Robust ICA analysis for model-free functional connectivity detection

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ABSTRACT

Resting state oscillations have been detected in functional MRI studies, and appear to be synchronized between functionally related areas. It has also been shown that these synchronized oscillations decrease in some pathological states. Thus, these fluctuations are important as a potential signal of interest, which could indicate connectivity between functionally related areas of the brain. A current challenge is to detect these patterns without using an external reference. ICA analysis is a promising model-free technique that finds the independent components in a data set. A drawback to using ICA is the possibility of convergence problems in the presence of noise, and signal mixing across components. This work utilizes a recently developed denoising method as a preprocessing step to condition task and resting state functional MRI data for ICA analysis. The advantages of this approach include increased reliability of ICA results and allowing region specific signal patterns to be separated using a model-free analysis.

Keywords: magnetic resonance imaging, functional imaging, functional connectivity, ICA

1. INTRODUCTION

Recent studies in functional MRI have shown slowly varying fluctuations that are temporally correlated between functionally related areas. These low-frequency oscillations (<0.08 Hz) seem to be a general property of symmetric cortices, and have been shown to exist in the motor, auditory, visual, and sensorimotor systems, among others[1-3]. Thus, these fluctuations agree with the concept of functional connectivity: a descriptive measure of spatio-temporal correlations between spatially distinct regions of cerebral cortex. Several recent studies have shown decreased low-frequency correlations for patients in pathological states (such as multiple sclerosis[4], or cocaine use[5]. Accordingly, low-frequency functional connectivity may be important as a potential indicator of regular neuronal activity within the brain.

A challenge is to detect and quantify these spatio-temporal patterns in functional imaging data without using an external reference. There is the obvious question of what reference waveform to use in a correlation analysis of resting-state data, where there is no external paradigm being presented. The use of investigator-defined regions of interest (ROIs) or "seed clusters" has been the primary method used in functional connectivity studies[1,2,6,7], in which the pixel timecourses in a particular slice are correlated with the ROI reference waveform to form functional connectivity maps. This use of "seed clusters" is not an optimal way of detecting functional connectivity, in that it is a) user-biased, and b) not applicable in cases where pre-supposed ROIs are not known or for which a task activating the ROI is unknown.

Independent component analysis (ICA) is a promising model-free technique that finds the independent components in a data set[8]. However, a drawback to using ICA is the possibility of non-convergence in the presence of noise. This work utilizes a denoising method as a preprocessing step to condition task and resting state fMRI data for ICA analysis. The advantages of this approach include ensuring the convergence of ICA iteration and allowing region-specific signal patterns to be separated using a model-free analysis.

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2. BACKGROUND

2.1. Independent Component Analysis (ICA)

Independent component analysis (ICA) is a more general form of PCA whereby higher order statistics are used in addition to second order moments, which PCA relies on, to determine the basis vectors[9]. Let v_i, i=1,…,m be the measured signals and s_j, j=1,…,r are the signals from independent components (ICs) with zero mean and unit variance. The basic problem in ICA is to estimate the mixing matrix A and the matrix of realizations of the independent components S such that the matrix of measured signals $\mathbf{V}=\mathbf{A}\cdot\mathbf{S}$. The major constraint of this problem is for r to be less than m. In most cases, r is assumed known and often r = m.

The basic algorithms for computing the independent components rely on measuring the non-Gaussianity of the different vectors within the whitened subspace of signals of interest. The most common method for this purpose is the use of the fourth central moment or kurtosis[10]. The value of kurtosis is zero for Gaussian random vectors while it assumes nonzero values for other distributions. Therefore, the iterative maximization of the kurtosis enables the non-gaussian components (or independent components) corresponding to the true underlying sources to be estimated. In this work, a fast fixed-point algorithm was used to perform this[9,10]. The matrix of data vectors V is first whitened using PCA. The whitened data matrix $\mathbf{X}$ is defined by $\mathbf{X}=\mathbf{M}\cdot\mathbf{V}=\mathbf{M}\cdot\mathbf{A}\cdot\mathbf{S}$, where $\mathbf{M}$ is the whitening matrix. The problem of finding an arbitrary full-rank matrix A is reduced to the simpler problem of finding an orthogonal matrix. Subsequently, this matrix can be used to compute the independent components as $\mathbf{S}=\mathbf{B}^{\mathbf{T}}\cdot\mathbf{X}$. In other words, we are looking for an orthogonal matrix $\mathbf{W}^{\mathbf{T}}$ such that the matrix $\mathbf{W}^{\mathbf{T}}\mathbf{X}$ is composed of good estimates of the independent components. To estimate all independent components, an orthogonalizing projection is added to the iteration to remove the previously estimated components.

Two strategies can be used to derive the independent components for fMRI data. The first relies on considering each input signal to represent a time course for a particular pixel and use the ensemble of time courses from all pixels to compute ICA. This approach is called temporal ICA. Alternatively, the points within each image can be arranged in a vector and the ensemble of such vectors from all images is analyzed using ICA. This approach, which is call spatial ICA, is the one of choice for this work since the nature of independent component spatial maps is similar to that of connectivity maps.

Note that in ICA there is no direct way to order the independent components based on their contribution, unlike the case of PCA, as a result of the whitening operation involved. In order to identify those independent components that provide the best discrimination between pathologies, we sort the independent components manually based on their comparison to the known anatomical connectivity in the brain.

2.2. Random Noise Suppression Using Spectral Subtraction

The poor signal-to-noise ratio (SNR) of fMRI data triggered several studies that address the denoising of such data. This denoising step is essential for subsequent analysis steps to work. In particular, in ICA, the main assumption is that the number of signals available is higher than the number of underlying independent sources. Given that each signal must contain an independent noise component in addition to the possible other physiological fluctuations and true activation components, denoising must be employed to reduce the number of effective noise components to satisfy the fundamental condition of ICA. The present techniques suffer from either the need to acquire substantially more data for averaging or the need to have an accurate model for the signal. Since the noise model can be accurately estimated from the data, a better way is to design a denoising strategy that depends only on the noise model. In this work, we use this approach and demonstrate its effectiveness as a preprocessing step to ICA.

The denoising technique relies on the spectra; subtraction class of denoising techniques, which is widely used in speech processing. This technique obtains the denoising signal power spectrum from the subtraction of noise power spectrum model from the power spectrum of the original signal. Then, the denoised signal is computed using magnitude reconstruction from the square root of this power spectrum. Simpler reconstruction can be obtained by using a phase estimated from phase of the Fourier transform of the original signal. We rely on the Rician noise model that accurately describes the fMRI data. The use of such denoising enables the subsequent use of ICA to be more robust computationally and enables the separation of different signal sources more efficiently.

Notice that the acquired k-space data consists of two quadrature components representing the real and imaginary parts of the signal. When both quadrature components belong to a zero-mean while Gaussian noise model, the resultant distribution for the magnitude is the Rayleigh distribution. When the component distributions have nonzero means, the magnitude belongs to the Rician distribution. This distribution depends on the value of the means of the component distributions. Given that these mean values are unknown for actual time courses (in fact their values represent the solution for the denoising problem), the actual distribution of each time point is also unknown. Nevertheless, the computation of the power spectrum can be shown to provide a simple expression of a constant component plus an impulse at the DC frequency. Even though this model looks similar to zero-mean white Gaussian noise power spectrum except for the additional impulse, the level of the constant component is not directly equal to the variance of the data. It can be shown that it depends in a complex manner on the mean values of the component distributions as well as the variance. When the magnitude of the mean is above five times the standard deviation of the noise, the distribution depends only on the variance of the noise (not equal to it though). Given that this case is the most common in fMRI, the level of this power spectrum was obtained from simulations that relate the calculated variance of Rician distributed points to the constant level of their power spectrum. Moreover, an additional control is provided to the user to set based on the performance of the subsequent ICA analysis and to account for the variance of the power spectrum estimate of the original signal. In this work, this control was set to the default value of unity to ensure consistency between different analyzed data sets.

3. METHODOLOGY

3.1. Spectral Subtraction

For denoising, the fMRI temporal signal will be modeled as sum of one deterministic component incorporating both the true signal and the physiological noise and an uncorrelated stochastic component. The noise power spectrum is estimated using the time courses of background pixels taken outside the slice of interest (and free of any ghosting). Assuming independence of the two components, the denoised signal power spectrum is obtained by spectrum subtraction of the noisy signal and noise power spectra. The estimated true signal is just the inverse Fourier transform of the magnitude of the denoised spectrum combined with the phase of the original spectrum. After applying this preprocessing step, the resultant data are better conditioned for further analyses.

3.2. Data Acquisition

A series of functional MRI experiments were performed on a 3.0 T Siemens Trio scanner (Siemens, Tubengin, Germany) using an echo-planar pulse sequence. The sequence acquired 280 images, with pulse sequence parameters were TR/TE/FA/FOV of 750 ms/34 ms /50°/22 cm. Five 5 mm thick axial slices were acquired in each TR, with an in-plane resolution of 3.44 mm x 3.44 mm.

Healthy human volunteers were studied under conditions of activation and rest. A sequential finger-tapping motor paradigm (21 seconds fixation, 21 seconds task, 5 repeats) was implemented for the activation data. The paradigm cues were visually presented to the subjects using Presentation (Neurobehavorial Systems, Albany, CA). Resting state data was acquired while the subjects were inactive (lying still, with fixation cross being presented), and matched to the duration of the activation data (210 seconds total). The respiratory and cardiac rhythms of the subjects were recorded during all runs, using an Invivo physiological monitoring unit connected to a PC data acquisition board. In-house MATLAB code sampled the physiological rhythms at a sampling rate of 200 Hz, triggered off the start of the MRI scans by a TTL pulse output by the scanner.

3.3. Data Analysis

ICA analysis was done on the task and resting-state data, with and without prior spectrum subtraction. This was done using the fixed point algorithm implanted in the FastICA[10] toolbox in MATLAB. The resultant components were analyzed for significant spatio-temporal patterns, especially those corresponding to either the task paradigm timing or the anatomically identified motor regions. Functional connectivity related components were identified based on simultaneous assessment of the frequency content of the time series and spatial pattern of the IC maps.

4. RESULTS

The standard ICA analysis was first performed on the task activation data. The ICA component corresponding to the task timing is shown in Figure 1 to be divided among several components, with no component having extensive spatial coverage in the motor region. Spectral subtraction was then performed on the data, and ICA analysis performed again. As seen in Figure 2, the motor component is now seen to be strongly occuring in one component, with a smoother temporal timecourse, and activity in the spatial components covering the bilateral motor areas. Figure 3 compares the third slice of the corresponding spatial components for the temporal components displayed in Figures 1 and 2. No apparent motor patterns can be seen before denoising, while the bilateral activation is strong after denoising. Thus, denoising using the spectral subtraction technique can prevent the mixing of signals across components due to the presence of noise.

Standard ICA analysis was then performed on the resting-state data. One run resulted in non-convergence of the ICA algorithm (after 1000 iterations). A second ICA did converge, with the component shown in Figure 4 identifed as the component corresponding to functional connectivity in the motor cortex. Spectral subtraction and ICA was then done, and a consistent spatio-temporal pattern was seen in one component in the denoised data, as shown in Figure 5. As compared to Figure 3, the bilateral motor is more pronounced, and the temporal timecourse is much smoother. Thus, the denoising algorithm can also enhance a temporal component, and sharpen its associated spatial pattern.

5. CONCLUSIONS

Spectral subtraction reduced the noise in the data, which resulted in improved ICA convergence and identification of functionally-related components. Improvements were seen in block task activation and in resting-state functional MRI studies, demonstrating the wide applicability of this approach to imaging studies. The results confirm the robustness of the new strategy and demonstrate its value for detecting functional connectivity patterns.

It is also of interest that the spectral subtraction denoising technique preserves the subtle low-frequency functional connectivity signal. Since the noise estimate is formed using the background voxels in the MRI images, the functional connectivity cannot be a background noise source, otherwise it would be suppressed by the spectral subtraction technique. This agrees with prior work that indicates functional connectivity might reflect "resting state" neuronal processing[1,7], though more work needs to be done to verify the source of the connectivity.

The denoising step combined with ICA provides a robust model-free method for functional connectivity detection. Functional connectivity patterns in the motor network were detected without use of external reference. This allows resting-state functional connectivity analysis without the need for a prior task activation scan to denote functional ROIs, as is done in the standard method. Also, all independent components are found in the denoised ICA analysis, while the standard functional connectivity analysis only generates a correlation map based on the seed cluster ROI waveform. Thus, all interesting signals can be investigated using the denoised ICA approach.

Future extensions to this work will examine functional connectivity in other functional networks, the isolation and analysis of the physiological noise in the data, the classification of all the independent components found for each data set, and ranking the components using different approaches such as canonical correlation analysis to make this process automated.

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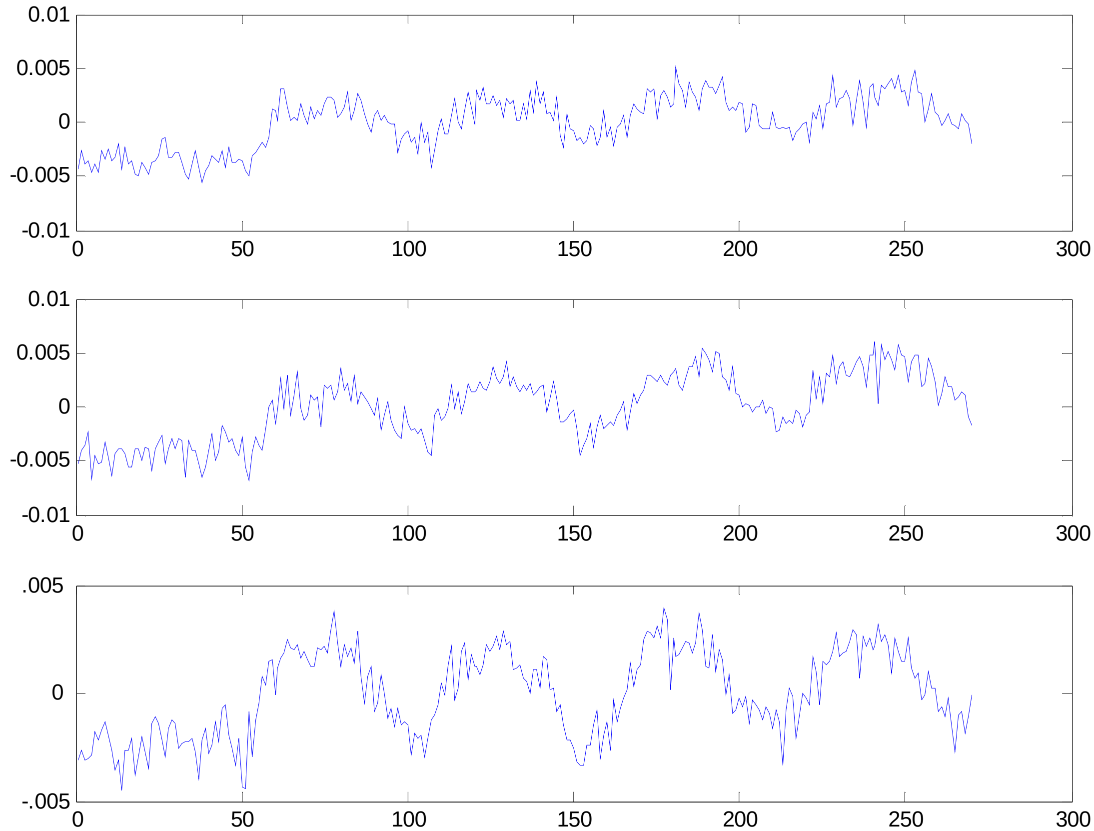

Figure 1. Multiple ICA temporal components identified as task functional connectivity in the motor network without denoising.

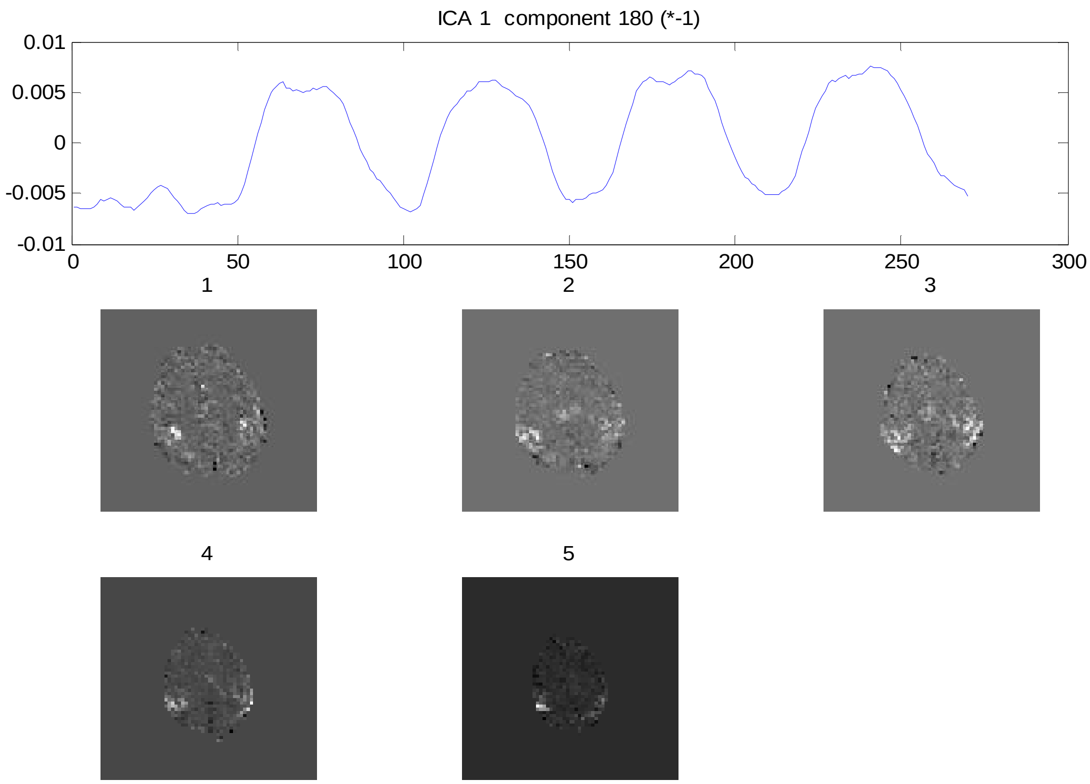

Figure 2. Temporal and spatial ICA component identified as task functional connectivity in the motor network after spectral subtraction.

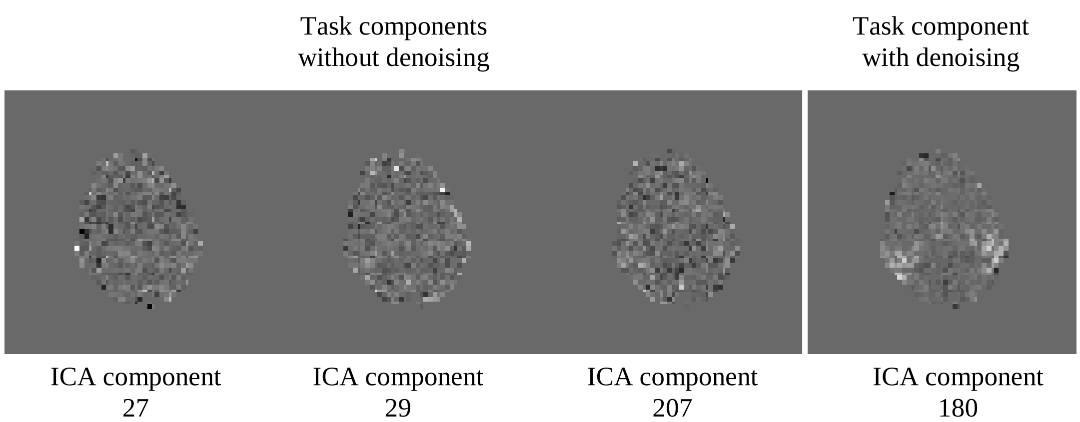

Figure 3. Comparison of the spatial patterns in the third slice for the components from Figures 1 and 2.

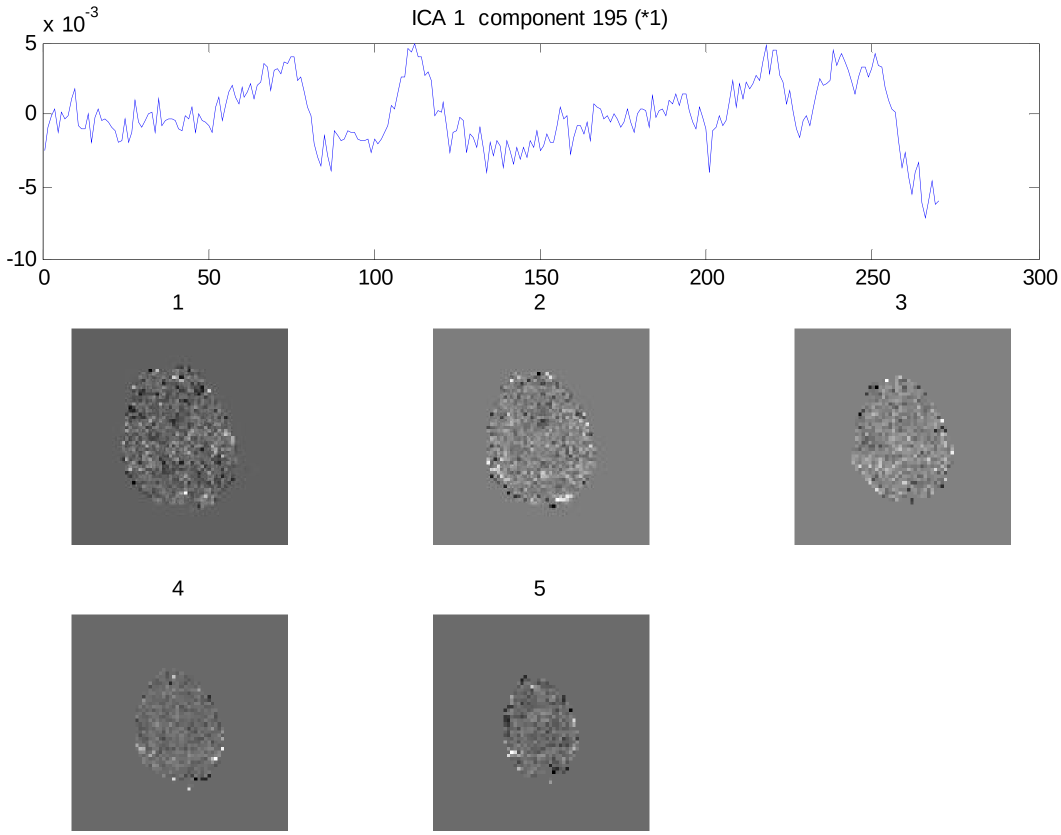

Figure 4. Temporal and spatial ICA component identified as resting state functional connectivity in the motor network without denoising.

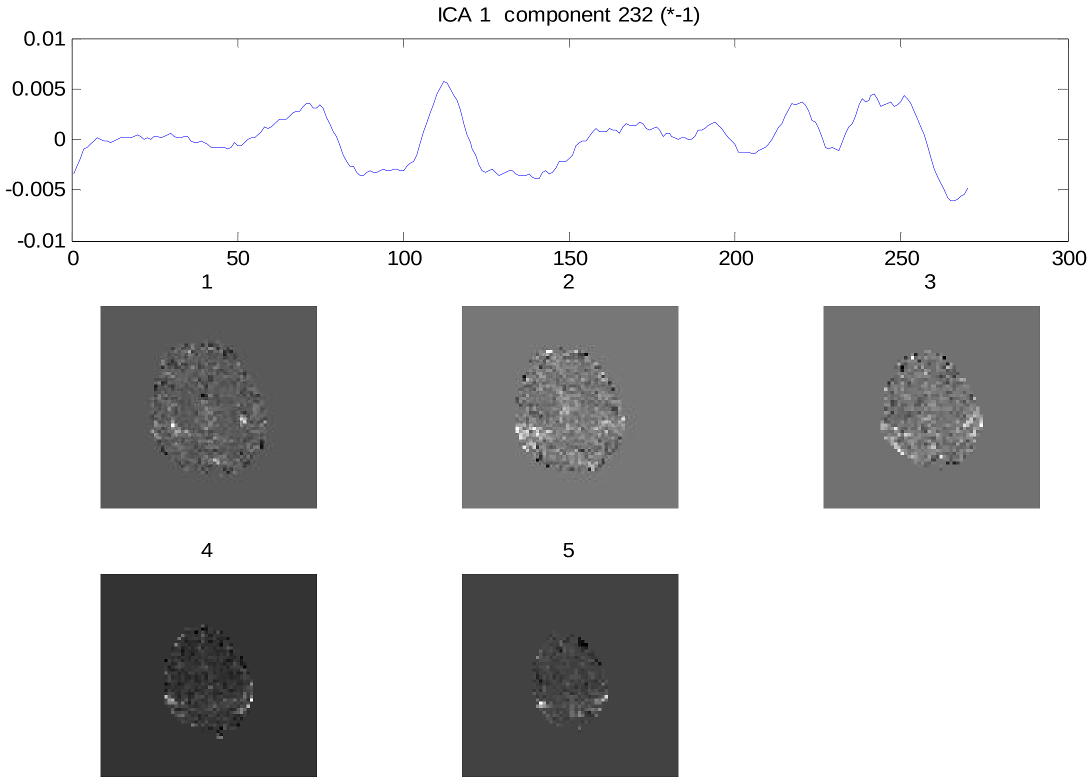

Figure 5. Temporal and spatial ICA component identified as resting state functional connectivity in the motor network after denoising.