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New time-shifted Z-score and Student's test in fMRI

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***Abstract*— A new approach to compute z-score and Student's test in functional MRI has been developed. This approach tends to involve standard z-score and Student's test computation. This approach is based on the delay of the response compared to the stimulation introduced by many authors. The results obtained prove the methods efficiency; moreover these methods can be easily adapted in a clinical context. This paper presents the new computation and the validation.**

I. INTRODUCTION

Emergence of functional MRI (fMRI) has opened up new research perspectives in many medical fields, such as pain management, human language knowledge, and so on. Complementary to usual MRI which provides morphological information, fMRI gives functional information, required by pre-surgical planning for instance.

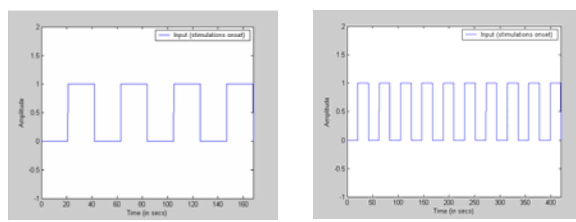
During fMRI examination, patient is submitted to a sequence of activation and rest phases (so called paradigm) while cerebral 3D images are acquired. Mainly two types of paradigm are used: block-design or event-related. A block-design paradigm (concerned by our study) consists in a succession of periods of rest and activation. Each period is covered by several images: the main interest is to improve signal to noise ratio thanks to summation of responses. An event-related paradigm consists in presenting the stimulus in a random way. After image acquisition, fMRI relies on the voxels classification: voxel activated/deactivated (time evolution was disturbed by the stimuli) or inactivated. During last decade, fMRI has been the subject of many studies and numerous approaches have been proposed to determine the activated zones: statistical tests, generalized linear model [1], hemodynamic response function [2-3]. Our paper is focused on statistical test approaches, the aim of which being to determine if an assumption relating to the observed phenomenon is checked or not according to a risk of error. Statistical approaches can be classified in two categories: parametric and nonparametric approaches. This paper describes our contribution to parametric approaches and proposes some improvements of z-score and Student's test. First, we present the data concerned by the study and methods of acquisition. Then we describe the principle of the z-score and of the Student's test. Finally we present our contribution to the z-score and to the Student's test computation.

II. MATERIAL

Five healthy volunteers (4 men, 1 woman, mean age 30 years, 4 right-handed/1 left-handed) as well as three epileptic patients (2 men, 1 woman, 2 left-handed/1 right-handed pre-surgical planning) were examined.

Images were obtained with a Philips MR scanner (Intera Achieva 1.5T). T1-weighted sequence (3D TFE) was used to acquire anatomical data (volume size 256*256*65, voxel size 0.977*0.977*2.0 mm^3). Functional images were acquired using T2-weighted EPI sequence (volume size 64*64*26 volume, voxel size 3.9*3.9*5 mm^3, T_R = T_acq = 3 sec).

Block-design paradigms were used for localization of motor and speech areas. 4 phases of rest (21 sec, 7 dynamics or volumes) and 4 phases of activation were alternatively presented during the motor paradigm (Fig 1.a), respectively 10 phases of rest and activation for speech stimulations (Fig 1.b).



(a) (b)

Fig. 1: Block-design paradigms alternating activation and rest phases.
(a) motor stimulations, (b) speech stimulations.

Motors stimulations were produced by dominant hand open-close (1 Hz), opposition between thumb and the 2nd-4th-3rd-5th fingers on dominant hand, toes open-close on dominant foot (1 Hz) or tongue movements from top to bottom. Speech stimulations were produced by word generation (countries, celebrities, animals), noun-verb association and text reading. The aim of the speech paradigm was to study the language lateralisation. To synchronize stimulations and acquisitions, these paradigms were implemented on E-Prime™ work station (MRI Devices, Invivo Corporation, Orlando, Florida U.S.A, www.mridevices.com) and were presented to the subject via IFIS™ equipment.

III. METHODS

A. Pre-processing

In fMRI, images require pre-processing such brain mask determination, slice timing, matching, and spatial smoothing. Brain mask determination is interesting to limit the working area, thus to decrease computing time. The mask extraction was done by successive morphological filter, classification and thresholding [4]. The EPI sequence is a 2D acquisition (slice by slice). Here, slices were acquired in interleaved mode (i.e. the odd slices are acquired before the even slices) and have to be synchronized on the same time origin. We used the method described in [5]. Taking into account the functional acquisition duration, patient's head movements are inevitable and have to be corrected. Matching of functional and anatomical images is also necessary to make possible the necessary superimposition of functional results on anatomical images. All algorithms used are described in [6-7].Images were filtered by a Gaussian smoothing to increase signal to noise ratio and to make data close to a Gaussian field model (that is absolutely required if Gaussian field theory is applied to make statistical inferences as assign p-values).

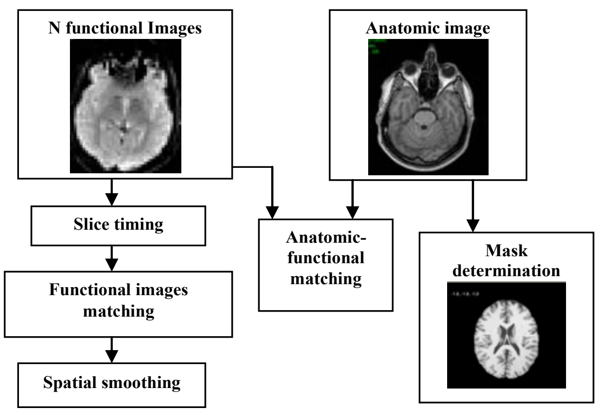


Fig. 2: Pre-processing diagram

B. Statistical treatments

In our study, the null hypothesis H_0 was: "There is no difference between the two states, rest and stimulation". For each voxel, we have computed statistical criteria with known distributions under H_0 and then we have performed tests to decide if the realization of the task leads to a significant variation of the signal in the voxel according to a risk α. The statistical tests used were z-score and Student tests which, unlike SPM methodology, do not require any thorough model specification.

In the following equations:

- A and R represent the phases of activation and rest, respectively.
- N_A and N_R are the numbers of dynamics acquired respectively during activation and rest.
- $Y_{A,k}(i)$ and $Y_{R,k}(i)$ are the value of the voxel K in the i[th] dynamic acquired during activation and in the j[th] dynamic acquired during rest, respectively.
- $\overline{Y}_{A,k} = \frac{1}{N_A}\sum_{i=0}^{N_A} Y_{A,k}(i)$ and $\overline{Y}_{R,k} = \frac{1}{N_R}\sum_{j=0}^{N_R} Y_{R,k}(j)$ are the estimated mean values of the voxel K during activation and rest, respectively.

In the following, upper-case letters represent random variables whereas lower-case letters correspond to the realization of the corresponding random variable. Thus, if X_k is a random variable, then x_k represents one of its possible realizations.

1) Z-score:

We assume, for a given voxel K, the following model:

$$
\begin{aligned}
Y_{A,k}(i) &= S_{A,k} + \varepsilon(i) \\
Y_{R,k}(j) &= S_{R,k} + \varepsilon(j) \qquad (1.1)
\end{aligned}
$$

$\varepsilon \sim N(0,\ \sigma^2 I)$ where I is an identity matrix

In Eq (1.1), σ is standard deviation of the noise, $S_{A,k}$ and $S_{R,k}$ are the signals measured in the voxel K during A and R, respectively, assuming that the signal is not disturbed by the noise ε.

The z-score is defined by:

$$
Z_k = \frac{\overline{Y}_{A,k} - \overline{Y}_{R,k}}{\sigma\sqrt{\frac{1}{N_A} + \frac{1}{N_B}}} \qquad (1.2)
$$

Under the null hypothesis H_0, the random variable Z_k is normally distributed with zero mean and unit variance. After the calculation of the z-score z_k of a given voxel, we evaluate the probability that Z_k takes the value z_k if Z_k is normally distributed with zero mean and unit variance. We can then reject or not H_0 according to a risk α, which is chosen (generally 0.01) so that the activated area is restricted to a possible limited area. It should be noted that the standard deviation σ is unknown, so it is estimated as the standard deviation of the image difference between two successive rest states.

2) Student's test

This test, often proposed in fMRI, is defined by:

$$
T_k = \frac{\overline{Y}_{A,k} - \overline{Y}_{R,k}}{\sigma_d} \qquad (1.3)
$$

$$\sigma_d = \sqrt{\frac{\sum_{i=0}^{N_A}\left(Y_{A,k}(i)-\overline{Y}_{A,k}\right)^2+\sum_{i=0}^{N_R}\left(Y_{R,k}(i)-\overline{Y}_{R,k}\right)^2}{N_A+N_R-2}\left(\frac{1}{N_A}+\frac{1}{N_B}\right)}$$

Under the hypothesis H_0, the variable T_k is distributed according to Student's law with N_A+N_R-2 degrees of freedom. As previously, we calculate t_k for a given voxel. Then we infer the probability that T_k takes the value t_k if it is distributed according to the Student's law with N_A+N_R-2 degrees of freedom. We can then reject or not the hypothesis H_0 according to a risk α.

3) *Our new test proposal*

In the approaches to estimate the hemodynamic response function (HRF) by parametric methods, many authors [8-9] have introduced a delay of the response compared to the stimulation.

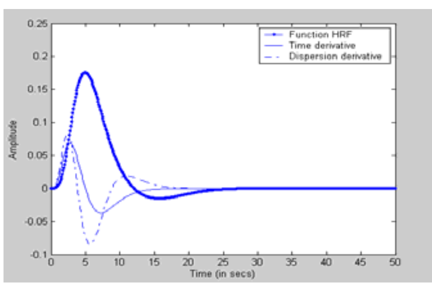


Fig. 3: Hemodynamic response function (HRF)

In the largely used model suggested by Friston (Fig. 3), the authors estimate a 5 sec delay from the stimulation.
Thus, if we use a block-design paradigm and consider that brain system is characterized by this HRF, the output of a dynamic system (Fig. 4) is the result of the convolution of the input function with the impulse response function, i.e. the HRF.

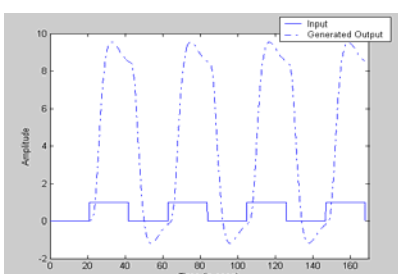


Fig. 4: Block-design input (solid line) and output (dashed line) obtained by convolution of the input with HRF.

It seems to us more convenient to define a new z-score and a new Student's test, by considering not directly the observed response but this response shifted in time (Fig 5).

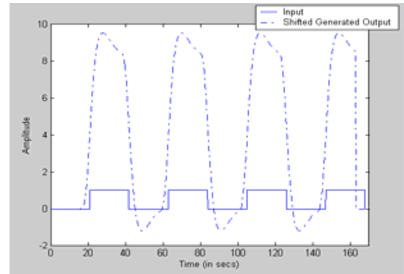


Fig. 5: Block-design input (solid line) and shifted output (dashed line).

The response was shifted of 5 seconds towards the left. We observe that this simple shift makes it possible to establish a better relation between input and response. Thus we choose to integrate this shift in the calculation of the z-core and of the Student's test.
Let us specify that within the framework of fMRI, the shift will have to be a multiple of T_acq. In our study, we considered a shift of 6 sec for a $T\_acq = 3$ sec.
Let define:

- $m = \frac{\text{Shift in secondes}}{\text{TR in secondes}}$ is the shift in number of dynamics.
- $\tilde{N}_A$ and $\tilde{N}_R$ are the numbers of dynamics in activation and rest after shift.
- $\tilde{Y}_{A,k}(i) = Y_{A,k}(i+m)$ is the value of the voxel K in the m^{th} dynamic acquired after the i^{th} activated dynamic.
- $\tilde{Y}_{R,k}(j) = Y_{R,k}(j+m)$ is the value of the voxel K in the m^{th} dynamic acquired after the j^{th} rest dynamic.
- $\tilde{\overline{Y}}_{A,k} = \frac{1}{\tilde{N}_A}\sum_{i=0}^{\tilde{N}_A}\tilde{Y}_{A,k}(i)$ et $\tilde{\overline{Y}}_{R,k} = \frac{1}{\tilde{N}_R}\sum_{j=0}^{\tilde{N}_R}\tilde{Y}_{R,k}(j)$ are the estimated averages of the voxel K during respectively activation and rest.

From these new notations and from Eq (1.2) and (1.3), we obtain:

$$\tilde{Z}_k = \frac{\tilde{\overline{Y}}_{A,k} - \tilde{\overline{Y}}_{R,k}}{\sigma\sqrt{\frac{1}{\tilde{N}_A}+\frac{1}{\tilde{N}_B}}} \qquad (1.4)$$

The variance σ is unknown, but it is also estimated as the standard deviation of the image difference between two successive rest states.

$$\tilde{T}_k = \frac{\tilde{\overline{Y}}_{A,k} - \tilde{\overline{Y}}_{R,k}}{\tilde{\sigma}_d}$$

$$\tilde{\sigma}_d = \sqrt{\frac{\sum_{i=0}^{\tilde{N}_A}\left(\tilde{Y}_{A,k}(i)-\tilde{\overline{Y}}_{A,k}\right)^2+\sum_{i=0}^{\tilde{N}_R}\left(\tilde{Y}_{R,k}(i)-\tilde{\overline{Y}}_{R,k}\right)^2}{\tilde{N}_A+\tilde{N}_R-2}\left(\frac{1}{N_A}+\frac{1}{N_B}\right)} \qquad (1.5)$$

These new criteria will be called thereafter "shifted z-score" and "shifted Student's test". Then, as previously, we will calculate probabilities and we will reject or not the hypothesis H_0 according to a risk α.

IV. RESULTS

We compare the results obtained with or without shift to the maps provided by SPM (Statistical Parametric Mapping: http://www.fil.ion.ucl.ac.uk/spm/).

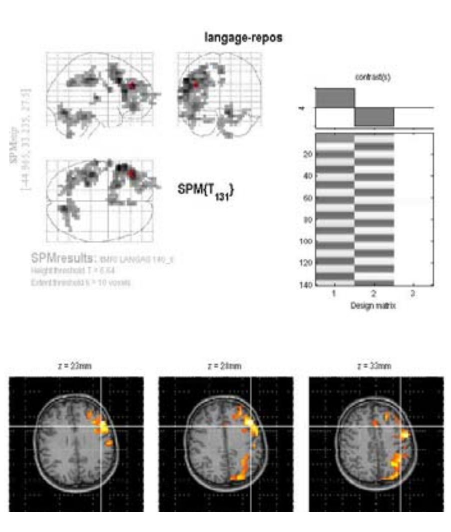
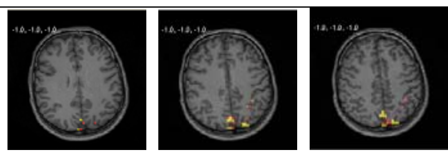
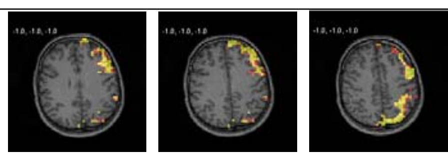
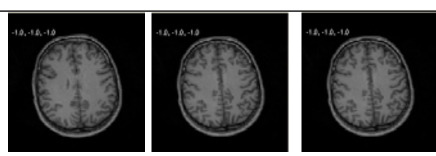
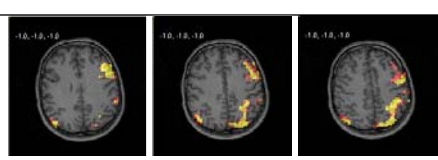
Method	Cartography results
SPM (Hemodynamic basis functions: HRF only. Without model interaction. Without parametric modulation. Without user specified regressors) P-value=0.001 Size of clusters=10.	
Standard z-score α=0.01 and size of clusters=20	
Shifted z-score α=0.01 and size of clusters=20	
Standard Student's test α=0.01 and size of clusters=20	
Shifted Student's test α=0.01 and size of clusters=20	

Table 1: Results obtained on a patient for a speech paradigm.

In Table 1.1, we presented the results obtained for a patient subjected to speech stimulations. The results obtained by SPM (1st line of the table) activation appears near the Broca's area. The results obtained with the shifted z-score and the shifted Student's test appear very close to those obtained by SPM, when the standard methods are not conclusive.

V. DISCUSSION AND CONCLUSION

Results from the shifted Student test give better results than the shifted z-score. Several reasons may justify that. One of the main lacks of the z-score, described in [5], is the estimation of the noise from two dynamics of rest. This supposes that the rest condition is the same at any moment and in all voxel, which is not the case.

For 7 of 8 subjects studied the majority of these subjects, the response time-shift gives a better determination of activations and the results agree visually with those of SPM.

For one patient and whatever the methodology (SPM, Standard z-score …) the results are not conclusive. This poor result may be due to an epileptic fit of the patient before the exam. Results for the 8 subjects were examined by a medical expert in functional MRI and functional activated areas were found very similar between SPM and our new time-shifted z-score and Student's tests.

The time-shift introduced in the response and so in the calculation considerably improves the results. The shifted z-score and the shifted Student's test bring an alternative to SPM. One of their advantages is they are very easily usable in clinical routine. Furthermore, unlike SPM methodology, z-score and Student's test do not require any thorough model specification. Indeed, it is useless to choose a model for the hemodynamic response function, which makes easy their adaptation in clinical context.

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