IDENTIFICATION OF FUNCTIONAL CORTICO-SUBCORTICAL NETWORKS IN
RESTING-STATE FMRI: A COMBINED NEDICA AND GLM ANALYSIS

C. Malherbe$^{1,3}$, M. Pélégri-Issac$^{1,3}$, V. Perlberg$^{1,3}$, S. Lehéricy$^{2,3}$, G. Marrelec$^{1,3}$, H. Benali$^{1,3}$

$^1$Inserm and UPMC Univ Paris 06, UMR_S 678, Laboratoire d’Imagerie Fonctionnelle, Paris, France

$^2$Inserm and UPMC Univ Paris 06, UMR_S 975 CRICM, Centre for NeuroImaging Research – CENIR, Pitié-Salpétrière Hospital, Paris, France

$^3$Univ Paris 11, IFR 49, DSV/IPBM Neurospin, Gif-sur-Yvette, France

caroline.malherbe@imed.jussieu.fr

ABSTRACT

While the cortical components of functional networks detected by spatial independent component analysis (sICA) in functional magnetic resonance imaging (fMRI) have been reproducibly described in various studies, little is known about their subcortical components. In this study, we propose a method that extracts cortico-subcortical networks from fMRI data by first detecting cortical networks with sICA and then by complementing them with subcortical components using multiple regression, at both the individual and the group levels.

Index Terms— fMRI, functional connectivity, functional networks, basal ganglia.

1. INTRODUCTION

The basal ganglia (BG) have anatomical and functional connections with the cortex and are known to be involved in cortico-subcortical circuits that are critical not only for controlling motor function, but also for mediating cognition, emotions, and motivation [1]. Such loops have been extensively studied in the primate brain [2, 3], in which biological tracers can be used to reveal the links between the BG and the cortex. On the other hand, in the human brain, few neuroimaging studies have attempted to identify the cortico-subcortical circuits either from diffusion tensor imaging (DTI) data [4] or by coupling functional magnetic resonance imaging (fMRI) and DTI data [5, 6].

In fMRI, a large-scale functional network is defined as a set of distant cortical, subcortical or cerebellar regions characterized by coherent dynamics [7]. At rest, such networks have been identified by various methods relying on spatial independent component analysis (sICA) [8, 9].

While the cortical parts of these networks have already been described quite precisely in the literature, little has been said about the associated subcortical regions [7, 10]. Indeed, sICA-based techniques usually assign a large part of the BG to a single ICA component [11]. This shows that we can not segregate the BG in subregions specifically associated with cortical areas by using sICA alone. That is probably due to signal differences between cortical and subcortical regions.

The aim of this paper was to provide a method that allows the precise detection of the subcortical components of the large-scale functional networks observed in fMRI. To do so, we proposed the following two-step method. We first extracted cortical networks using sICA in functional data in which the BG were masked out. These networks were very similar to the networks obtained without masking. We then detected the subcortical components corresponding to these cortical components using group multiple regression. Each network was finally defined as the union of its cortical and subcortical components.

2. MATERIAL AND METHODS

2.1. Data and preprocessing

Two runs of resting-state fMRI were acquired for 20 healthy volunteers who gave their informed consent. This protocol was approved by the local ethics committee. Subjects lied still in the scanner, eyes closed, refraining from any particular mental activity. Acquisition parameters were: FOV = 224 × 224 mm; 160 volumes of 41 contiguous slices; 3.5 mm isotropic voxels; (TR, TE) = (30, 2500) ms; flip angle: 90°. All data were acquired using a 3 T Siemens Trio 32 channel TIM system at the Montreal Geriatric Institute Research Center, Montreal, QC, Canada. Data preprocessing using the SPM5 software included slice-timing correction, spatial smoothing with an isotropic Gaussian kernel (full-width-at-half-maximum (FWHM) 5 × 5 × 5 mm), an affine and nonlinear transformation \( T \) was calculated between each individual anatomical volume and the MNI template, after coregistering all fMRI images on the subject’s anatomical image. Then, an immunohistochemical post-mortem atlas of the BG [12] was used to provide a mask image \( \text{BG}_{\text{MNI}} \) of the BG in the MNI space (2 mm isotropic voxel size), which was registered on each individual fMRI dataset using the inverse of the transformation \( T \), yielding one BG mask \( \text{BG}_{\text{ind}} \) per subject. This procedure finally yielded two (MRI datasets for each subject: one including the whole brain (wfMRI), and one comprising only cortical regions, the BG being masked out (mfMRI).

2.2. Identification of cortical networks

The first step of our method consisted of extracting cortical networks from the mfMRI data using sICA. More specifically, we used the NEDICA procedure [9], which proceeded in two steps: it first computed spatial independent component analysis (sICA) decomposition on each individual fMRI data independently, and then used hierarchical clustering on all individual ICA components to define group maps. The resulting group maps characterized the functional

1http://www.fil.ion.ucl.ac.uk/spm/software/spm5/
networks. Importantly, NEDICA provided information at both the group and the individual levels. At the group level, it provided one map per network; at the individual level, each spatial ICA component and corresponding temporal component was associated to one group map (and, therefore, one network); conversely, each group map (and, therefore, each network) was related to individual time courses that are characteristic of the network for those individuals.

In our case, since we applied NEDICA to mfMRI data, the method was not influenced by the behaviour of the BG and no group map contained voxels belonging to these structures. To test the validity of the results obtained using such an approach, we compared them with the networks identified using NEDICA on the whole dataset (i.e., wtMRI). The spatial similarity derived from spatial correlation of the networks extracted from wtMRI and mfMRI data was assessed using multidimensional scaling (MDS). The power spectra were also compared as follows. We first computed the power spectrum of each individual temporal ICA component. The power spectrum of a given network was then obtained as the average of all individual power spectra that were related to that network. Then, for each mfMRI network, we computed a “match-correlation”, which was the correlation between the power spectra of that mfMRI network and one wtMRI network that was matched with it by an expert based on their spatial similarity.

### 2.3. Identification of the corresponding subcortical components

The second step of our method consisted of complementing the cortical networks with their subcortical components. To this end, we assumed that the time courses of BG regions that were part of a given network were correlated to those of the cortical regions of the network. For each subject, the individual time components of all networks extracted by NEDICA were used as regressors in a general linear model (GLM) applied to data in the BGmask mask. This analysis, carried out with SPM5 [13], yielded a parametric map per regressor, reflecting how the time course of each voxel in the mask was similar to that of the regressor.

A group analysis was then conducted for each network to identify the BG voxels that were reproducibly detected across subjects. All parametric maps were normalized to the MNI space with 2 mm isotropic voxel size using the transformation T. These normalized maps were then spatially smoothed with an isotropic Gaussian kernel (FWHM $8 \times 8 \times 8$ mm). The images were then masked using BGmask. The group analysis was performed using a Student's t-test to test the null hypothesis, that the mean across subjects of the parameter maps obtained at the individual scale for one functional network was zero. Voxels where this hypothesis was rejected at a $p < 0.001$ threshold (uncorrected for multiple comparisons) were considered to be reproducible across subjects and were assigned to the corresponding functional network.

This two-step approach allowed extracting networks including cortical obtained with NEDICA and basal ganglia regions obtained with a multiple regression and a group analysis.

### 3. RESULTS

Using NEDICA, 14 functional networks were extracted from mfMRI data and 16 from wtMRI data. Among these 16 networks, 14 were found to be very similar to the 14 extracted from mfMRI and were consequently labelled identically: one left and one right ventral attentional networks (LvATT, RvATT), one limbic network (LIMB), one network related to executive control (EXCTR), one salient network (SAL), two default mode networks (DM, DM2), two motor networks (MOT, MOT2), two visual networks (VIS, VIS2), one dorsal attentional network (dATT), one attentional-default network (DMATT) and another attentional network (ATT) [7, 10]. The two additional networks that were extracted from wtMRI datasets and could not be matched with mfMRI networks were: one pertaining to executive control and one including only subcortical structures such as the caudate nuclei, the putamen and part of the thalamus. Figures 1 and 2 show the default mode network and the motor network extracted by NEDICA using mfMRI and wtMRI; Figure 3 shows the network of subcortical structures extracted from wtMRI data. MDS analysis (Figure 4) shows the spatial similarity between the networks extracted from the two datasets. Regarding the power spectra, the “match”-correlations were all greater than 0.95, further confirming the similarity of sICA results from mfMRI and wtMRI data. Figure 5 shows the group maps resulting from the multiple regression analysis and corresponding to the default mode and the motor networks, respectively.

![Fig. 1. Default mode network obtained with NEDICA from mfMRI data (top row) or wtMRI data (bottom row).](image)

![Fig. 2. Motor network obtained with NEDICA from mfMRI data (top row) or wtMRI data (bottom row).](image)
4. DISCUSSION

In this paper, we proposed a novel method that extracts cortico-subcortical networks from fMRI data by first detecting cortical networks with sICA and hierarchical clustering on data where the BG have been masked, and then by complementing these cortical networks with their subcortical components using multiple regression on the BG data.

Unlike existing approaches, our method allowed the segregation of different subcortical regions that were specifically associated with functional large-scale networks. In particular, it detected new subcortical parts of the motor network such as the caudate nucleus and the putamen, and seemed to be more focused for the default mode network especially regarding the caudate nuclei.

NEDICA appeared to be particularly sensitive to the difference in BOLD signal that existed between BG and cortical regions and it was not possible to extract segregated components in BG structures. Indeed, the mean signal in the BG was 5.35% lower than that measured in the cortex, and the signal standard deviation in the BG was 11.81% higher than that measured in the cortex. Moreover, using NEDICA in the BG only was not possible because ICA requires some physiological noise to separate the different components. By contrast, multiple regression was able to separate the BG into areas that could be associated with different networks. In this perspec-
Fig. 5. Group map of the default mode (top row) and the motor (bottom row) subcortical components obtained by regression.

tive, our method seemed to better characterize functional cortico-subcortical loops than NEDICA. One possible reason why our approach succeeded where NEDICA failed could be that the fMRI signal within the BG is composed of two components: one that is rather homogeneous within the BG (due to either similar localization, anatomy, or metabolic/hemodynamic features) and another one that is specific of the functional network they belong to. The first component being larger than the second, sICA essentially segregates most of the BG from the cortex. By contrast, when using multiple regression on the time components of the cortical components, one does not consider the first part of the signal but rather focuses on the second part of the signal. Whether this assumption is accurate remains to be proved.

Some aspects of the proposed method still need to be improved, such as the subcortical mask used and the optimization of the GLM analysis. The BG found in this paper to belong to specific functional networks will have to be compared with functional regions of the atlas [12] to further assess our results. Nonetheless, the proposed method gives access to cortico-subcortical functional networks and is thus a promising technique to study specific pathologies which are known to be associated with dysfunctions of cortico-subcortical loops, such as the Huntington disease, the Parkinson disease, or the Tourette syndrome.

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6. REFERENCES


