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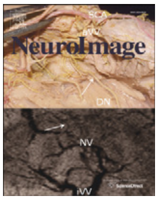

Contributive sources analysis: A measure of neural networks' contribution to brain activations

Ewa Beldzik [a,b,d,*], Aleksandra Domagalik [a,d], Sander Daselaar [c], Magdalena Fafrowicz [a,d], Wojciech Froncisz [b], Halszka Oginska [a], Tadeusz Marek [a,d]

[a] *Department of Neuroergonomics, Institute of Applied Psychology, Jagiellonian University, Krakow, Poland*
[b] *Department of Molecular Biophysics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland*
[c] *Donders Institute for Brain, Cognition, and Behaviour, Radboud University Nijmegen, The Netherlands*
[d] *Neurobiology Department, Malopolska Centre of Biotechnology, Jagiellonian University, Krakow, Poland*

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ABSTRACT

General linear model (GLM) is a standard and widely used fMRI analysis tool. It enables the detection of hypothesis-driven brain activations. In contrast, Independent Component Analysis (ICA) is a powerful technique, which enables the detection of data-driven spatially independent networks. Hybrid approaches that combine and take advantage of GLM and ICA have been proposed. Yet the choice of the best method is still a challenge, considering that the techniques may yield slightly different results regarding the number of brain regions involved in a task. A poor statistical power or the deviance from the predicted hemodynamic response functions is possible cause for GLM failures in extracting some activations picked by ICA. However, there might be another explanation for different results obtained with GLM and ICA approaches, such as networks cancelation.

In this paper, we propose a new supplementary method that can give more insight into the functional data as well as help to clarify inconsistencies between the results of studies using GLM and ICA. We introduce a contributive sources analysis (CSA), which provides a measure of the number and the strength of the neural networks that significantly contribute to brain activation. CSA, applied to fMRI data of anti-saccades, enabled us to verify whether the brain regions involved in the task are dominated by a single network or serve as key nodes for particular networks interaction. Moreover, when applying CSA to the atlas-defined regions-of-interest, results indicated that activity of the parieto-medial temporal network was suppressed by the eye field network and the default mode network. Thus, this effect of networks cancelation explains the absence of parieto-medial temporal activation within the GLM results. Together, those findings indicate that brain activations are a result of complex network interactions. Applying CSA appears to be a useful tool to reveal additional findings outside the scope of the "fixed-model" GLM and data-driven ICA approaches.

Introduction

Over 1600[1] papers applying Independent Component Analysis (ICA) to fMRI data have been published since McKeown et al. (1998) used it as a blind source separation technique based on the work of Bell and Sejnowski (1995). Growing interest in ICA is clearly due to the fact that it is a very powerful and reliable data driven technique with little presumptions (Beckmann, 2012; Calhoun et al., 2001a, 2008). The technique separates fMRI data into maximally independent components; representing either task or non-task related physiological changes as well as artifacts. A component map presents a pattern of coactivated regions, which can be called a network, as it assumes that they have temporally coherent activity (Calhoun et al., 2008). In contrast to data-driven ICA, the widely used general linear model (GLM) analysis of fMRI data is constrained by a fixed model-based hypothesis regarding the task at hand. GLM identifies regions significantly correlating to a model based on the hypothetical hemodynamic response function linked to stimuli and task conditions. The regions identified by this model are generally referred to as "brain activations." Simple associations among activated regions with unknown connectivity or causality are referred to as systems (Huettel et al., 2008). In summary, GLM enables the detection of hypothesis-driven brain activations, while ICA enables the detection of data-driven spatially independent networks. The former is a traditional analysis tool, highly accepted in neuroimaging field, whereas the latter has been found to be able to identify additional regions involved in the task (Bartels and Zeki, 2004; Calhoun et al., 2005; Domagalik et al., 2012; Malinen et al., 2007). Malinen et al. (2007) suggest that GLM failure in extracting

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* Corresponding author at: Institute of Applied Psychology, Jagiellonian University, Lojasiewicza 4, 30-348 Krakow, Poland. Fax: +48 126645856.
E-mail address: ewa.beldzik@uj.edu.pl (E. Beldzik).

[1] PubMed search of "(fmri OR functional magnetic resonance imaging) AND (ica OR independent component analysis)" since 1998.

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expected activations might be due to too small sample size of the study or deviance from the predicted hemodynamic response functions. Thus, it is important to develop new methods, which take advantage of both techniques and might explain the inconsistencies of the results.

GLM is still the most widely used fMRI analysis tool. The results obtained with any novel techniques are therefore typically compared to this standard fMRI analysis approach (e.g. Moeller et al., 2011), as it has provided numerous crucial findings in neuroscience in the last two decades. However, nonhypothesis-driven ICA can lead to more unexpected findings that are not fixed by model restraints, and that can enhance our insight into the functional role of regions (Eichele et al., 2008; Schmithorst, 2005; St Jacques et al., 2011; Stevens et al., 2009). In the opinion of Friston (1998) the hypothesis based scientific process was serving the imaging community extremely well at the time. The ICA community responded with foreseeing the development of hybrid methods that will attempt to take advantage of these two complementary approaches (Makeig et al., 1998). Indeed, there have been few attempts in combining both techniques (Beckmann et al., 2000; Hu et al., 2005; McKeown, 2000). Hybrid methods are two-stage processes, i.e. data-driven ICA exploration leads to data-driven component time courses, which are subsequently used as a set of fixed model regressors within the context of GLM. Thus, this approach focuses on post-processing of ICA results in order to increase statistical interferences, rather than giving a new insight into the data. In the end, it may still yield slightly different results in comparison to those obtained with GLM.

In our recent study (Domagalik et al., 2012) ICA was applied to the fMRI data obtained from fifteen subjects performing the prosaccade (PS) and antisaccade (AS) tasks. The results revealed that the parieto-medial temporal pathway, described by Kravitz et al. (2011), plays a crucial role in vector inversion process evoked in AS task. The brain regions identified in this study were not reported in previous studies implementing the same task design. This might relate to the fact that most of these studies employed standard GLM to analyze the data. As an explanation for those inconsistencies, we hypothesized that there could be some deactivation that cancels the parieto-medial temporal activity. Moreover, a very common findings concerning comparison of PS to AS, is that the latter evokes stronger activations of frontal and parietal regions than PS (see review by McDowell et al., 2008). It is still unclear what stands behind this difference. For instance, the same process could be involved in both PS and AS, but AS demands more neurocognitive resources leading to increased activation in frontal/parietal regions. Alternatively, it could be the case that multiple processes engage the same brain regions.

Here, we present a new approach for combining GLM and ICA, which allowed us to investigate the effect of networks cancelation as well as to clarify how different neural networks together contribute to brain activation detected with GLM. In contrast to other approaches, this one gives no statistical advantages over those two techniques, but may reveal additional findings outside the scope of the “fixed-model” GLM and data-driven ICA and help to interpret ambiguous results. We introduce a parameter named Contributive Sources (CS), which reflects the contribution of each independent component, obtained with ICA, to brain activation obtained with GLM. Our approach differs from hybrid methods on two points: (1) a standard GLM analysis is used to identify significant regions and (2) parameter estimates of component time-course is multiplied by the weight of the component map. Once this product – CS – is extracted from significant region, it provides a measure of the components' contribution to the brain activation. The sum of CS is mathematically equivalent to parameter estimates value of the hypothesized response to stimuli extracted with GLM at the given voxel or region-of-interests. In this paper, we introduce a theory and a formula supporting that equivalence. Then, we verify the formula with experimental fMRI data obtained from fifteen subjects performing an AS task. Finally, we present the results of applying contributive sources analysis (CSA) to those data and provide an example on how to explore the fMRI data with this method. To our knowledge, the matter of the contribution of different neural networks to the activation within a single brain region has not been investigated so far.

Theory

If GLM and ICA are conducted separately on the same data set and the latter is not reducing its dimensionality, ICA results can be reconstructed into GLM results through a simple mathematical substitution. This indicates the approximate equivalence between the GLM and ICA results for the chosen parameter of the model.

Assuming n time points, m regressors, and v voxels, the GLM parameter estimates are a linear subspace of the data:

$$\beta_{\mathrm{GLM}} = \mathrm{M}^{+}\mathrm{X} \qquad (1)$$

where β is a $\mathrm{m} \times \mathrm{v}$ matrix of GLM parameter estimates, M is the $\mathrm{n} \times \mathrm{m}$ GLM design matrix (M^{+} designates Moore–Penrose pseudoinverse) and X is the $\mathrm{n} \times \mathrm{v}$ data matrix. Assuming ICA has occurred without dimensionality reduction $\mathrm{X} = A \cdot S$ where A is an $\mathrm{n} \times \mathrm{n}$ square mixing matrix and S is the $\mathrm{n} \times \mathrm{v}$ matrix of independent sources, and thus Eq. (1) can also be written as

$$\beta_{\mathrm{GLM}} = \beta_{\mathrm{IC}} \cdot S \qquad (2)$$

where β_{IC} ($= \mathrm{M}^{+}\mathrm{A}$) is an $\mathrm{m} \times \mathrm{n}$ matrix of parameter estimates applied to ICs time courses.

In case of a single voxel the equation can be formulated using the following vector notation:

$$\hat{\beta}_{\mathrm{GLM}} = \sum_{i=1}^{\mathrm{nr\ of\ IC}} \beta_{\mathrm{IC}i} \cdot s_i \qquad (3)$$

We label this multiplication product as CS parameter, where $\mathrm{CS} = \beta \cdot s$ for the selected component.

According to Eq. (3), the sum of CS values from each component equals the parameter estimates of standard GLM at a given voxel of a given regressor. Therefore, CS parameters provide a measure of the components' contribution to the brain activation obtained with GLM. Hence, they can be referred to as “contributive sources” (CS).

Materials and methods

Procedure

The details concerning participants, procedure, data acquisition and preprocessing have been described in detail in our previous article (Domagalik et al., 2012). Briefly, fifteen healthy, male volunteers, with a mean age of 27.4 years (SD = 5.6) participated in the study. An anti-saccadic (AS) task interspersed with rest periods was used in a block design fashion (each block lasted 30 seconds). In the rest block, a fixation point was displayed in the center of the screen. In the AS block a target stimulus was randomly presented at one of the five right- or five left-side situated squares, while the fixation point remained continuously visible (an overlap paradigm). The subjects were instructed to direct their attention and gaze straight ahead toward the fixation point and, as soon as the stimulus appeared, refrain from following it. Instead, they were instructed to focus their attention and gaze at the point in the opposite direction and at the same distance from the fixation point as the stimulus. The task block consisted of 18 stimuli each lasting 1500 ms with a gap of 500 ms between them. There were five scanning runs, each containing a 5 min AS task session. Magnetic resonance imaging was performed using a 1.5 T General Electric Signa scanner (GE Medical Systems, Milwaukee, WI). Standard preprocessing procedure was applied to fMRI data with Analysis of Functional NeuroImage (AFNI) software (Cox, 1996).