CORSICA: Correction of structured noise in fMRI by automatic identification of ICA components

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Abstract

When applied to functional Magnetic Resonance Imaging (fMRI) data, spatial Independent Component Analysis (sICA), a data-driven technique that addresses the blind source separation problem, seems able to extract components specifically related to physiological noise and brain movements. These components should be removed from the data to achieve structured-noise reduction and improve any subsequent detection and analysis of signal fluctuations related to neural activity. We propose a new automatic method called CORSICA to identify the components related to physiological noise, using prior information on the spatial localization of the
main physiological fluctuations in fMRI data. As opposed to existing spectral priors, which may be subject to aliasing effects for long-TR datasets (typically acquired with \( TR > 1 \) s), such spatial priors can be applied to fMRI data regardless of the TR of the acquisitions. By comparing the proposed automatic selection to a manual selection performed visually by a human operator, we first show that CORSICA is able to identify the noise-related components for long-TR data with a high sensitivity and a specificity of 1. On short-TR datasets, we validate that the proposed method of noise reduction allows a substantial improvement of the signal-to-noise ratio evaluated at the cardiac and respiratory frequencies, even in the gray matter, while preserving the main fluctuations related to neural activity.

Key words: Physiological noise, functional Magnetic Resonance Imaging (fMRI), spatial Independent Component Analysis (sICA), noise reduction.

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1 INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a non invasive technique that uses BOLD (Blood Oxygen Level-Dependent) effect to explore neural activity [1]. BOLD signal depends on blood oxygenation, blood flow and blood volume variations due to neural hemodynamics [2]. The fractional changes in BOLD signal compared to baseline during tasks that involve primary or sensory motor areas are typically less than 5% but can be less than 1% for memory tasks or single-event fMRI studies [3]. Hence, the expected effects are small and it is therefore critical to improve the signal-to-noise ratio (SNR) of fMRI signals when analyzing the functional activity of the brain [4,5].

The major fluctuations of no interest that corrupt BOLD signal include rapid and slow head movements, physiological activity (breathing and heartbeat) and possible acquisition artifacts. It has been shown that physiological noise (respiratory and cardiac noise) is preponderant in gray matter (GM) and in cerebrospinal fluid (CSF) [6]. The effects due to respiration and heartbeat in fMRI have been described and are quite different. On the one hand, respiration induces two types of fluctuations. Susceptibility variations in the lungs during respiration cause small variations in the static magnetic field [7] and worse, movements of the chest induce movements of the head at the respiratory frequency [8], which is much more problematic in fMRI datasets. Moreover, respiratory effects depend on the breathing frequency and are preponderant in CSF pools such as the ventricles or the outline of the brain, but have however non negligible effects in the whole brain [9]. On the other hand, heartbeat induces blood flow variations and tissue movement, which are preponderant near major blood vessels while being almost negligible elsewhere [10].

Despite the fact that the origin of physiological noise and its effects on fMRI
acquisitions are well known, the correction of this noise is still an active field of investigation, especially on long-TR datasets (typically TR > 1 s). Various techniques have been tested so far to reduce physiological noise using either retrospective correction [11,12], digital filters [13], selection of physiology-related independent components [14] or regression using the general linear model with noise modelling [5]. Unfortunately, these techniques suffer from some important limitations. In [13], noise reduction was achieved by adapted digital filtering from cardio-respiratory monitoring signals, which might however suppress part of the fMRI signal related to neural activity, whose power spectrum was located in the aliased frequency bandwidth of cardio-respiratory signals. In [11] the cardio-respiratory monitoring signals was also used as priors for retrospective correction of the raw k-space data, which allowed one to process long-TR datasets. In [12] was then proposed a retrospective correction of the reconstructed images, without using any cardio-respiratory monitoring as priors but by hypothesizing that the cardio-respiratory effects remained quasi-periodic during the acquisitions. Smarter models of structured noise were used in [5] where a large panel of sources of structured noise (including low-frequency drifts, movements and physiological noise) were taken into account. However, such modelling is based on external cardio-respiratory monitoring that might miss some specific effects in fMRI data. Finally, in [14] was used spatial Independent Component Analysis (sICA), which has a great potential for identifying physiological noise patterns in fMRI datasets with a great flexibility [15]. However, the method could process only short-TR data because the physiology-related components were identified based on frequency priors that did not take aliasing effects in long-TR data into account.

So, to actually reduce the noise in fMRI data using a sICA decomposition, it is necessary to be able to identify noise-related components at any TR, without
the use of any time-frequency prior knowledge.

In this paper, we take advantage of the fact that the spatial distribution of physiological noise or head-motion signals is independent of the TR of the acquisitions. In particular, CSF pools such as the ventricles appear to act as detectors of head motion and physiology-related movements [10,9] and the major blood vessels (e.g. the basilar arteries) as detectors of cardiac activity. Such regions can be used as specific masks of interest, whose signals mainly characterize physiological noise and can be then extracted from the data itself. On the other hand, as sICA decomposition provides spatial components characterized by a specific time course, the sICA components whose time courses are significantly correlated to the aforementioned noise characteristic signals are considered to be related to structured noise and are set to zero. The new method presented hereafter makes no assumption on the time-frequency profiles of this structured noise. Consequently, a key feature of our approach is that it allows us to reduce the effects of physiological noise not only from short-TR series, but also from long-TR series. This method will be called CORSICA (CORrection of Structured noise using spatial Independent Component Analysis). It comprises three successive steps, namely sICA decomposition, selection of noise-related components and removal of those components.

The outline of the paper is as follows. In the next section, we describe in detail the different steps of the CORSICA method. In the second section, we present the context of validation and an application of the method on some real datasets. The proposed method is compared to a manual selection of noise-related components based on visual inspection for long-TR data, and to a selection based on spectral priors, using cardio-respiratory monitoring, for short-TR datasets. Then, the effects of CORSICA method are evaluated on short-TR datasets signals in terms of SNR improvement. In the third section,
we present the results of the different validation procedures, before discussing both the methodology and the application in the last section.

2 THEORY

2.1 Spatial Independent Component Analysis (sICA) and noise reduction

Independent Component Analysis addresses the problem of blind source separation and allows one to separate independent processes from a mixture of signals [16]. In the present context, fMRI data is hypothesized to be a linear mixture of different brain processes whose spatial distributions are time invariant and statistically independent. Even under such general hypotheses, spatial Independent Component Analysis (sICA) has proved its ability to decompose fMRI data into components that represent a specific brain phenomenon [15]. More precisely, sICA assumes the following linear model:

\[ X = AS, \]

where \( X \) is the \( T \times N \) matrix of fMRI time series with \( T \) time samples and \( N \) voxels; \( S \) is a \( K \times N \) matrix of \( K \leq T \) spatially independent sources (comprising \( N \) voxels each); \( A \) is the \( T \times K \) matrix of the \( K \) corresponding time courses (comprising \( T \) samples each).

In our context, sICA is aimed at separating physiology-related components and possible movement-related components from the other processes captured by the BOLD signal. To this end, the Infomax algorithm [17] as implemented in FMRLAB software\(^1\) is used to perform sICA on the fMRI datasets, with Principal Component Analysis (PCA) as a preprocessing step in order to whiten

\(^1\) http://www.sccn.usd.edu/fmrlab.
the data (without reducing the data dimension, i.e. $K = N$).

The spatial sources $\hat{S} = (\hat{S}_i)_{i=1}^K$ are estimated by computing a mixing matrix $W$ that represents a linear transformation of the data:

$$\hat{S} = WX.$$ 

Given the data $X$, the spatial sources $S$ are estimated by searching for the matrix $W$ that minimizes the mutual information between the spatial sources. The time courses $\hat{A} = (\hat{A}_k)_{k=1}^K$ corresponding to the estimated spatial sources $\hat{S}$ are then obtained straightforwardly as the columns of the inverse mixing matrix $W^{-1}$.

To reduce the physiological noise using such linear decomposition into spatially independent components, it is necessary to identify a subset $\hat{A}_{\text{noise}}$ of $\hat{A}$, which comprises components that are a good approximation of the noise fluctuations corrupting the fMRI time series. Assuming that a relevant subset $\hat{A}_{\text{noise}}$ of noise-related independent components has been selected, one can correct this structured noise using a hard thresholding in the sICA base that approximate the data [18]: the contributions of the noise-related components are set to zero and the data is reconstructed from the remaining components $\hat{A}_{\text{int}}$ (such that $\hat{A} = \hat{A}_{\text{noise}} \cup \hat{A}_{\text{int}}$) only, yielding:

$$\hat{X} = \hat{A}_{\text{int}}\hat{S}_{\text{int}},$$

$\hat{X}$ being the matrix of the data corrected for structured noise and $\hat{S}_{\text{int}}$ being the matrix of the spatially independent sources corresponding to $\hat{A}_{\text{int}}$. Obviously, the efficiency of physiological noise reduction based on sICA components critically relies on the quality of the selection of noise-related components.
2.2 Selection of noise-related components

The key issue remains the automatic selection of the components related to physiological fluctuations and possible head movements among all the independent components $\hat{A}$ calculated by sICA. This part of the CORSICA method involves three steps. First, a set of noise characteristic signals is defined by extracting time courses from regions that are known to exhibit major physiological fluctuations, and which are defined a priori as masks of interest (section 2.2.1). Then, independent components that explain (in terms of correlation) these noise characteristic signals are selected by using stepwise regression (section 2.2.2). Finally, the repetition of the previous procedure allows one to calculate for each component a score that discriminates the noise-related components from the others (section 2.2.3).

2.2.1 Noise characteristic signals

Parallel to sICA, one (or more) mask(s) of interest including regions where physiological fluctuations are known to be preponderant are manually delineated (i.e. around the ventricles and major blood vessels). The signals of the voxels belonging to those masks are considered to be characteristic of the physiological activity of the subject under study. This information is then available without any external monitoring.

Given the large spatial extent of the masks (typically between 500 and 1000 voxels), the number of characteristic signals is reduced further by clustering the voxels of each mask into $N_C$ clusters by using a conventional k-means algorithm, with distance $d$ between two voxels being a function of the correlation
between the time courses of the voxels [19]:

\[ d^2(z_i, z_j) = (1 - \text{corr}(z_i, z_j))^2, \]

where \( z_i \) and \( z_j \) are the time courses of voxels \( i \) and \( j \), respectively. This clustering allows one to define, from each mask, an arbitrary number of \( N_C \) small homogeneous clusters \( (R_i)_{i=1}^{N_C} \). From these \( N_C \) clusters of interest, \( N_C \) signals characterizing physiological noise are finally extracted by averaging the time courses in each cluster.

2.2.2 Stepwise regression

After sICA decomposition has been performed as described in section 2.1, the purpose is then to select, among the \( K \) temporal components \( \hat{A} = \{\hat{A}_1, \ldots, \hat{A}_K\} \), the components whose time courses explain the \( N_C \) noise characteristic signals defined in section 2.2.1. Let \( Y = \{Y_1, \ldots, Y_{N_C}\} \) be those characteristic signals. For each cluster \( R_i \) \((i = 1, N_C)\), we wish to select from \( \hat{A} \) a subset of independent components that explain its characteristic signal \( Y_i \). To this end, we use a stepwise regression procedure (stepwise forward-backward) [20], which is detailed in the appendix section. For each signal \( Y_i \), this iterative algorithm selects at each step a new independent component that is significantly partially correlated with \( Y_i \) (stepwise forward), and then removes the already selected components that are no longer significantly partially correlated with \( Y_i \), given the new set of selected components (stepwise backward). The procedure stops when no more significant component (according to a given statistical threshold, see the appendix section) is found in stepwise forward. This procedure is repeated for each signal \( Y_i \), finally yielding \( N_C \) subsets \( (V_i^1)_{i=1}^{N_C} \) of components for each mask or interest.

Moreover, to limit the potential variability introduced by the k-means cluster-
ing, which relies on a random initialization, the selection procedure (k-means clustering followed by stepwise regression) is repeated \( N_R \) times, leading to \( N_R \times N_C \) subsets of components denoted by \((V_j)_{j=1}^{N_R \times N_C}\). The influence of the number of repetitions \( N_R \) as the choice of the number of clusters \( N_C \) is studied hereafter.

### 2.2.3 Influence of each component in the masks of interest

We wish to remove from the data the major phenomena that influence the most clusters defined in each mask, which captures specific physiological activity. Indeed, to prevent us from false selection (i.e. the selection of components related to functional activity), only the components that exhibit the most influence in the masks are finally considered as noise-related. To do so, the influence of each component in each mask is evaluated by calculating the proportion of subsets \( V_j \) that contain this component (in other words, the frequency of selection of this component), denoted by \( F_q \). If more than one mask is available, \( F_q \) for a given component is calculated for each mask independently (because all masks may not capture the same type of fluctuations) and the final value of \( F_q \) for this component is the maximum \( F_q \) value across all masks.

The component selection is achieved by thresholding the distribution of the score \( F_q \). The independent components with suprathreshold scores are considered to be related to structured noise. Different thresholding strategies are considered in the following section. Once the components related to noise are identified, noise reduction of the fMRI dataset is achieved by reconstructing the data with all the other components only (the noise-related components are set to zero).
3 MATERIALS AND METHODS

The CORSICA method was validated on real datasets, acquired with both short-TR and long-TR, as described hereafter. Firstly, the component selection procedure was compared to a manual selection by visual inspection of the sICA components for long-TR datasets, and to a selection based on spectral priors for short-TR datasets. Secondly, the quality of CORSICA noise reduction was evaluated on short-TR datasets.

3.1 Real datasets

MR images were acquired on three right-handed volunteers with a 3T Bruker scanner at the fMRI center in Marseille (France), according to a protocol approved by the regional ethic committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, CCPPRB number RBM 01-04). For each subject, a high-resolution T1-weighted scan was first acquired (FOV: 256×230×182 mm with a 256×192×104 matrix size, TR/TE = 11.6/5.67 ms and $\alpha = 30^\circ$). Functional data were also recorded during three different conditions: continuous rest (R) consisting of remaining eyes closed, continuous motor task (C) consisting of performing with the left hand a finger sequence of 5 items at 2 Hz, and a block-design paradigm (B) alternating rest and the previous motor sequence task. For each subject, 7 long-TR datasets (1R, 4C, 2B) and 3 short-TR datasets (1R, 1C, 1B) were acquired. For long-TR datasets, 136 T2*-weighted volumes of 42 contiguous slices covering the whole brain were recorded (the in-plane FOV was 192×192 mm with a 64×64 matrix size and a 3×3 mm in-plane voxel size, TR/TE = 2333/30 ms and $\alpha = 81^\circ$). For short-TR datasets, as the number of slices that can be acquired is limited, 950 T2*-weighted volumes of 2 groups of 3 contiguous 3-mm-thick slices each
were recorded, one group centered on the motor cortex and the other on the ventricles (the in-plane FOV was 192×192 mm with a 64×64 matrix size and a 3×3 mm in-plane voxel size, TR/TE = 333/30 ms and α = 40°). Such a volume of interest allowed us, on the one hand, to obtain in the ventricles the prior information necessary to select noise-related components and, on the other hand, to assess the quality of the noise reduction in functional regions of the cortex. The heartbeat rhythm was recorded during both acquisitions by plethysmography, as well as the respiratory rhythm by using a respiratory belt, at a sampling rate of 100 Hz. The first 42 volumes of each short-TR run and the first 6 volumes of each long-TR run (corresponding to the first 14 seconds of acquisition) were discarded to account for T₁ saturation effects. The resulting raw data were corrected for slice-timing effects by using the SPM2 software², corrected for quadratic drifts by using linear regression, and mean corrected.

Two masks of interest were manually designed as prior on the T₁-weighted volume of each subject to serve as prior information for CORSICA: a mask comprising the first three ventricles to detect especially global and respiration-related movements, and a mask including the brainstem, comprising a part of the fourth ventricle and the basilar arteries to detect local cardiac fluctuations (see figure 2). These masks were then resliced at the spatial resolution of the functional images. For short-TR datasets, only one mask around the ventricles was used as prior information (since the brainstem was not in the field of view of these acquisitions).

² http://www.fil.ion.ucl.ac.uk/spm/spm2.
3.2 Validation of component selection

The components related to physiological noise are known to have typical time-frequency distributions (related to the physiological rhythms), which might be used to identify them, provided the acquisitions are sampled fast enough to avoid aliasing effect (if we hypothesize also that the signals related to physiology in fMRI datasets are stationary in time). Furthermore, these components also have typical spatial distributions described in [15]. Thus, it is possible to select the components related to structured noise by visual inspection of all components. In order to provide a basis of comparison to assess the CORSICA method, this visual identification was performed for all independent components sets calculated for all datasets\(^3\).

For each long-TR dataset (TR = 2333 ms), the first 60 components \(^4\) were visually inspected by an expert and classified into three groups (see figure 1 where all spatial components are z-corrected and thresholded at \(|z| > 2\) as in [15]). Group #2 comprised components related to physiological fluctuations or movements with major influence in the CSF pools (component number 4 in figure 1), near major blood vessels (component number 7 in figure 1) or in the outline of the brain, and whose corresponding time-course was well localized in the frequency domain. Group #1 comprised the components clearly related to functional activity, which exhibited a spatially organized network with a low-frequency (below 0.8 Hz) related time-course – for instance the activity-related component, which could be identified only for the block-design task (component number 8 in figure 1), or resting-state network components [21]

\(^3\) almost 100 components were calculated for the long-TR data and 900 for the short-TR data.

\(^4\) the components were sorted in the decreasing order with respect to the part of data variance they explained.
(component number 9 in figure 1). Finally, group #0 comprised all other components, some of them were organized neither in space nor in frequency, some exhibited structures related to acquisition artifacts – as some alternated positive and negative bands (component number 6 in figure 1) – and some others were partially structured in space but not well localized in frequency (this last category of components, illustrated by the component number 26 in figure 1, was the most difficult to classify).

For short-TR datasets (TR = 333 ms), the expert used an alternative strategy. Indeed, given the sampling rate, the physiological signals were not aliased in the Nyquist bandwidth and spectral priors could therefore also be used to select the components of interest. Then, in addition to visual inspection, we used the cardio-respiratory monitored signals as a reference to identify physiology-related components of group #2. These physiological signals were preliminarily band-pass filtered (0.5-1.5 Hz for the cardiac signal and 0.1-1.5 Hz for the respiration signal) and undersampled to a sampling frequency of 1/TR. The criterion for selecting the noise-related components was the coherence value $C$ (i.e. the correlation of the power spectra) between the reference monitored signals and the time courses of the components obtained from sICA decomposition. To do so, the power spectra of the time courses of all $K$ independent components were linearly regressed on the power spectra of the two physiological signals. An $F$-score was then calculated to test for the null hypothesis $H_0 : C = 0$. Each component for which this null hypothesis was rejected with a significance level $p < 0.001$ was considered to be related to physiology and included in group #2. Then, the first 60 components of each dataset, except those already classified in group #2, were visually inspected to identify the components clearly related to functional activity, which were included in group #1. All other components were included in group #0. This
expert selection was then used as a gold standard to assess the quality of the automatic selection procedure proposed in this paper.

The CORSICA selection procedure was then performed on the 21 long-TR datasets. Then, for each dataset, a score $F_q$ was assigned to each of the 60 first components as described in section 2.2.3. Ideally, one would expect this score to be high for the components of group #2 and lower for the components of group #1. Besides, the number of components selected depends on the value of the threshold, denoted by $t$ (i.e. one selects the components whose score $F_q$ exceeds the threshold $t$). Thus, the sensitivity of the CORSICA method was defined as the ratio between the number of components of group #2 selected by the CORSICA approach and the total number of components assigned to group #2 by the expert. The specificity of the method was defined as one minus the ratio between the number of components of group #1 selected by the CORSICA approach and the total number of components assigned to group #1 by the expert.

The sensitivity and the specificity of the selection method were studied by considering two thresholding strategies. On the one hand, we used an arbitrarily fixed threshold $t'=0.25$ for all datasets. On the other hand, we used an adaptive threshold $t^*$ for each dataset, whose value was automatically determined by using Otsu’s algorithm [22]. This algorithm consists in dividing, for each dataset, the histogram of $F_q$ scores in two classes by minimizing the inter-class variance. It then allows one to separate automatically the distribution of the scores $F_q$ associated to group #1 from the distribution of the scores associated to group #2. For these two thresholding approaches, two reference thresholds were also defined, based on the expert’s classification. On the one hand, a dataset reference threshold $t^*_{ref}$ was defined for each dataset, as the upper $F_q$ value for the components of this dataset classified in group #1 by
the expert. On the other hand, a global reference threshold $t^f_{ref}$ was defined as the maximum value of $t^r_{ref}$ across all datasets.

### 3.3 Evaluation of noise reduction

Once the physiology-related components were identified, noise correction consisted of reconstructing the data with all the other components only. We then studied the effect of this correction on short-TR datasets, for which cardiorespiratory rhythms are well localized in the frequency domain. On the one hand, we studied global effects by computing the variations of the variance between uncorrected and corrected data in the cerebrospinal fluid (CSF), in the gray matter (GM), and in the white matter (WM) segmented by using the SPM2 software:

$$vvar(\hat{X}) = \frac{\text{var}(X) - \text{var}(\hat{X})}{\text{var}(X)}.$$

On the other hand, to evaluate more precisely the efficiency of the CORSICA method in the GM, we computed the relative power in the cardiac frequency band ($POW_c$) and in the respiratory frequency band ($POW_r$) of fMRI signals in the GM before and after noise correction respectively:

$$POW_c = 20 \log \left( \frac{\sum_{\nu \in B_c} (ps(\nu))}{\sum_{\nu \in B_{ni}} (ps(\nu))} \right),$$

$$POW_r = 20 \log \left( \frac{\sum_{\nu \in B_r} (ps(\nu))}{\sum_{\nu \in B_{ni}} (ps(\nu))} \right),$$

where $\nu$ denotes the frequency, $ps(\nu)$ is the average power spectrum of the fMRI data in the GM, $B_c$ (resp. $B_r$) is the cardiac (resp. respiratory) frequency band of width 0.1 Hz centered, for each dataset, on the main cardiac (resp. respiratory) frequency captured by monitoring (respiratory rhythms were measured from 0.2 to 0.45 Hz and cardiac rhythms from 0.9 Hz to 1.2
Hz), and \( B_m \) is the [0.6-0.7 Hz] bandwidth, in which we assume no influence from neither cardiac nor respiratory rhythms.

4 RESULTS

4.1 Selection of noise components

As CORSICA should not remove any functional effects from the data, the specificity of the method must be equal to one. We therefore studied the influence of the parameters \( N_C \) and \( N_R \) on the sensitivity of the CORSICA method for the threshold value \( t^*_\text{ref} \) referred to as the optimal sensitivity. Figure 3 shows the average optimal sensitivity for different values of \( N_C \) and \( N_R \), calculated firstly on the 60 first components and, secondly, on the 20 first components. It appears that the maximum sensitivity was reached for \( N_C \geq 15 \) and \( N_R \geq 3 \). As the higher \( N_C \) and \( N_R \), the longer the score calculation time, we chose \( N_C = 15 \) and \( N_R = 3 \) for all tests throughout the study. Furthermore, for these values of \( N_C \) and \( N_R \), the average sensitivity reached 0.85 on the 60 first components and 0.98 on the only 20 first components. This suggests that the method seems, as expected, more sensitive on the components that explain the most data variance.

We then studied more precisely the sensitivity and the specificity of component selection on both long-TR and short-TR datasets, and evaluated the influence of the threshold \( t \). Figure 4 shows that the calculated score \( F_q \) allowed us to separate group #2 (of components to be removed) from group #1 (of components to be retained) on long-TR datasets as well as on short-TR datasets. The fixed threshold of reference \( t^*_{\text{ref}} \) is determined here for long-TR datasets \( (t^*_{\text{ref}} = 0.20) \) and for short-TR datasets \( (t^*_{\text{ref}} = 0.24) \). The discrimi-
nation between the two groups appears to be better on the 20 first components (explaining the most data variance).

To evaluate the relevance of the score $F_q$ for identifying components related to structured noise, we calculated the average sensitivity of the method across short and long-TR datasets for the thresholds $t^f = 0.25$ and $t^*$ compared to the references $t^f_{ref}$ ($t^f_{ref} = 0.20$ for long-TR datasets and $t^f_{ref} = 0.24$ for short-TR datasets) and $t^*_{ref}$. On the one hand, figure 5 shows the distribution of $t^*$ compared to the optimal threshold $t^*_{ref}$ and the chosen value $t^f$ compared to the optimal value $t^f_{ref}$. On the other hand, table 1 shows the average sensitivity of the component selection using the four types of thresholding (the specificity was equal to one for all datasets for the four thresholding approaches, in other words, no component belonging to group #1 was selected). For the fixed threshold $t^f = 0.25$ the sensitivity of the method ranged from 0.45 to 0.65 (long-TR datasets) and from 0.7 to 0.89 (short-TR datasets) when considering the first 60 components, and reached 0.71 to 0.89 (long-TR datasets) and 0.76 to 0.93 (short-TR datasets) when considering only the first 20 components. Besides, as the values of $t^*_{ref}$ are scattered from 0 to 0.24 for long and short-TR datasets (see figure 5), choosing a unique threshold is obviously not the best strategy. In the opposite, for the optimal threshold adapted for each dataset, $t^*_{ref}$, the mean sensitivity of the method reached 0.87 on average on all datasets (both short and long-TR datasets) when considering the first 60 components, and 0.96 when considering only the first 20 components. Then, the use of the automatic adaptive threshold $t^*$, by using Otsu’s algorithm to separate the component scores of group #2 from those of group #1 for each dataset, allows one to increase the sensitivity of the selection compared to that obtained with the threshold $t^f$. So, even though the sensitivity of the component selection method using the adaptive automatic thresholding may
not reach the optimal sensitivity, Otsu’s method yields a sensitive selection while avoiding the inclusion of some components related to functional activity.

4.2 Effects of noise reduction

The effects of noise reduction were studied on the short-TR datasets that were processed using the automatic adaptive threshold. Table 2 shows the variations of the variance between uncorrected data and corrected data in the CSF, the GM and the WM. These results show that the correction was preponderant in the CSF, as expected, but was also efficient in the GM, where the correction of the structured noise is necessary to capture cleaner functional signals. On the other hand, figure 6 shows the values of \( POW_c \) and \( POW_r \) for uncorrected and corrected data for each subject. \( POW_c \) and \( POW_r \) decreased on average for the three subjects by 86% and 62% respectively. Finally, figure 7 illustrates the effects of noise reduction on the average power spectrum in the GM, for the block-designed dataset of the first subject. The respiratory (around 0.38 Hz) and cardiac (around 1 Hz) effects decreased whereas the part of the signals related to the task (the paradigm frequency was 0.018 Hz) remained unchanged after correction. This confirms that the CORSICA method allows one to reduce specifically cardio-respiratory effects while preserving the functional part of the signal.

5 DISCUSSION

In brief, the method relies on two key parts: the separation of the components related to structured noise by sICA (a data-driven method), and the use of structured noise signals extracted from the data itself (using the CSF and the
major blood vessels as detectors of structured noise) as references for selecting the components of interest.

Firstly, the main advantage of using sICA is that it does not require any assumption on the time and frequency profiles of the processes to extract and has proven its ability to identify some processes of interest from fMRI datasets. The CORSICA approach is able to remove some undesirable effects due to cardio-respiratory activity or to head movements even if they are very distorted (for instance, when the subject stops breathing during short periods of the acquisition or breathes irregularly due to stress). Besides, it appears that the correction of noise-related effects is obviously narrowly linked to this ability of sICA to separate physiology-related phenomena from other brain processes. Thus, if the processes related to neural activity and those related to noise remain mixed into several components, the method of selection we proposed may suppress part of the functional signals of interest.

Secondly, the CORSICA approach provides a procedure to select the components related to structured noise, by using spatial priors. The use of spatial priors has two main advantages. On the one hand, it allows one to apply the method not only on short-TR datasets (where physiological rhythms are not aliased in the spectral bandwidth of interest), but also on long-TR datasets, which are more commonly used in fMRI studies. On the other hand, it avoids assumptions on the stationarity or the frequency localization of physiological signals, such as those used in many other methods of noise correction in fMRI. Yet, the design of the masks of interest seems to be a sensitive part of the procedure because, since such masks must allow one to select only signals related to noise but not to other processes of interest on the functional point of view. The method was tested with two manually designed masks of interest for long-TR datasets, one consisting of the three first ventricles and the other
comprising a part of the brainstem and including some major blood vessels. It would be possible to replace the manual design of the masks by an automatic one (for example, the first mask may be built using a procedure based on CSF segmentation). Alternatively, the masks of interest may be designed on a template (provided by MNI [23] for instance) once and for all. These masks may be then resampled in the individual functional raw data space by applying an inverse normalization transformation. Finally, from these masks, the use of k-means clustering and the extraction of the mean time course in each cluster makes sense, in that it favors only consistent effects in this specific cluster, while removing marginal ones. The use of the mean time course in each homogeneous cluster to define noise characteristic signals allows also to increase the signal-to-noise ratio of these signals. So, since no extreme precaution was taken when designing the masks, these last steps decrease the effects of the possible inclusion of voxels that would exhibit other phenomenon than the expected ones (due to the partial volume effect for instance), and the designing step appears less crucial than expected.

After these two main steps of the CORSICA method, each component is associated with a score $F_q$ that reflects its involvement into the masks of interest. Thus remains the problem of choosing the threshold for the distribution of this score, which should ideally be adapted for each dataset. An automatic thresholding using Otsu’s approach allows one to select the most of noise-related components, however it appears to remain too conservative in several cases (see table 1). Thus, in addition to the index $F_q$, another index calculated from time-frequency priors or other criteria (including visual ones) may be used to complete and refine the selection. Such refinement would also allow

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5 The individual normalization parameters, used to resample the fMRI volumes into the space defined by the template, are calculated independently.
one to catch (and remove) some effects that CORSICA does not specifically search for, such as some acquisition artifacts (which are also identified by sICA separation). This approach may be called the semi-automatic CORSICA procedure.

It appears that the main limitation of the proposed method is the separation of independent components. Indeed, one has no control on the quality of the separation, particularly if there remains some mixture of functional effects with structured noise processes. To improve the separation between the physiological phenomena one wishes to remove and the phenomena related to neural activity of interest, some prior information may be introduced to guide the separation [24].

Finally, the strategy of evaluation of the CORSICA method is certainly perfectible. An efficient and quantitative evaluation of the noise reduction on real datasets can be achieved only if the fMRI signals components are known exactly, which is far to be true. Therefore, an alternative way to proceed would be to use synthetic datasets that would take into account all the parameters, the physics of acquisition, physiological fluctuations or neuronal activation for instance, to generate simulated fMRI datasets. Even if some MRI simulators have been recently proposed [25], there exists no fMRI simulator generating synthetic BOLD $T_2^*$-weighted images, that captures all the sources of variations such as activation, physiological noise, movements or acquisition artifacts. This kind of simulator would allow one to really compare the different methods of noise reduction in fMRI.

Last but not least, despite these limitations, the structured-noise reduction in fMRI appears to be a key preprocessing step, particularly in functional connectivity studies [26]. Indeed, functional connectivity is based on the measure
of correlation between two regional time series [27]. Yet, as physiological fluctuations or movements induce spurious correlations between distant regions in the brain, it remains therefore impossible to interpret any correlation between two regions as a pure functional link [4]. This artefactual confounding correlation can be problematic when comparing several correlation values, for instance the correlation value between a region in the primary motor cortex and a region in the premotor cortex, at different stages of a motor learning process. As the level of correlation due to structured noise may vary from one step to another (which can be a few weeks apart), the comparisons are no more meaningful. As the CORSICA method allows one to remove the main cardio-respiratory effects from the fMRI datasets, it is expected to be a valuable preprocessing step for functional connectivity studies.

6 Conclusion

In this paper, we proposed a new method called CORSICA for physiology-related noise reduction in fMRI, which selects noise-related ICA components based on spatial priors. We showed that the method provides a score for each component, which can be used not only in a fully-automatic procedure by automatic thresholding, but also in a semi-automatic procedure, as the first step of a refined visual selection. This noise correction approach, by removing selected independent components, proved to be efficient on long-TR datasets as well as on short-TR datasets, in that it reduced the cardio-respiratory effects in functional brain areas. The main possible improvement of the method is to adapt a technique of data separation guided by spatio-temporal priors. This would allow to do the separation and the selection of undesirable effects at the same time. Finally, as CORSICA led to a global decrease in relative power
of the fMRI signal in the respiratory and cardiac frequency bands in the gray matter, where the functional part of the data is corrupted, it is expected to be an important preprocessing step for functional connectivity studies in fMRI.

Appendix

**Stepwise regression**

This section describes the stepwise regression algorithm. At step $n$, let $V^1$ be the set of the $q$ already selected components and $V^2$ the set of components that have not been selected yet ($\hat{A} = V^1 \cup V^2$). The procedure starts with $V^1$ being empty and $V^2 = \hat{A}$. To select a new component (forward selection), one considers the following $K - q$ models $V^1_{+j}$ as candidates for the new set of selected components:

$$V^1_{+j} = V^1 \cup \hat{A}_j,$$

for each $\hat{A}_j$ in $V^2$.

Then, one tests for the significance (see the next section for the details on the significance tests) of the large model $V^1_{+s}$ (of cardinal $q + 1$) conditional on the smaller one $V^1$ (of cardinal $q$). The most significant model $V^1_{+s}$ according to a given statistical threshold is selected. $\hat{A}_s$ is then added to the set of selected components, $V^1$ is set to $V^1_{+s}$ and $V^2$ is set to $V^2 \setminus \{\hat{A}_s\}$. Once the new component is added to the set of selected components, one wishes to remove redundancy in this new subset. Thus, one tests whether each component in this new subset $V^1$ is still significant with respect to the other components of the subset (backward elimination). To do so, the following $q$ models $V^1_{-j}$ are considered as candidates for the new set of components:

$$V^1_{-j} = V^1 \setminus \{\hat{A}_j\},$$
for each $\hat{A}_j$ in $V^1 \setminus \{ \hat{A}_s \}$.

Then, one tests the significance of the large model $V^1$ (of cardinal $q + 1$) conditional on the smaller ones $V^1_{-j}$ (of cardinal $q$) and the components that are no more significant are removed, according to the same threshold as that used for the forward selection.

**Testing for the significance of a component**

The significance of a given component in a model is tested by evaluating the variance explained by the model that includes this component (the so-called large model $V_l$) with respect to the variance explained by the model without this component (the so-called small model $V_s$). Let vector $Y$ be a signal to explain, $Y$ is orthogonally projected onto the subspace spanned by $V_l$ and onto the subspace spanned by $V_s$, successively:

$$Y = \hat{Y}_l + \varepsilon_l$$

and

$$Y = \hat{Y}_s + \varepsilon_s,$$

where $\hat{Y}_l$ (resp. $\hat{Y}_s$) denotes the orthogonal projection of $Y$ onto the subspace spanned by $V_l$ (resp. $V_s$) and $\varepsilon_l$ (resp. $\varepsilon_s$) is the residual. Then, the following partial correlation is calculated:

$$R^2_{\text{partial}} = \frac{R^2_l - R^2_s}{1 - R^2_l} (K - q - 1),$$

where

$$R^2_l = \frac{\text{var}(\hat{Y}_l)}{\text{var}(Y)},$$

$$R^2_s = \frac{\text{var}(\hat{Y}_s)}{\text{var}(Y)}.$$
This partial correlation value quantifies the proportion of the total variance that is explained by $V_l$ but not by $V_s$, and follows an $F$-distribution with 1 and $K-q-1$ degrees of freedom [28]. A component $A_i$ is then considered significant in the large model $V_l$ if one can reject the null hypothesis $H_0 : R_{\text{partial}}^2 = 0$ with $p < 0.001$.

References


| Subj. 1 | 0.89 | 0.97 | 0.68 | 0.85 | 0.63 | 0.84 | 0.55 | 0.78 |
| Subj. 2 | 0.86 | 0.98 | 0.71 | 0.93 | 0.71 | 0.92 | 0.65 | 0.89 |
| Subj. 3 | 0.88 | 1.00 | 0.54 | 0.81 | 0.52 | 0.78 | 0.45 | 0.71 |
| Mean    | 0.88 | 0.98 | 0.64 | 0.86 | 0.62 | 0.84 | 0.55 | 0.79 |

| Subj. 1 | 0.91 | 1.00 | 0.79 | 0.86 | 0.73 | 0.80 | 0.70 | 0.76 |
| Subj. 2 | 1.00 | 1.00 | 0.89 | 0.93 | 0.89 | 0.93 | 0.89 | 0.93 |
| Subj. 3 | 0.70 | 0.84 | 0.70 | 0.84 | 0.70 | 0.84 | 0.70 | 0.84 |
| Mean    | 0.87 | 0.95 | 0.79 | 0.88 | 0.77 | 0.86 | 0.76 | 0.84 |

Table 1

Average sensitivity on long-TR datasets and short-TR datasets for each subject, calculated on the first 60 components and on the first 20 components using either $t^*_\text{ref}$, $t^*$, $t^f_{\text{ref}}$ or $t^f$. 

30
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<th>GM</th>
<th>WM</th>
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<tr>
<td><strong>Mean</strong></td>
<td><strong>0.19</strong></td>
<td><strong>0.12</strong></td>
<td><strong>0.11</strong></td>
</tr>
</tbody>
</table>

Table 2

*Variations of the variance (in %) in cerebro-spinal fluid (CSF), gray matter (GM) and white matter (WM) for short-TR datasets.*
Fig. 1. From top to bottom, components of subject 2 belonging to groups #2, #1 and #0. For each component are shown (a) four slices of the spatial component (z-corrected and thresholded at $|z| > 2$) superimposed on the $T_1$-weighted images (the positive values are shown in orange and the negative ones in blue), (b) the corresponding time-course and (c) its Gaussian window Fourier transform.
Fig. 2. The two regions of interest used for subject 2: the brainstem (left) and the ventricles (right).

Fig. 3. Long-TR data: average optimal sensitivity (i.e. sensitivity calculated by using the threshold of reference $t^*_{\text{ref}}$) function of $N_C$ on the 60 first components (a) and on the 20 first components (b), for $N_R$ equal to 1, 2, 3, or 5.
Fig. 4. Distribution of $F_q$ of the components assigned by the expert to group #1 and to group #2, among the 60 first components (left) and among the 20 first components (right) for all long-TR datasets (a) and all short-TR datasets (b). For each distribution, the box has lines at the lower quartile, median and upper quartile values, and the whiskers are lines extending from the minimum value to the maximum value. The horizontal line corresponds to the fixed threshold of reference $t_{\text{ref}}^j$, that is the lower value of $t$ for which the specificity is equal to one for all datasets.
Fig. 5. Distribution of $t^*_\text{ref}$ and $t^*$ and values of $t^I_{\text{ref}}$ and of $t^I$ for Long-TR data (a) and Short-TR data (b). The boxes are described in the caption of figure 4.

Fig. 6. Short-TR data: $\text{POW}_c$ (left) and $\text{POW}_r$ (right) mean values for each subject before (black) and after correction (gray).
Fig. 7. Block-designed short-TR data, subject 1: average power spectrum in the GM before (top) and after (bottom) correction. Interesting parts of the spectrum are scaled independently to show the influence of the block paradigm (at 0.018 Hz) on the left and the influence of the cardiac (around 1 Hz) and respiratory (around 0.4 Hz) effects on the right.