Brain Activation Inhomogeneity Highlighted by the Isotropic Anomalous Diffusion Filter

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Abstract— **The visual appealing nature of the now popular BOLD fMRI may give the false impression of extreme simplicity, as if the the functional maps could be generated with the press of a single button. However, one can only get plausible maps after long and cautious processing, considering that time and noise come into play during acquisition. One of the most popular ways to account for noise and individual variability in fMRI is the use of a Gaussian spatial filter. Although very robust, this filter may introduce excessive blurring, given the strong dependence of results on the central voxel value. Here, we propose the use of the Isotropic Anomalous Diffusion (IAD) approach, aiming to reduce excessive homogenity while retaining the natural variability of signal across brain space. We found differences between Gaussian and IAD filters in two parameters gathered from Independent Component maps (ICA), identified on brain areas responsible for auditory processing during rest. Analysis of data gathered from 7 control subjects shows that the IAD filter rendered more localized active areas and higher contrast-to-noise ratios, when compared to equivalent Gaussian filtered data (Student t-test, $p<0.05$). The results seem promising, since the anomalous filter performs satisfactorily in filtering noise with less distortion of individual localized brain responses.**

I. INTRODUCTION

Magnetic resonance imaging provides several useful tools for studying the human brain and functional brain imaging (fMRI) is one of the most widespread technique for the study of many aspects of brain constitution, like its activity, aging, tumors, and other diseases [1], [2], [3], [4]. The now ubiquitous term BOLD effect, discovered in 1992, is a surrogate of the neuronal activity, which arises from differences in blood oxigenation levels and depends on regional cerebral metabolic demands. In order to correctly assess the brain function with fMRI, serial image preprocessing procedures are necessary prior to data analysis, in order to account for differences in slice scan time, head movement and thermal noise. One of the crucial steps in preprocessing is the BOLD spatial filtering. Usually, a Gaussian kernel is used for noise attenuation in fMRI and a consequent rise in signal-to-noise ratio.

Although widely used, the Gaussian filtering approach should be cautiously applied, because excessive smoothing could bring errors to the final results. The main problem is the intense image blurring, which affects local variations in the data and leads to errors. The blurring effect could also cause data loss, since the excessive homogenity of the resulting signal across space avoids detection of fine details due to individual brain traits.

In recent years, a novel image filtering technique has been proposed to account for complex structures and preserve local subtle traits. The anomalous diffusion equation is the base for this new filtering technique, applying the generalized anomalous paradigm [5], [6], [7]. This approach has already been applied in other areas such as Economics, Physics and Biology [6]. The Isotropic Anomalous Diffusion Filter (IAD), which relies on the anomalous distribution, provided by the porous media equation discretization [8], could bring enhancement in local inhomogeneity and long range preservation effects to the filtering process, helping to maintain the local natural variability.

The anomalous diffusion algorithm is based on an iterative filter that generates an anomalous diffusion distribution, known as *q-Gaussian* probability distribution. The long and short tail distribution characteristic from the anomalous diffusion behavior [6] has an important enhancement factor for human imaging, that has been studying in recent researches [8]. In fMRI context, the temporal series components of the fMRI signal when filtered with local *q-Gaussian* iterative kernels could present a decreasing in the noise intensity present in this imaging technique and also preserve the natural signal variation that is usual in the BOLD signal.

The ICA algorithm is a popular benchmark algorithm aimed at extracting signal in a blind data-driven fashion. The algorithm is applied to whole- brain voxels in order to separate the information set into networks with maximally independent fluctuations [9]. The resulting individual ICA maps reveal two complementary principles underlying the study of brain organization: localization and connectionism. While the localization approach considers that a given brain function is accomplished by a finite set of specific and segregated brain areas, connectionist views consider that these areas may be widely distributed and functionally connected across space [10]. The balance between segregating or connecting brain regions is well characterized by ICA maps. Usually, the maps present z-transformed statistical values, a measure of the relative amount a given voxel is modulated by the activation of a certain component. Above a certain threshold, surviving voxels can be labeled as 'active' for that component. [9].

ICA algorithm identifies long range relationships between voxels across distant regions, on the other hand, classic Gaussian approach distorts the local fluctuation, causing

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information loss within these activation areas. Here we propose the use of the IAD filter for a better characterization of active regions found by the ICA algorithm, that could preserve local fluctuations while providing confidence for cluster segmentation.

II. MATERIALS AND METHODS

A. Functional MRI Parameters

Seven healthy subjects (gender: 2 males, 5 females; mean age: 33 years, range 21-60 years) with no reported history of auditory, neurological, or psychiatric disorders were selected from the image database in the Clinics Hospital of Faculty of Medicine of Ribeirão Preto (CHFMRP). No auditory stimulation where used in all image acquisition procedure.

The images were acquired with a Philips Achieva 3.0-T MRI equipment (Best, The Netherlands) using a standard 8-channel head coil. Echoplanar sequences had the following parameters: 200 volumes, 32 slices in ascending order, 4-mm slice thickness, .5 mm gap thickness, voxel size = 3 × 3 mm, field of view = 240 × 240 mm, TR/TE = 2000/30 ms. The silent sequence was used by setting the "soft-tone" parameter, offered by the MRI equipment, decreasing the noise level in 3.65 dB, which decreases the gradient slew rate leading to lower coil vibration levels [11].

B. Image Processsing

The image were processed using FSL software [12]. Functional volumes were corrected for 3-D motion with reference to the middle volume, using the Affine non linear image registration algorithm, that is part of the FSL MCFLIRT tools [13]. After the filtering process, the functional image entered the ICA algorithm, which resulted in individual ICA maps. We fixed 30 ICA maps in order to lead to sufficient clustering estimation, what in fact it is a usual adoption for ICA analysis in fMRI. Auditory BOLD components were identified by visual inspection of bilateral clusters in superior temporal areas. A profile was delineated along the antero-posterior direction of these clusters and z-ICA values were verified for further comparison between the spatial filters (Gaussian versus Anomalous).

The filters used here were the classical Gaussian filter, and the Isotropic Anomalous Diffusion (IAD) filter. For the Gaussian approach, the filtering intensity is regulated by the Full Width at Half Maximum ($FWHM$) parameters, and usually it is defined between 5 and 12 mm. In our study we used $FWHM = 7mm$ for Gaussian filtering. The IAD filter has three parameters: time t, the generalized diffusion coefficient D_q and the anomalous parameter (q). The values for t and D_q used here were $t = 12$ and $D_q = 1.0$. The IAD filtering parameters were chosen based on previous studies done with T1 and DTI MRI protocols [14], [8], where the filter showed improvements in filtering performance, attenuating the noise in those image modalities. For this reason the q parameter was set fixed to $q = 1.3$. These parameters values are equivalent to the $FWHM$ parameter as seen in Equation (1), which are derived using the generalized Einstein equation ($\sigma^2\ proptot^{2/3-q}$) and the FWHM definition [15].

$$t = \left(\frac{FWHM}{2.\sqrt{2.\ln 2.D_q}}\right)^{3-q} \xrightarrow{D_q=1} t = \left(\frac{FWHM}{2.\sqrt{2.\ln 2}}\right)^{3-q} \quad (1)$$

Some local measurements were chosen in order to analyze a quantitative behavior conducted from the IAD and Gaussian filter. The first metric used is the total brain activated area, that is supposed to be lower in the IAD method due to natural variability preservation. Other metrics such as the minimum and maximum value were chosen to note the gray value preservation, i.e. the IAD filter must preserve the general voxel information presented in the whole activation region. Finally, a Contrast-to-noise ratio (CNR) measurement was chosen to quantify the enhancement differences between the spatial filters [16]. The CNR formulation used here is defined in Equation 2.

$$CNR = \frac{\overline{\sigma}_S^2}{\overline{\sigma}_N^2} \quad (2)$$

Where $\overline{\sigma}_S^2$ and $\overline{\sigma}_N^2$ are defined by the ratio between the variances of active (signal) and background (noise) z-ICA values of auditory maps.

C. Isotropic Anomalous Diffusion Filter

The IAD filter is a generalization of the classical diffusion process, i.e. the Gaussian filter. The numerical algorithm is shown in Equation (3) and it is basically the same algorithm as seen in the classical approach. The Equation (3) simulates the diffusion process in each neighborhood in the image in discrete form, regulated by the anomalous parameters such as the q value (a parametric curve adjust) and the generalized diffusion coefficient (D_q).

$$I_{t+1,\beta} = I_{t,\beta} + \left[D(\overrightarrow{r})_q.\nabla I_{t,\beta-1}^{2-q} + D(\overrightarrow{r})_q.\nabla I_{t,\beta+1}^{2-q}\right] \quad (3)$$

For simplicity, $I_{t,\beta}^{2-q}$ represents the image at time t according to locating a 3×3 neighborhood of the center pixel for a defined anomalous parameter q. The parameter β informs the spatial position of the neighbor relative to the central pixel and, upon this orientation, the pixel gets a weighted value based on the anomalous solution generated by Equation (3). There are two main points to discuss about these differences: the anomalous *q-distribution* and the generalized diffusion coefficient (D_q). The *q-distribution* is in fact the probability distribution function that represents the solution of the Equation (3). The q-distribution in this case could be called the q-Gaussian probability distribution and it is well know in Physics simulation problems [6]. The diffusion coefficient, D_q, is a parameter that regulates the diffusion intensity in the image neighborhood and it is defined by Equation (4). It is close to the relationship between D_q and the q parameter, and both create a specific q-Gaussian distribution in each neighborhood on the image.

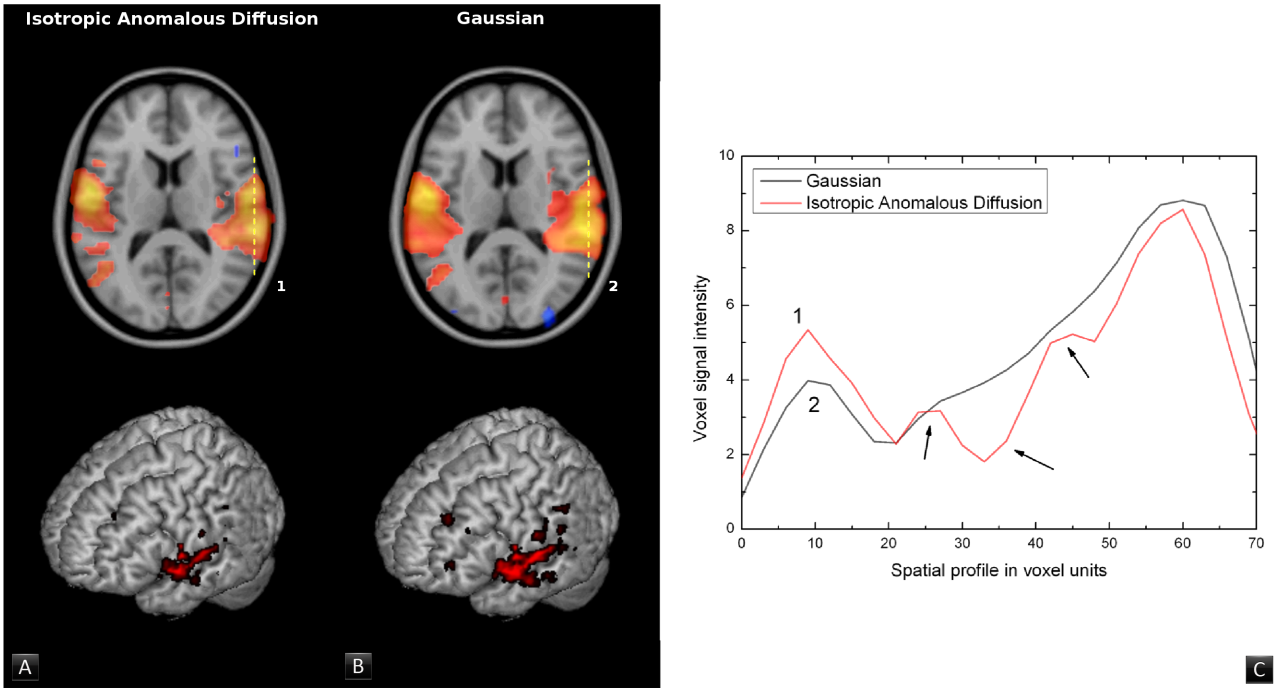

Fig. 1. Brain auditory activation thresholded on maps calculated with the two filters: A) Isotropic Anomalous Diffusion (IAD) and B) Gaussian filter. The dotted lines, 1 and 2, define the profiles are shown in C) where z-ICA values keeps the natural inhomogeneity pertaining to this individual brain. The Gaussian filter intensively smooths the whole area, distorting the natural signal fluctuations present in the BOLD signal and losing some BOLD signal peaks (arrows).

$$D_q = \begin{cases} \frac{\alpha}{2}.D.\left(\sqrt{\frac{(q-1)}{\pi}}.\frac{\Gamma(\frac{1}{q-1})}{\Gamma(\frac{1}{q-1}-\frac{1}{2})}\right)^{\frac{2-2q}{3-q}} & ,1<q<2 \\ \frac{\alpha}{2}.D & ,q=1 \\ \frac{\alpha}{2}.D.\left(\sqrt{\frac{(1-q)}{\pi}}.\frac{\Gamma(1+\frac{1}{1-q})}{\Gamma(\frac{3}{2}+\frac{1}{1-q})}\right)^{\frac{2-2q}{3-q}} & ,q<1 \end{cases} \quad (4)$$

Where $\alpha = (2-q)(3-q)]^{2/(3-q)}$ and $0 < q < 2$ are the range for the q parameter for numerical stability in Equation (3). In summary, the anomalous diffusion generates another probability distribution function that is supposed to be more suitable for the processing of images with complex features. The time, t, parameter can be adjusted in comparison with the variance (σ^2) [6], with a relationship given by $\sigma^2 = 2.D_q.t^{2/(3-q)}$. Furthermore, the full width at half maximum (FWHM$= 2.3548.\sigma$) parameter, which is usually defined for fMRI image processing, has a similar relationship with t. This variance dependence with time is know as the generalized Einstein equation and it describes the smoothing behavior with the IAD filter.

TABLE I

BRAIN ACTIVATION AREAS MEASUREMENTS

Filter	Area	CNR	Minimum	Maximum
IAD	3367 ± 826	118 ± 25	1.6 ± 0.8	9.9 ± 2.1
Gaussian	4447 ± 982	87 ± 12	1.8 ± 1.1	10.61 ± 2.8

III. RESULTS AND DISCUSSION

Table I shows values of area, Contrast-to-noise ratio (CNR), and minimum and maximum z-values of thresholded auditory maps (z-ICA $>$ 2.09). Values for area above threshold and CNR were different depending on the filter used (Student t-test, bicaudal, homocedastic, p<0.05). Gaussian filtering renders larger areas than isotropic anomalous diffusion filtering. CNR were computed under each filter condition for each individual data set using a automatic threshold, i.e. maximum entropy threshold algorithm, to select the activated area. Contrast-to-noise was calculated by dividing the variance inside the active area by the variance of an equivalent area without activation. A t-test showed that CNRs are different depending on the filter used (Student t-test, bicaudal, homocedastic, p<0.05), with larger CNR for anomalous filters (p=0.01). Figure 1 shows the results of an ICA map of a representative subject under each filtering condition, representing the auditory brain areas. The interrupted lines on axial slices (top) represent the profiles whose values are depicted in 1-C.

An interesting result that could be discussed with the CNR measurement is the signal fluctuation into each brain activated area, segmented by the ICA maps. As defined in the Equation (2), the CNR measure represents the signal deviation presented in determined region. The IAD filter show a higher CNR value than the Gaussian filtering, which represent a higher signal variability. Even with a low sample size, the statistical analysis shown a promising result with the IAD filter. Its behavior could be partially explained by the anomalous relationship between neighborhood voxel influence. The anomalous approach, based on q-Gaussian probability distribution, adds a non linear relationship in each processing site, and this information is helpful to modulate the MRI signal decay [17].

Figure 1-A and Figure 1-B illustrate 3D rendering of brain surface showing active areas for both filters and image profiles revealing additional activity peaks for IAD. Some aspects can be highlighted in our results, pointing to advantages in using the anomalous filter for functional data analysis. First, IAD filter render more localized areas, which are coincident with anatomical landmarks, as can be observed in Figure 1-A. Also, the profile shown in Figure 1-C retains local variation of the underlying anatomy, thus preserving two main points: the local BOLD signal variation and an effective noise smoothing. On the contrary, Gaussian filtering results in more widespread activations, that can be explained by a strong dependence on the central voxel value. Furthermore, the local z-ICA values distribution shows an excessively smooth central region, implying in low signal variation inside active areas.

IV. CONCLUSIONS

The non homogeneous media provide a spatial signal complexity that must be preserved by the filtering process for more accurate and consistent ICA segmentation. Usually, the Gaussian filtering process is commonly applied in much functional magnetic resonance imaging (fMRI) research. However, the strong blurring and signal loss provided by this classical filtering approach is well know and could provide some errors in future image analysis. The isotropic anomalous diffusion (IAD) filter showed to be a better filtering method for BOLD smoothing. In comparison with the Gaussian filter, the IAD filter demonstrated a local natural signal fluctuation suitable for fMRI processing. The Gaussian filter does not have a robust noise suavization, that can be seen with the IAD filter.

This study reports preliminary results obtained with a specific parameter set. In a future research, we will study the noise suavization effect that could be found with the other q value range, between $0 < q < 1$. Here we used the long range q-Gaussian approach, with $q = 1.3$, but a study is necessary with the local finite q-Gaussian approach which is defined with $q < 1$ values. A further study with more extensive images groups is necessary to guarantee statistical equivalence between the filters. In addition, a more accurate results should be reached with higher image sample. Even with a limited sample, the ICA segmentation outcomes highlighted here suggest a promising application using the IAD filtering approach for fMRI studies.

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