After sphering the matrix $\mathbf{X_c}$, the hierarchical (deflation) mode of the FastICA algorithm is used and the components were estimated one-by-one.

Additional analysis was performed also using the Infomax algorithm [12]. Results were very similar to the ones presented here. An extended, experimental comparison on fMRI data between the FastICA and the Infomax algorithms has been previously reported in [17].

2.5 Functional MRI data

We apply cbICA to several fMRI data sets collected using either a blocked design or an event-related design. These data-sets had been collected and analyzed using conventional statistical methods in the context of two previous fMRI studies from our group [18, 19].

Both blocked- and event-related fMRI data-sets were collected using a 1.5 T MR scanner (Siemens Magnetom

Vision), a standard head coil and a gradient echo EPI sequence (TE=60ms, FA=90˚). For each subject, a high-resolution T1-weighted 3D data set covering the whole brain was collected with a 3D MP-RAGE sequence (Magnetization-Prepared Rapid Acquisition Gradient Echo, TR=9.7ms, TE=4 ms, FA=12°, matrix=256 x 256, thickness=1 mm, number of partitions=170-180, voxel size=1x1x1 mm^3) during the same session as the functional measurements.

Blocked-design experiment
Blocked-design data consisted of a functional time-series (TR=3000ms, FOV=200x200mm^2, voxel size = 1.6x1.6x3 mm^3 126 scans/time-series) from a control subject that took part in an fMRI study of blindsight patients [18]. Colored images of natural objects (fruit and vegetables) subtending 5.2° by 5.2° were presented in the upper visual field 7° off-axis in one hemifield at a time. Each stimulation block lasted for 30s and was repeated four times within each recording session. Stimulation blocks were separeted by fixation blocks of equal length. Within a stimulation block, an image was shown for 1s and then replaced by the next image without an interstimulus interval (for further experimental details see [18]).

Event-related experiment
Event-related data sets consisted of four functional time-series (TR=2000ms, voxel size = 2.8 x 2.8 x 5 mm^3, 16 slices, 126 scans/time-series) from a normal subject participating in an fMRI study of visuo-spatial imagery [19]. In this srtudy, subjects were asked to imagine two analogic clock faces showing two hours verbally presented by the examiner (e.g. 9.30 and 10.00) and to push a button with her index finger if the hands of the first clock formed the greater angle or with their middle finger if the hands of the second clock formed the greater angle. Four functional time-series, during which the hand used for the button press response was counterbalanced in an ABBA design (for further experimental details see [19]).

Previous to cbICA all functional data-sets were pre-processed using 3D motion correction, slice scan time-correction and high-pass filtering in the temporal-frequency domain [18, 19].

3. RESULTS AND DISCUSSION

3.1 Blocked-design experiment

Figure 3 (left) shows the results of cbICA decomposition of a blocked design data set. The components corresponding to the cortical response to the visual stimulation (objects presented in the right and left visual hemifield alternately) were identified by using the a priori information of the stimulation protocol. Components visualized in the figure (CSC1 and CSC2) are the two components whose TCs were most highly correlated (R=0.76 and R=0.73) with hemodynamic predictor functions computed on the basis of the stimulation protocol by a linear model. The components were z-normalized and voxels with |z|-values > 2 and belonging to a 3D-cluster >100 mm^3 were color-coded. The resulting maps were projected onto the inflated representation of the subject's cortex.

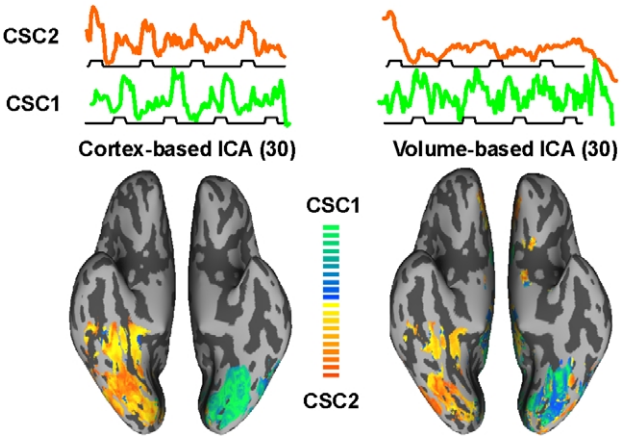

Figure 3*. Comparison between the cbICA and vbICa decomposition using the same number of components (=30) and the same z-threshold (z>2). The spatial layout and the time-courses of the pair of cortical components obtained with the cbICA were considerably more accurate than the ones obtained with the vbICA.

The brain areas integrated in these components included all early visual areas in the occipital cortex and in the ventral stream that responded to the presentation of the objects in the contralateral hemifield. Early areas of the visual processing stream were represented in a single component, while more ventral areas received the contribution of both the components, indicating that their response was less selective to the hemifield of stimulation. The spatial locations of these areas corresponded very well to the locations of the areas identified by the multiple regression analysis (see [18] for a comparison).
Figure 3 (right) shows the results of a similar analysis using anatomically unconstrained spatial ICA (volume-based ICA or vbICA) when using the same number of components (N=30). Again, the two components that mostly correlated to the stimulation protocol were selected. The visual inspection of the CSCs shows that the spatial layout and the time-courses of the task-related cortical activations obtained with cbICA were more accurate. In particular, it is evident that the estimation of the time-course of CSCs was drastically improved by the cortex-based approach.

3.2 Event Related Experiment

Figure 4 illustrates the results of the ICA decomposition of individual fMRI time-series in the case of the event-related fMRI experiment. The subsets of cortical components whose time-courses reflected task-related activation, were selected and projected on the flattened representation of the subject's cortex

In the case of complete ICA decomposition ($N = T =$ 126, Figure 4, middle row), surface maps and time-courses of task-related components accurately confirmed the topography as well as the sequence of activation of the brain regions that were obtained with the hypothesis-driven analysis (see [19] for a comparison). Indeed, separate components were obtained that reflected the activation of the transverse temporal gyrus and of the superior temporal sulcus bilaterally (blue color in Figure 4), of fronto-parietal regions (green and yellow color), and of the sensorimotor cortex contra- and, at minor extent, ipsi-lateral to the response hand (red color).

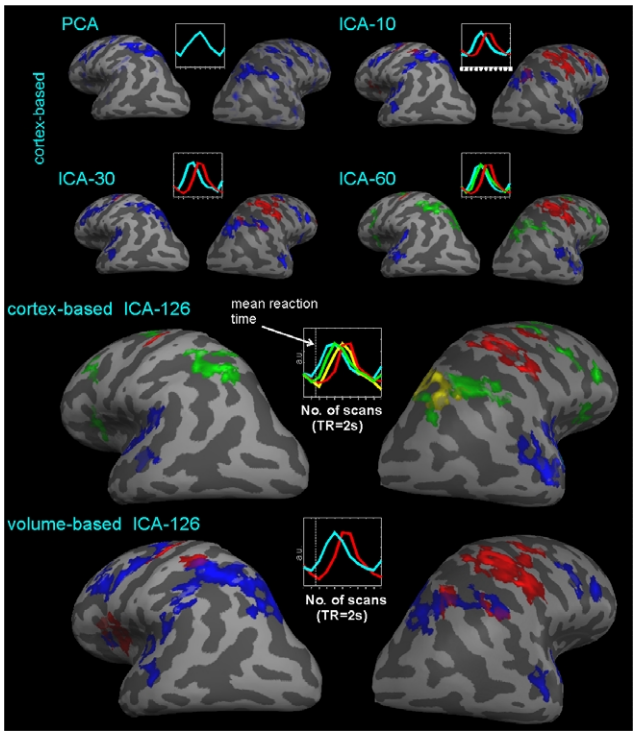

Figure 4*. Cortex-based PCA, ICA (with IC=10, 30, 60 and 126), and volume-based ICA (IC=126) of an event-related functional data set from a study of visuospatial imagery [19].

The average time-courses (see insert in Figure 4) of these two components confirmed the results, with the activation of the component lateralized in the right PPC following the activation of the other, less lateralized, component. Figure 4A shows the results of using cortex-based principal component analysis (PCA), and ICA after a PCA-based dimensionality reduction to 10, 30 and 80 components. It is evident that, for this event-related fMRI data set, a reduction of dimensionality had a negative effect on differentiation of the spatio-temporal pattern of cortical activation (Figue 4A-B). These results suggest that caution should be taken in reducing excessively the dimensionality of fMRI time-series previous to their ICA decomposition.

Figure 4C shows the results of a conventional anatomically unconstrained ICA decomposition (with no dimensionality reduction) of the same data-set. Compared to the cbICA, this analysis gave much poorer results only detecting two task related components. Note that these results are comparable to the cbICA decomposition with a dimensionality reduction with N=30 (see Figure 4A).

In order to compare results between conventional and cortex-based ICA in a more quantitative way we performed a log-likelihood analysis (see ref. [11] for details). For a varying number of components the mean values of the -log-likelihood function were computed. When computing the mean of the –log-likelihood function across all voxels included in the ICA decompositions, lower values (indicating a better fit to the data) were obtained for the vbICA. This apparent contradiction with the previously described qualitative analysis of the CSCs is easily explained by considering that many of the voxels included in the vbICA are white-matter voxels. In these voxels, the signal is simpler and much lower values of -log-likelihood are expected [11]. However, when computation of E{-log-likelihood} for both approaches was performed on the same subset of gray matter voxels, lower values were obtained in the case of the cbICA. This confirms the results of the qualitative analysis and indicates that, when using the same number of components, cbICA is better suited than vbICA for the modeling of fMRI-signals from gray-matter voxels.

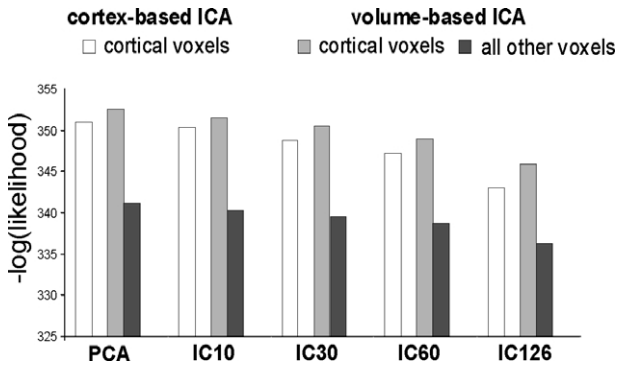

Figure 5*. Analysis of the -log-likelihood function for the cbICA and the vbICA. Lower values of this function indicate a better fit of the ICA model (see ref. [11] for details). The vbICA model fits better in the extra-cortical than cortical voxels. The cbICa model fits better than the vbICA model in the cortical voxels.

4. CONCLUSIONS

We have presented a method for the analysis of fMRI data that combines techniques for the reconstruction and morphing of the cortex from anatomical MR images and spatial ICA of functional time-series (cortex-based ICA or cbICA).
We have demonstrated the validity of cbICA by analyzing locked and event-related fMRI data. In both cases, cbICA could reliably generate a subset of surface-components that clearly resembled the expected task-related brain activation patterns. The spatial layout and time-course of these cbICA-generated components can be used to model the spatio-temporal dynamics of fMRI cortical activation with greater accuracy than with conventional, anatomically unconstrained spatial ICA.

11. REFERENCES

[1] M. I. Sereno, A. M. Dale, J. B. Reppas, K. K. Kwong, J. W. Belliveau, T. J. Brady, B. R. Rosen, and R. B. Tootell, "Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging," *Science*, vol. 268, pp. 889-93, 1995.

[2] R. Goebel, D. Khorram-Sefat, L. Muckli, H. Hacker, and W. Singer, "The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery," *Eur J Neurosci*, vol. 10, pp. 1563-73, 1998.

[3] A. M. Dale, B. Fischl, and M. I. Sereno, "Cortical surface-based analysis. I. Segmentation and surface reconstruction," *Neuroimage*, vol. 9, pp. 179-94, 1999.

[4] R. Goebel and W. Singer, "Cortical surface-based statistical analysis of functional magnetic resonance imaging data," *Neuroimage*, vol. 9, pp. S64, 1999.

[5] A. Andrade, F. Kherif, J. F. Mangin, K. J. Worsley, A. L. Paradis, O. Simon, S. Dehaene, D. Le Bihan, and J. B. Poline, "Detection of fMRI activation using cortical surface mapping," *Hum Brain Mapp*, vol. 12, pp. 79-93, 2001.

[6] S. J. Kiebel, R. Goebel, and K. J. Friston, "Anatomically informed basis functions," *Neuroimage*, vol. 11, pp. 656-67, 2000.

[7] M. Castelo-Branco, E. Formisano, W. Backes, F. Zanella, S. Neuenschwander, W. Singer, and R. Goebel, "Activity patterns in human motion-sensitive areas depend on the interpretation of global motion," *Proc Natl Acad Sci U S A*, vol. 99, pp. 13914-9, 2002.

[8] P. Comon, "Independent Component Analysis, a new concept?," *Signal Processing*, vol. 36, pp. 287-314, 1994.

[9] M. J. McKeown, S. Makeig, G. G. Brown, T. P. Jung, S. S. Kindermann, A. J. Bell, and T. J. Sejnowski, "Analysis of fMRI data by blind separation into independent spatial components," *Hum Brain Mapp*, vol. 6, pp. 160-88, 1998.

[10] M. J. McKeown, T. P. Jung, S. Makeig, G. Brown, S. S. Kindermann, T. W. Lee, and T. J. Sejnowski, "Spatially independent activity patterns in functional MRI data during the stroop color-naming task," *Proc Natl Acad Sci U S A*, vol. 95, pp. 803-10, 1998.

[11] M. J. McKeown and T. J. Sejnowski, "Independent component analysis of fMRI data: examining the assumptions," *Hum Brain Mapp*, vol. 6, pp. 368-72, 1998.

[12] A. J. Bell and T. J. Sejnowski, "An information-maximization approach to blind separation and blind deconvolution," *Neural Comput*, vol. 7, pp. 1129-59, 1995.

[13] V. D. Calhoun, T. Adali, G. D. Pearlson, and J. J. Pekar, "Spatial and temporal independent component analysis of functional MRI data containing a pair of task-related waveforms," *Hum Brain Mapp*, vol. 13, pp. 43-53, 2001.

[14] N. Kriegeskorte and R. Goebel, "An efficient algorithm for topologically correct segmentation of the cortical sheet in anatomical mr volumes," *Neuroimage*, vol. 14, pp. 329-46, 2001.

[15] E. Formisano, F. Esposito, N. Kriegeskorte, G. Tedeschi, F. Di Salle, and R. Goebel, "Spatial independent component analysis of functional magnetic resonance imaging time-series: characterization of the cortical components.," *Neurocomputing*, vol. 49, pp. 241-254, 2002.

[16] A. Hyvärinen, "Fast and robust fixed-point algorithms for independent component analysis.," *IEEE Trans on Neural Networks*, vol. 10, pp. 626-634, 1999.

[17] F. Esposito, E. Formisano, E. Seifritz, R. Goebel, R. Morrone, G. Tedeschi, and F. Di Salle, "Spatial independent component analysis of functional MRI time-series: to what extent do results depend on the algorithm used?," *Hum Brain Mapp*, vol. 16, pp. 146-57, 2002.

[18] R. Goebel, L. Muckli, F. E. Zanella, W. Singer, and P. Stoerig, "Sustained extrastriate cortical activation without visual awareness revealed by fMRI studies of hemianopic patients," *Vision Res*, vol. 41, pp. 1459-74, 2001.

[19] E. Formisano, D. E. Linden, F. Di Salle, L. Trojano, F. Esposito, A. T. Sack, D. Grossi, F. E. Zanella, and R. Goebel, "Tracking the mind's image in the brain I: time-resolved fMRI during visuospatial mental imagery," *Neuron*, vol. 35, pp. 185-94, 2002.

*__Note__: A color version of the figures is available on the electronic copy of the paper or upon request to:
e.formisano@psychology.unimaas.nl .