

NEDICA: DETECTION OF GROUP FUNCTIONAL NETWORKS IN FMRI USING SPATIAL INDEPENDENT COMPONENT ANALYSIS

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ABSTRACT

Functional Magnetic Resonance Imaging (fMRI) has recently proved its utility in studying brain large-scale networks through fluctuations in resting-state data. To process such rest acquisitions, exploratory methods such as Independent Component Analysis (ICA) are of particular interest. Yet, while successfully applied at the individual level, existing ICA methods still fail to provide robust functional network detection at the group level.

In this paper, we propose a method for detecting group functional large-scale networks in fMRI using ICA, which allows to systematically control the consistency of the group results with the individual ones. This approach, called NEDICA (NETwork Detection using ICA), was applied on resting-state data from twenty healthy subjects and the robustness of the resulting networks was assessed by a bootstrap sampling procedure.

We found seven functional networks that were very representative of the population and highly reproducible on the basis of bootstrap tests. These results were in good agreement with the existing literature and confirmed the ability of fMRI to noninvasively reveal large-scale interactions in the brain.

Index Terms— fMRI, ICA, group analysis, functional networks

1. INTRODUCTION

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) makes it possible to noninvasively track metabolic and hemodynamic changes in the brain [1]. Recently, it has been reported that fMRI resting-state fluctuations in the frequency range below 0.1 Hz can reflect several structures of functional brain networks [2]. Biswal et al. introduced the functional connectivity approach to explore in individuals the brain regions that were functionally related to a seed region in the primary motor cortex [3]. This approach has been further applied to other brain systems including the auditory system [4] or attentional networks [2]. Even though the relation between fMRI low-frequency fluctuations and neural activity synchronization remains controversial [5], the spatial structures characterizing functional networks have been reproducibly found through different imaging modalities such as PET [6] or simultaneous EEG/fMRI acquisitions [7]. In this context, one of the most accepted assumptions is that each fMRI time-series is the linear mixture of spatially distributed processes related to brain activity, as well as those related to other specific brain phenomena such as cardiac activity, respiration or movements. Under this assumption, spatial ICA (sICA) has proved its ability to blindly separate these different processes from fMRI acquisitions

[8] and to reveal functional connectivity networks from individual resting-state data without any priors regarding the brain regions involved in these networks [9].

However, the results consistently found at the individual level have now to be extended to the group level. Recent methodological developments based on sICA allow one to extract distinct functional networks characterizing the activity of a group of subjects from resting-state data [10, 11, 12]. However, the exact nature and composition of these networks remain a matter of debate. Indeed, while DeLuca et al. [11] have described five networks at rest, including visual, motor or attentional networks, other investigators have identified up to ten networks [10, 12]. The variability of these results might be explained by the diversity of approaches. The first approaches proposed to apply sICA decomposition on the pooled individual data [10, 13]. These approaches assume that the same processes exist for all subjects. However, the probable between-subject variability in activity location may bias the estimation of the components at the group level. Recently, the tensor-PICA approach [14] has proposed to take between-subject variability into account in the estimated model. However, to our knowledge, its application on resting-state data [12] has been limited to low-frequency power spectra of the time-series instead of the time-series themselves and unfortunately, according to the results showed, some networks found did not seem highly reproducible.

Thereby, the aim of this work is twofold: first, to propose a method for identifying functional networks at the group level, which would benefit the best from the application of sICA at the individual level; second, to test the reproducibility of the revealed networks on a large dataset. The method, called NEDICA for NETwork Detection using ICA, was applied to a dataset of twenty healthy subjects acquired at rest. Its robustness was assessed using a bootstrap sampling procedure. This procedure allowed one to evaluate the reproducibility of the resulting networks.

2. MATERIALS AND METHODS

2.1. Data

Magnetic resonance imaging data were acquired on twenty right-handed volunteers (age: 24-30 years; twelve male) on an MRI Siemens TRIO system at 3.0 Teslas at the Centre de Recherches de l'Institut Universitaire de Gériatrie de Montréal, Canada, according to a protocol approved by the local ethic committee. Functional data were recorded during continuous rest consisting of remaining eyes closed. FMRI acquisitions were performed using a single-shot, gradient-recalled echo-planar imaging sequence (TR = 3500 ms; TE

= 40 ms; flip angle = 90°; matrix 64 × 64 voxels). One hundred and sixty T₂-weighted images were acquired for each run consisting of 41 contiguous axial slices (voxel size: 3.5 mm isotropic). Two successive runs were acquired for each subject, leading to 40 resting-state fMRI time series in total. Prior to data analysis, a slice timing correction was performed on the fMRI data using the SPM2 software¹. The resulting raw data were corrected for quadratic drifts by using linear regression, and mean corrected (i.e. the mean of each time course was set to 0).

2.2. Identification of group networks (NEDICA)

The main objective of the subsequent data analysis was to identify functional processes that are temporally and spatially structured during rest. Akin to Esposito et al. [15], we chose to use the efficiency of sICA decomposition applied at the individual level, which has been extensively reported. The extension of the results to the group level consisted then of finding the patterns obtained from the single-subject procedure that were robustly reproducible across the population.

In our application, 40 independent components (IC) were computed for each run by using the infomax ICA algorithm [16] and each spatial component was scaled to z -scores, yielding

$$20 \text{ subjects} \times 2 \text{ runs/subject} \times 40 \text{ ICs/run} = 1600 \text{ ICs.}$$

To reduce anatomical differences between subjects, the 1600 spatial ICs were registered to the MNI standard space by using nonlinear spatial transformations as implemented in the SPM2 software. The aim of the analysis was then to cluster ICs across subjects and runs based on their spatial similarity. To quantify this notion, a distance d was derived from the spatial correlation coefficient r between two ICs (IC₁ and IC₂) as follows:

$$d(\text{IC}_1, \text{IC}_2) = \sqrt{1 - r(\text{IC}_1, \text{IC}_2)}.$$

Clustering of the 1600 ICs was performed using a hierarchical clustering algorithm that minimizes the intra-class similarity [17], yielding a similarity tree.

From this similarity tree, the main issue was then to partition all 1600 ICs into a certain number of classes gathering similar ICs from different runs. We proposed an original automatic way to define the classes that were the most representative of the population. Indeed, each class should ideally be composed of one and only one IC from each run. Thus, from the similarity tree (describing IC clustering as a function of intra-class similarity), group-representative classes were chosen using an ad hoc algorithm optimizing both the degree of representativity (DR) and the degree of unicity (DU) of each class. For a given class, DR was defined as the number N_R of distinct runs that contributed to it, divided by the total number of runs. However, each run may contribute to a class through more than one IC. Therefore, among the N_R runs, the degree of unicity DU was defined as the number of runs that contributed to the class with one and only one component, divided by N_R . With these definitions, an optimal class was characterized by DR=1 and DU=1. In our procedure, the scores limits were set to DR>0.5 and DU>0.75, i.e. for each class, at least half of the runs contribute to this class and at least 75% of these runs contribute with only one IC. When both conditions were not simultaneously fulfilled, DR was privileged compared to DU. For instance, when a class B with DR(B)>0.5 and DU(B)<0.75 was obtained from the merging of two classes A_1 and A_2 with DR(A_1)<0.5 and

DR(A_2)<0.5, the procedure retained the merged class B instead of the two classes A_1 and A_2 .

Finally, for each class so defined, we searched for clusters of voxels that systematically revealed high z -scores in the spatial ICs contributing to this class. To do so, we computed a fixed-effect group map of t -scores for each class, by dividing, for each voxel, the mean by the variance of the z -scores of all ICs belonging to the class. These maps were thresholded at $p < 0.05$ with a false discovery rate procedure to control for multiple comparisons [18] and were visually inspected to exclude classes related to noise processes, which had known spatial distributions [19]. The remaining group maps represented the networks of interest and were considered as group maps of reference for the following evaluation procedure.

2.3. Reproducibility test

To assess the confidence level of IC clustering and evaluate the robustness of the networks detection, we used a general procedure based on bootstrap [20] for making statistical inference from the whole procedure. Once group maps of reference were identified from the whole dataset as described above, NEDICA was applied again using only half of the runs randomly selected, yielding new group maps. The spatial correlation between each group map and each group map of reference was computed. For each group map of reference, the group map with the highest correlation with this map of reference was selected. If the maximum correlation was lower than 0.3, the corresponding group map of reference was considered as not represented. This procedure was repeated 100 times. Then, scores of reproducibility and similarity were computed for each map of reference. The reproducibility score was defined as the ratio between the number of bootstrap tests where the group map of reference was found to be represented and the total number of bootstrap samples (i.e., 100). The similarity score was defined as the average spatial correlation between the map of reference and its bootstrap representative maps.

3. RESULTS

Applied to the 40 resting-state runs, NEDICA provided seven functional networks distributed into cortical, sub-cortical, and cerebellar areas (see Figure 1). The final degrees of group representativity and unicity were higher than 0.6 and 0.7, respectively. The resulting networks included functionally relevant regions involved in memory, attention, motor processing, or visual processing.

The dATT network, known as the dorsal attentional network [2], involved the superior and inferior parietal cortices (BA 7/40), the medial and lateral premotor (BA 6/8), the ventral and dorsal prefrontal cortices (BA 44/46), the posterior cingulate gyrus (BA 31), and the middle and inferior temporal cortices (BA 21/37). The vATT network, often called ventral attentional network [2], included regions of the dorsolateral prefrontal cortex (BA 9), the ventral prefrontal cortex (BA 46), the anterior supplementary motor area (BA 6), of the supramarginal gyrus (BA 40), and the middle temporal gyrus (BA 21). The DM network, known as the default-mode network [6], involved the lateral superior (BA 8) and rostromedial frontal cortices (BA 10), the anterior and posterior cingulate (BA 24/31), the angular gyrus (BA 40), the precuneus (BA 7), the middle temporal gyrus (BA 21/39), and the hippocampus and parahippocampal gyrus. The network denoted MESOL involved, in particular, anterior (ACC) and posterior (PCC) cingulates (BA 24/31), the dorsolateral prefrontal cortex (BA 9), the dorsomedial thalamus, the parahippocampal gyrus, and the ventral tegmentum

¹<http://www.fil.ion.ucl.ac.uk/spm/spm2>.

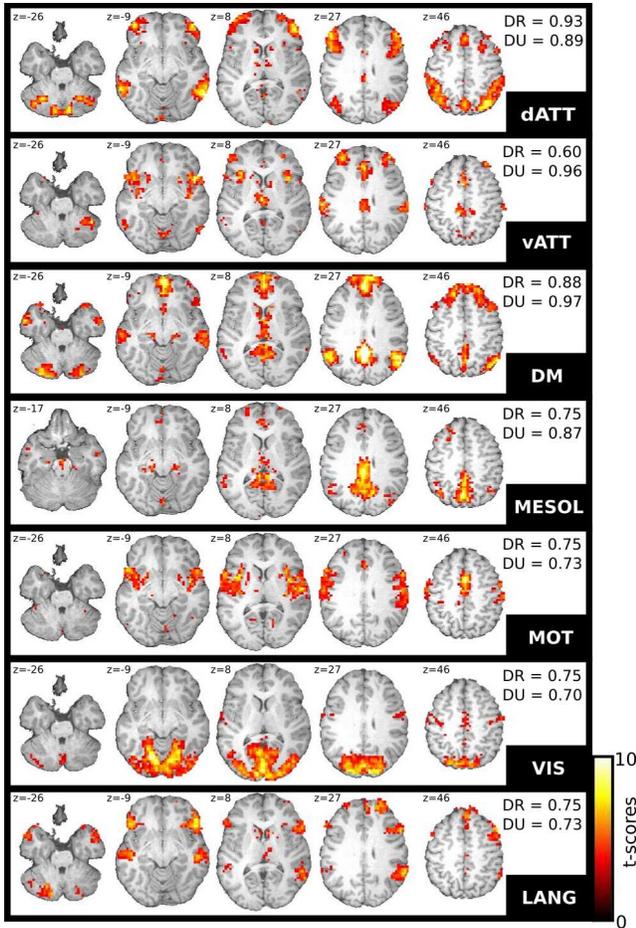


Fig. 1. Functional networks identified by NEDICA. Five representative axial slices of each thresholded map are presented, overlaid on a high-resolution structural scan transformed into MNI standard space (MNI512). The left hemisphere is on the right side of the images. The degrees of representativity (DR) and unicity (DU) are given for each network. dATT: dorsal attentional; vATT: ventral attentional; DM: default-mode; MESOL: fronto-mesolimbic; MOT: motor; VIS: visual; LANG: language.

area (VTA). These regions are known to belong to dopaminergic pathways, from the midbrain (VTA and substantia nigra) to the cortex (ACC and prefrontal cortex) and to subcortical areas [21]. The spatial structure of this network, close to that of the default-mode network, revealed parts of the fronto-mesolimbic system. The MOT network involved sensorimotor areas such as the primary motor cortex (BA 4), the supplementary motor area (BA 6), the postcentral gyrus (BA 3), and the secondary somatosensory cortex (BA 40/43). The VIS network exhibited regions of striate and parastriate areas (BA 17/18), and lateral middle and superior occipital gyri (BA 19). Finally, the LANG network included regions in Broca's (BA 45) and Wernicke's areas (BA 22/39). This network involved also the angular gyrus (BA 39), the medial superior frontal cortex (BA 8/9), the dorsolateral prefrontal cortex (BA 9), the middle temporal gyrus (BA 21/39), and the temporal pole (BA 21). This network was clearly left-lateralized, suggesting that it represents the language system [4].

The results of the bootstrap reproducibility test are presented in Figure 2. They show that the resulting functional networks were very reproducible (each network was identified at least 95 times out of 100) and very robust (the average similarity scores were never lower than 0.73).

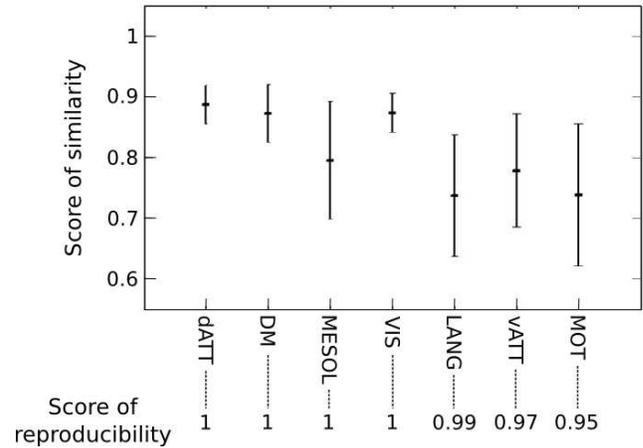


Fig. 2. Scores of reproducibility and similarity for the seven networks. The mean and standard deviation of the similarity scores are plotted.

4. DISCUSSION

The NEDICA procedure we have proposed allowed one to identify seven functional networks from a group of twenty healthy subjects. These networks appeared to be not only highly representative of the population, but also highly robust to bootstrap sampling tests. To our knowledge, three other studies have applied ICA-based methods on fMRI datasets to identify group resting-state networks [10, 11, 12]. Even if the number of resulting networks varied from one study to another, their spatial structures were very similar. Studies [10] and [12] revealed almost the same networks as the present study, but sometimes splitted (for example the dATT network was found separated into two distinct networks, one in the right hemisphere and the other in the left hemisphere). Five networks found by NEDICA were also identified by the three other studies (dATT, vATT, DM, MOT, and VIS). The network LANG was partly identified (the temporal part) only in [12] and the MESOL was never revealed. Conversely, two studies [10, 12] identified an auditory network, which NEDICA did not find. Besides, our results are consistent with the existing literature on the brain organization. Indeed, we found primary networks (motor and visual systems) as well as networks related to higher level functions (attentional or memory networks). Finally, we showed that our results were highly reproducible by using a bootstrap sampling procedure on the population. This procedure allowed us to increase our confidence in the seven networks we selected.

The approach based on hierarchical clustering of individual ICs is similar to the sogICA method proposed by Esposito et al. [15]. Computation of individual sICA decomposition prior to the clustering of similar effects across subjects allows one to account for possible high between-subject variability. Moreover, the criteria we proposed to automatically define the classes from the similarity tree allow one to control relevance of these classes relative to individual sICA decompositions. Indeed, the unicity criterion ensures, to

a certain extent, that two (or more) effects separated in a majority of individual cases are not merged into the same final cluster. This prevents from defining inhomogeneous classes. At the same time, contrary to the approach proposed in [15], which consisted in manually choosing the classes on the basis of constraints on DR and/or on intra-class similarity, NEDICA can automatically identify classes with a relatively low DR (until 0.5). This allows one to possibly detect effects with a low level of covariance that may not be systematically found for each subject but well-differentiated from the other structures of interest.

As it is now largely accepted that brain functions involve distributed large-scale networks, it is of particular interest to study the modulation induced by different cognitive conditions on the basis of the functional networks identified at rest by using NEDICA. So the method could be applied on the same population under different experimental conditions or on different populations (healthy subjects versus patients for instance). However, exploratory methods based on sICA decomposition are sensitive only to high levels of covariability. Therefore, slight modulations or differences in interactions due to different conditions and/or populations may not be systematically detected by such methods. These questions will be addressed in our future investigations.

5. CONCLUSION

Spatial ICA applied on individual fMRI datasets has proved its efficiency to extract structured brain processes, related to functional connectivity in particular. Yet, existing methods fail to provide robust results at the group level. The method we proposed, NEDICA, allows one to identify in a robust manner functional networks at the group level, which are relevant relative to the individual sICA decompositions. We believe that this method, so far evaluated on resting-state data, will prove an efficient tool to explore functional brain reorganizations induced by different experimental conditions.

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