VENOUS BLOOD CONTRIBUTION TO fMRI SIGNAL IN THE AUDITORY CORTEX

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Abstract: In this work a method to assess the venous blood contribution to functional Magnetic Resonance Imaging (fMRI) signal during brain activation studies based on the Blood Oxygen Level Dependent (BOLD) effect is proposed. This method exploits the state-of-art techniques performing high resolution brain venography and the methodologies for statistical data processing in the detection of neuronal activation. The combination of these two techniques gives out as a result a tool that allows at the same time the study of brain functional activation and of vascular structures. This procedure led to a preliminary characterization of the fMRI signal of venous and non-venous regions, in terms of both their spatial and temporal development.

Introduction

Nowadays functional MRI is a widespread technique to accomplish brain functional studies, and encounters more and more the favour of clinical users because of its effectiveness, non-invasiveness and good temporal and spatial resolution [1, 2].

In spite of its effectiveness, anyway, some limitations of the techniques can be found considering that functional MRI is not able to detect directly neuronal electrical activity foci, but locates the activation sites through a transfer function by measuring the transient changes of the physiological parameters that occur in the brain during neuronal activation. It is known, for instance, that activation induces an increase in the local cerebral blood flow (CBF) and cerebral blood volume (CBV): exploiting these physiological effects, MR techniques for perfusion assessment, like Arterial Spin Labelling (ASL) [3] or Time-of-Flight (TOF) [4], can be useful tool to evaluate cortex brain activation.

The most used fMRI technique is based anyway on the BOLD (Blood Oxygen Level Dependent) effect [5]. During activation, in fact, the local CBF, the cerebral blood volume (CBV) and the cerebral metabolic rate of oxygen ($CMRO_2$) change in order to satisfy the higher energy demand by the neurons supplying more oxygen to the cortex [6, 7]. The temporal evolution of this quantity, though, is such that the oxygen extraction fraction from arterial blood actually decreases, so that the blood has for some time a higher oxygenation fraction. In a typical magnetic resonance scan deoxyhemoglobin (dHb) produces a stronger signal than oxyhemoglobin (Hb) because the former is paramagnetic and the latter is diamagnetic: the result of all these processes is that in the activated regions the MR signal has a temporary increase following a typical pattern (Figure 1).

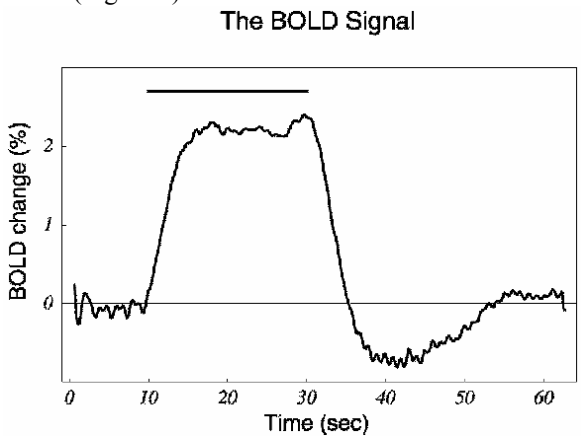

Figure 1: Typical time course of BOLD MR signal during functional activation.

Consequently, the statistic procedures to detect BOLD activation are based on the recognition of a particular pattern within the temporal series of each voxel [8]. For this pattern several theoretical models are given [9, 10]; the result of this data processing is normally a map where the degree of activation (i.e., the degree of correlation) of a pixel, measured for instance by the cross-correlation with a theoretical function, is displayed in colours on an anatomical slice.

Though in the recent literature the principle underlying the BOLD technique is straightforward, concern arises about the actual meaning of the activation maps. The goal is in fact to find the regions of neuronal activation and not the vessels that change their oxygenation during activation: we still use the latter to infer about brain activation, finding "highly" activated pixels that define the spatial importance of sub-regional zone in the activated areas, leading as well to important medical decision in the health care treatment of patients.

Thus, several issues still need to be addressed: the relation between the veins and the BOLD activated areas, the vein contribution to the BOLD signal, and

ISSN: 1727-1983

how to eliminate the venous artefacts from the activation maps.

In order to give an answer to these questions it is necessary to develop a methodology to integrate the information of a functional analysis with the one provided by anatomical studies, taking into special account the brain vasculature for the above mentioned reasons.

The BOLD effect can be exploited also for this purpose, since the spin dephasing due to deoxygenated blood makes the signal coming from venous regions easily identifiable [11].

In the latest years, in fact, several techniques have been developed to enhance the characteristics of the venous MR signal in order to perform brain venographies [12]. Anyway, the data processing step necessary to draw the venograms can be noticeably shortened using high magnetic field scans: it is known, in fact, that the Contrast-to-Noise (CNR) ratio of MR signal has a supralinear dependence with the field strength [13], which means that data obtained with magnetic fields equal or greater than 3 Tesla can be easily processed to obtain brain venographies [14].

With this approach, based on the main idea of merging MR venography and functional MRI, we managed to set up a method that allows inferring about the relationships between vasculature and activation sites. The method is explained in detail in the following paragraphs and the preliminary results of this analysis are discussed.

Materials and Methods

MR scanning

A healthy volunteer underwent through an anatomical and a functional MR scan with a GE Signa 3 Tesla scanner.

The anatomical scan used an SPGR (Spoiled Gradient Recalled Echo) sequence and produced 60 T1 weighted anatomical slices. The imaging parameters were the following: TE 25 ms, TR 30 ms, Flip Angle 25°, Field of View 24 x 24 cm^2 with a 512 x 512 matrix, voxel size 0,5 x 0,5 x 1 mm^3.

For the functional scan a Gradient Echo EPI (Echo Planar Imaging) sequence was used throughout the stimulation, which gave sets of 10 T2* weighted axial slices covering the auditory cortex. The imaging parameters were TR 1 s, TE 30 ms, FA 90°, Field of View 24 x 24 cm^2 with a 64 x 64 matrix, voxel size 3,7 x 3,7 x 3 mm^3.

Stimulation

The stimulation paradigm consisted of a series of 1 kHz sounds with different durations, namely 0.5, 1, 2, 4, 5 seconds long, followed by a rest period so that each stimulus *plus* rest period lasts 20 seconds. This timing was chosen in order to attempt avoiding signal superposition due to two consecutive stimulations.

The acoustic stimulation was provided to the subject with the commercial software *Presentation*™ by means of earphones, which had also to reduce the influence of the coil noise on the experiment.

The stimulation pattern was repeated 4 times and the results averaged to reduce the noise in the signal.

Data analysis

All data processing was performed with AFNI suite software [15].

From the anatomical dataset, a high resolution brain venography was extracted by applying directly on 10 anatomical slices a minimum Intensity Projection (mIP) algorithm [14] (Figure 3, left).

For each voxel of the functional dataset, the cross-correlation was calculated between the voxel time series and a theoretical function obtained through the linear model proposed by Cohen [9]. The function was obtained by convolving the stimulus function, represented by a series of step functions, with the impulse response function indicated in [9]. Activation maps were drawn by thresholding the value of the correlation coefficients ($r>0.6$, Figure 3 right) and displayed on the central anatomical slice.

The activation maps were then superimposed on the venogram and the relation between activated regions and venous structures was assessed. To test the potentiality of this tool we extracted the time series of a venous and of a non-venous voxel and compared them.

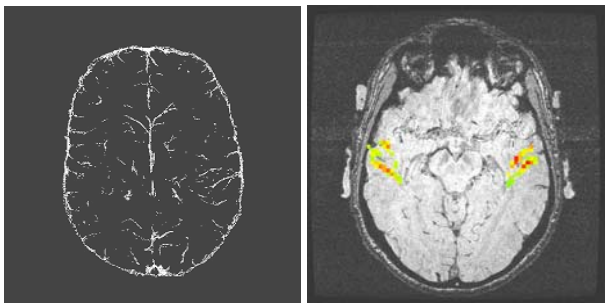

Figure 3: Gray-scale inverted brain venography (left) and activation map superimposed on an anatomical slice (right).

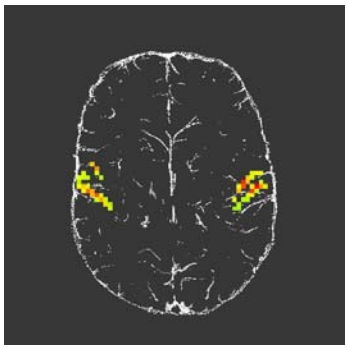

Figure 2: Activation map of the auditory cortex superimposed on the corresponding brain venography.

ISSN: 1727-1983

Results

Figure 3 shows the fusion between the anatomical and the functional images: the result is an image where functional activation is shown together with the venous structures.

If we look closer at this picture (Figure 4) we can notice that activated regions are in proximity of small vein networks, which can be considered responsible for the BOLD activation.

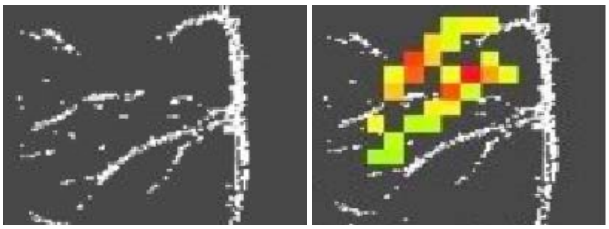

Figure 4: Zoom of the activated areas shown on the right side of Figure 3. The same area is shown with (right) and without (left) the activated pixels.

In Figure 5 a comparison is done between the time course of an activated voxel containing venous blood and a non-venous voxel. The analysis of the graph shows that the response intensity of venous voxel is higher than that of a non-venous voxel.

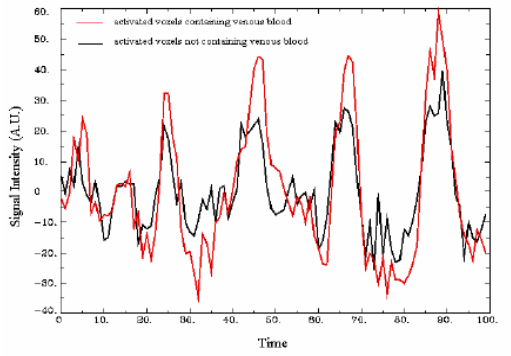

Figure 5: Example of a voxel time course of an activated venous and non-venous pixels. The response intensity of a venous pixel is about 50% greater than non-venous voxels.

Discussion

BOLD functional activation is a complex phenomenon that involves several physiological mechanisms and parameters. The main source of this phenomenon is blood and the changes that occur during functional activation. These changes appear mainly as a transient variation of the transverse relaxation rate, and produce an MR signal change ΔS which can be expressed quantitatively with the following relation [1]

$$\Delta S = \rho S_0 \left(e^{-TE\,\Delta R_2^*} - 1 \right) \qquad (1)$$

where ρ is the fraction of voxel volume that is active in a single voxel, S_0 the signal during the resting period, TE the echo time and ΔR_2* the change of the apparent transverse relaxation rate.

As to the intravascular BOLD effect, a direct dependence between oxygen saturation and the relaxation rate has been proposed in [16] according to the formula

$$R2^*(Y) = R2_0^* + k(1-Y) \qquad (2)$$

with Y being the blood oxygenation, and $R2_0$* the relaxation rate of fully oxygenated blood.

The variations of the transverse relaxation rate are due mainly to two different mechanisms: magnetization dephasing in the presence of field gradients in large vessels and water diffusion within the field gradients in small vessels [17].

These changes can be detected with functional MRI both with Gradient echo (GE) and Spin Echo (SE) sequences; in particular, GE sequences result more sensitive to the BOLD activation than SE, but the functional data collected with GE sequences are also strongly affected by the large vein contribution [18], whose relation with the actual neuronal activation is uncertain.

Besides, BOLD-based fMRI is meaningful as long as the physiological changes occur in the same area as the neuronal activation. It is generally thought that the spatial extent of the metabolism changes that give rise to the BOLD effect is consistent with the locations of neuronal activity; still some studies have shown that this is not always the case and that the area with metabolic response may be larger than the area of electrical activity [19].

As to the vein depiction, BOLD venography is able to overcome the limits of other venographic techniques based on flow measurements, like Phase Contrast Angiography (PCA) [20] or Time-of-Flight [21] and to produce high resolution venograms with details up to 1 mm. A good resolution of the venography is of course highly desirable, but it has also to be compared with the one of the functional scans, which usually is coarser in order to get a good temporal resolution.

Thus all these issues merge together when dealing with the BOLD effect. The issue of the vascular origin of the BOLD activation and the possible venous artefacts coming from there can be analyzed with the help of the tool described in this work. This method can give important insight in the spatial distribution of the activated regions with special regard to the vascular structures surrounding the BOLD activated areas.

More information can be extracted with this procedure if it is taken into account also the time series of the activated pixels, as discussed previously and shown in Figure 5. We demonstrated, for instance, that BOLD activated venous pixels have special features that can help to discriminate them from the actual activation sites; further studies in this sense can provide the basic knowledge to characterize the venous activated regions,

ISSN: 1727-1983

and eventually to develop the tools that can provide a better understanding of the real meaning of the BOLD activation maps.

Conclusions

The questions about the significativity and reliability of the BOLD activation maps are still far to be completely answered, and they fall within the general problem of understanding how the electrical activity of the neurons is *transferred* to the metabolic and physiological changes which can effectively be detected by BOLD fMRI.

These issues are of the highest importance, because they represent the current limitations of BOLD fMRI: as long as a thorough theoretical knowledge of the BOLD phenomenon is not provided, it is impossible to exploit fully its clinical potentiality.

The analysis method developed in this work moves in this direction and can be a starting point for further investigations. In fact, we demonstrated how through a simple approach consisting of a pixel by pixel comparison analysis of high resolution anatomical and functional information can give important details on the correlations existing between venous blood and the BOLD generated functional signal. Automatic implemented algorithm performing such kind of analysis in an accurate way, could have a strong impact in any kind of brain functional investigation.

Acknowledgements

We would like to deeply thank Dr. Tommaso Scarabino and his team for his helpful collaboration and for hosting us in the MR Radiology center of the IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Foggia, Italy, where we carried out all our functional experiments.

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ISSN: 1727-1983